

Blood 2018



ABSTRACT BOOK

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The combined Annual Scientific Meeting of the:



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001. Coagulation and clotting in children: Medicine of the future, or the future of medicine

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Understanding the coagulation system in humans and the effective use of anticoagulants has been a major medical drive since the 1930s, when our rudimentary understanding of such things really began. To this day disorders of coagulation are a major cause of morbidity and mortality in our communities. The recognition and treatment of Vitamin K deficiency, then termed "haemorrhagic disease of the newborn", was one of the stunning early victories. But subsequently, for decades, children were seen and not heard. However, in recent years there is renewed interest in the coagulation system of children, in part brought about by the increased frequency of thrombosis in children, coined as the "new epidemic" of tertiary paediatric care.

This presentation will focus on our current understanding of the coagulation system in neonates and children, and the ramifications of this for the management of thrombosis, including the use of anticoagulants. There remains much to be learned, and truthfully a good understanding of paediatric coagulation physiology and pathophysiology is medicine of the future. However, in an aging population, where the major burden of disease is due to pathological processes that start in early life (potentially even in utero) then one can reasonably ask whether understanding coagulation physiology and pathophysiology of children, who appear protected against many clotting complications compared to adults, is in fact the future of medicine and we ignore it to the detriment of our entire population.

002. Sometimes it gets bloody – the challenges we face

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Transfusion of blood products is an essential aspect of resuscitation in critically bleeding patients, although at times empirical. In critical bleeding it is important to clearly identify surgical or coagulopathy associated haemorrhage and to restore the haemostatic defect through appropriate surgical interventions or guided blood product use.

Hospitals have recognized the importance of providing blood products quickly to severely injured and bleeding patients by developing massive transfusion protocols (MTP) whereby a fixed quantity of products can be rapidly available. A number of observational studies and randomized clinical trials suggest that patients with severe trauma and coagulopathy have improved survival when the ratio of transfused red cells, plasma and platelets approaches 1:1:1. However this may not be directly applicable in non-trauma critical bleeding.

Coagulation management in critical bleeding must be based on an understanding of the pathophysiological processes and functional assessment of the entire coagulation system leading to targeted replacement of platelets, fibrinogen, other clotting factors or use of anti-fibrinolytic agents. Standard coagulation tests may be unsuitable in such situations due to long turnaround times, being poor predictors of transfusion requirements and only providing an indirect correlation with the clinical picture.

Ongoing studies examining the use of point of care testing in product replacement are underway providing more evidence that early and directed replacement of appropriate coagulation factors particularly fibrinogen and platelets may improve outcome. The use of fibrinogen concentrates rather than plasma-based replacement in trauma, obstetric and perioperative bleeding is now being proposed as the preferred approach.

Although there have been recent significant changes in transfusion practice in critically bleeding patients, controversy continues to surround the use of a pre-defined massive transfusion response. Therefore, to be successful, it is important to consider ways to implement a patient specific response to critical bleeding to better guide timely and appropriate use of blood products directed at the patient's own specific needs.

003. Haematology - the journey

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Kerry Taylor will take the audience on his path to Medicine and Haematology. He will tell of his beginnings in a small country town, the influence of family and experiences that made him choose medicine. He will relate what it was like to undertake Medicine and Haematology in the 70's and 80's and will detail life in a clinical school and hospital that Carl De Gruchy had made famous. He was fortunate to be a member of fellow clinicians making inroads in supportive care in the U.S. in the 80's and then in Australia pioneering a new drug therapy in CML in Australia. He will elaborate on the many influential and colourful fellow clinicians who shaped his life as a haematologist, and he will detail the challenges on building a unit in Queensland and the later move to private practice.

He will conclude by giving a personal opinion on what is good about life as a haematologist and what could be better.

004. Donor-derived piggyBac transposon-generated CAR T-cells induce remission of relapsed/refractory B-cell malignancy post allogeneic haematopoietic stem cell transplant

Bishop D^{1,2,3,4}, Blyth E^{1,2,3,4,5}, Clancy L^{1,5}, Burgess J¹, Mathew G¹, Atkins E³, Simms R¹, Maddock K³, Stephen K⁶, O'Brien T^{7,8,9}, Shaw P^{2,6}, Gottlieb D^{1,2,3,4,5}, Micklethwaite K^{1,2,3,4,5}

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Aim

CD19-specific chimeric antigen receptor (CAR19) T-cells effectively induce remissions of relapsed/refractory B-cell malignancy. However, their implementation is limited by costs associated with viral vectors used during production. Inexpensive CAR19 T-cells generated using the non-viral piggyBac transposon system demonstrated potent pre-clinical activity, so we now assess safety and activity in a first-in-human trial.

Methods

Patients with relapsed/refractory CD19⁺ malignancies post HLA-matched sibling HSCT were enrolled onto an ongoing phase I/II trial of donor-derived CAR19 T-cells. Donor T-cells genetically modified using piggyBac to express a second-generation CAR19 were expanded *ex vivo* over 15 days with CD19 stimulation and IL-15. Patients satisfying eligibility criteria immediately prior to first CAR19 T-cell infusion were included on trial. Up to 3 escalating doses of CAR19 T-cells (10⁶, 50⁶ and 100⁶/m²) were administered following lymphodepleting cyclophosphamide (and fludarabine for dose #1), according to response and CAR19 T-cell persistence at specified time-points.

Results

CAR19 T-cell products were successfully generated from 50x10⁶ peripheral blood mononuclear cells for all patients (n=5), and comprised 1.5-2.5x10⁹ cells with 61-93% CAR⁺ T-cells. Two patients were ineligible for trial analysis due to infection and poor performance status. Three eligible patients (DLBCL and 2 cases of ALL) have been followed for 2 to 5 months. Those with ALL achieved complete remission after dose #1, and with DLBCL after dose #2. Longest CAR19 T-cell persistence was 5 months. All 3 patients experienced CD19⁺-relapse associated with declining CAR19 T-cells, and are proceeding to dose escalation. Toxicity included: cytokine release syndrome (n=1), B-cell aplasia with hypogammaglobulinaemia (n=3), and prolonged neutropenia (n=2). No CAR T-cell-related encephalopathy syndrome or acute GVHD occurred.

Conclusions

Manufacture of piggyBac CAR19 T-cells for clinical use is feasible. Early trial results demonstrate similar safety and activity to that of virus-generated CAR19 T-cells. The optimal CAR19 T-cell dose and lymphodepletion strategy remain to be determined.

005. High, durable MRD negativity (MRD-) with venetoclax + rituximab (VenR) in relapsed/refractory (R/R) CLL: data from phase 3 MURANO study

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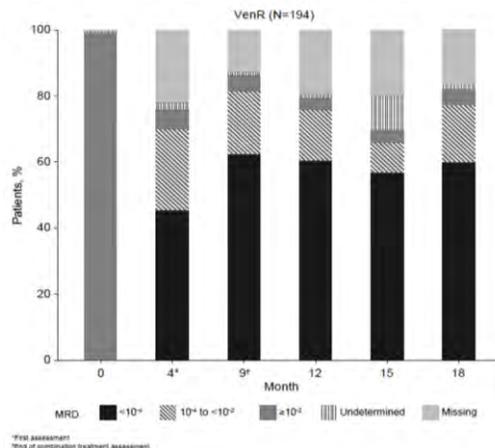
Background: Survival with chemoimmunotherapy is associated with MRD-, but the importance of MRD with targeted agents and in the R/R setting remains unclear, mostly due to low MRD- rates. In MURANO (NCT02005471), VenR showed superior PFS (HR 0.17) and peripheral blood (PB) and bone marrow (BM) MRD- vs bendamustine + R (BR) in R/R CLL patients. We now report MRD kinetics.

Methods: Randomization was to VenR for 6 months then single-agent Ven for 1.5 years maximum, or BR for 6 months. PB samples collected serially and BM samples at end of combination treatment (EOCT; Month 9) or at best response; MRD analyzed centrally by ASO-PCR and/or flow cytometry; MRD-: <1 CLL cell/10⁴ leukocytes.

Results: Higher concordance in MRD- between BM and PB in VenR (45/50 [90%]) vs BR (3/10 [30%]) in patients with paired samples. EOCT PB MRD- rates were higher with VenR (62% vs 13% with BR), and independent of high-risk factors: del(17p) and/or TP53mut, and unmutated IGVH (present vs non-present: 57% vs 66% and 61% vs 64%, respectively). PB MRD kinetics for VenR are shown in **Figure**. 121/194 (62%) patients on VenR were MRD- at EOCT: 100 (83%) maintained MRD- and were progression-free at median follow-up of 13.8 months; 2 developed PD; 2 died (unrelated); 2 developed Richter's (1 immediately after MRD+); 15 (12%) converted to confirmed MRD+, 11 of whom remained progression-free at median MRD+ follow-up of 5.6 months.

Conclusions: High concordance of PB and BM MRD with VenR confirms value of PB MRD for correlation with outcome. VenR achieves high, early, deep, durable PB MRD- regardless of risk features, unlike BR. Some reemergence of MRD+, mainly intermediate level (<1 CLL cell/10²-10⁴ leukocytes), was seen in a few patients, and rarely led to clinical PD within 6 months, consistent with the PFS benefit observed.

Figure: MRD kinetics for VenR at various timepoints



006. Daratumumab plus bortezomib-melphalan-prednisone (D-VMP) in elderly (≥75 y) patients with newly diagnosed multiple myeloma (NDMM) ineligible for transplantation (ALCYONE)

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Aim: We examined the efficacy and safety profiles of D-VMP vs VMP in elderly (≥75 y) and non-elderly (<75 y) NDMM patients in ALCYONE.

Methods: Patients received ≤nine 6-week VMP cycles (V: 1.3 mg/m² SC twice weekly during Cycle 1 and QW during Cycles 2-9; M 9 mg/m² PO and P 60 mg/m² PO on Days 1-4 during Cycles 1-9) ± daratumumab (16 mg/kg IV QW during Cycle 1, Q3W during Cycles 2-9, and Q4W during Cycles 10+).

Results: The study included 211 ≥75 y (104 D-VMP; 107 VMP) and 495 <75 y (246 D-VMP; 249 VMP) patients. After median follow-up of 16.5 months, PFS was prolonged with D-VMP vs VMP in both the ≥75 y (median not reached [NR] vs 20.4 months; HR 0.53; 95% CI 0.32-0.85) and <75 y (median NR vs 17.9 months; HR 0.49; 95% CI 0.36-0.68) patients. ORR and ≥CR rates were consistently higher for D-VMP vs VMP in ≥75 y (ORR: 88% vs 70%; ≥CR: 41% vs 24%) and <75 y (ORR: 92% vs 76%; ≥CR: 43% vs 25%) patients. Minimal residual disease–negative rates (10⁻⁵ threshold) also increased with D-VMP vs VMP in ≥75 y (24% vs 8%) and <75 y (22% vs 6%) patients. Rates of the most common (≥10%) grade 3/4 TEAEs, peripheral sensory neuropathy, and infections are listed (**Table**).

Conclusions: Efficacy and safety of D-VMP vs VMP in patients ≥75 y of age were consistent with the overall study population.

	≥75 y		<75 y	
	D-VMP	VMP	D-VMP	VMP
Grade 3/4, %				
Most common TEAEs				
Neutropenia	52	42	35	38
Thrombocytopenia	51	43	28	35
Anemia	24	23	13	19
Leukopenia	13	9	6	9
Lymphopenia	10	10	7	4
Pneumonia	18	9	9	2
Peripheral sensory neuropathy	0	6	2	3
Infections	28	20	21	13

007. Overall survival with carfilzomib/dexamethasone (Kd56) versus bortezomib/dexamethasone (Vd) by prior line of therapy and previous exposure to bortezomib

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Background: In the ENDEAVOR overall survival (OS) analysis, median OS was significantly longer with Kd56 versus Vd. Here, we present OS and safety analyses comparing Kd56 with Vd according to prior lines of therapy and previous exposure to bortezomib.

Methods: Full details of the study design have been presented elsewhere. The Kaplan-Meier OS rate and median OS time were estimated up to the time point where there were ≤10 patients (Kd56 and Vd combined) in the risk set. The study was not powered to detect differences in OS between subgroups. Adverse events (AEs) are presented as preferred terms and were not adjusted for exposure.

Results: Patients were randomized to receive Kd56 (n=464) or Vd (n=465). The proportion of patients with 1 (Kd56, 49.8%; Vd, 49.2%) or 2-3 (Kd56, 50.2%; Vd, 50.8%) prior lines of therapy was balanced between the treatment arms. The proportion of patients with prior exposure to bortezomib was also balanced between the Kd56 and Vd arms (54% in each arm) and within the subgroups of patients with 1 prior line (Kd56, 42.0%; Vd, 42.8%) and 2-3 prior lines of therapy (Kd56, 65.7%; Vd, 65.3%). Survival outcomes and rates of grade ≥ 3 adverse events of interest by prior treatment are shown (Table).

Conclusions: Treatment with Kd56 showed a survival benefit compared with Vd in patients with RRMM irrespective of the number of prior lines of therapy and previous exposure to bortezomib. Kd56 reduced the risk of death by 17% (1 prior line) and 24% (2-3 prior lines). Kd56 prolonged PFS by 7.5 months and OS by 14.8 months vs retreatment with bortezomib in proteasome inhibitor-sensitive patients. The rate of AEs in this subgroup analysis was consistent with that reported in the overall population. Moreover, no unexpected safety events occurred during longer follow-up.

Outcome	1 Prior line		2-3 prior lines		No prior V		Prior V	
	Kd56 (n=231)	Vd (n=229)	Kd56 (n=233)	Vd (n=236)	Kd56 (n=214)	Vd (n=213)	Kd56 (n=250)	Vd (n=252)
Median OS, months, (95% CI)	–	–	40.5 (31.7, –)	28.7 (22.9, 40.0)	–	42.2 (36.8, –)	47.6 (33.6, –)	32.8 (26.5, 41.8)
HR (95% CI)	0.83 (0.61, 1.14) P=0.125		0.76 (0.59, 0.99) P=0.020		0.75 (0.55, 1.04) P=0.040		0.84 (0.65, 1.08) P=0.086	
Median PFS, ^{a,b} months	22.2	10.1	14.9	8.4	–	11.2	15.6	8.1
HR (95% CI) ^{a,b}	0.45 (0.33, 0.61) P<0.0001		0.60 (0.47, 0.78) P<0.0001		0.48 (0.35, 0.66) P<0.0001		0.56 (0.44, 0.73) P<0.0001	
Grade ≥ 3 AEs, ^{c,d} %	78.4	68.3	84.5	73.7	83.2	77.3	79.9	65.7
Grade ≥ 3 hypertension, ^{c,d} %	15.2	4.0	13.8	2.6	19.2	5.2	10.4	1.6
Grade ≥ 3 cardiac failure, ^{c,d} %	3.0	0.4	2.6	0.9	3.3	0.5	2.4	0.8
Grade ≥ 3 dyspnoea, ^{c,d} %	5.6	2.2	6.9	2.2	5.1	1.9	7.2	2.4
Grade ≥ 3 PN, ^{c,d} %	2.2	6.3	0.4	6.0	1.9	8.5	0.8	4.1

–, not estimable. ^aPFS outcomes by prior lines of therapy and prior BTZ treatment (Moreau et al. *Leukemia*, 2017;31: 115-122). ^bKd56- and Vd-treated patients evaluated for PFS in treatment subgroups: 1 prior line, 232 (Kd56) and 232 (Vd); 2-3 prior lines, 232 (Kd56) and 233 (Vd); no prior BTZ, 214 (Kd56) and 213 (Vd); prior BTZ, 250 (Kd56) and 252 (Vd). ^cKd56- and Vd-treated patients evaluated for safety in the treatment subgroups: 1 prior line, 231 (Kd56) and 224 (Vd); 2-3 prior lines, 232 (Kd56) and 232 (Vd); no prior BTZ, 214 (Kd56) and 211 (Vd); prior BTZ, 249 (Kd56) and 245 (Vd). ^dAEs were coded using MedDRA version 15.1 and patients were counted once for each Preferred Term; AEs were not adjusted for exposure.

008. ACTN1-related macrothrombocytopenia: an Australian experience using NGS and diagnostic biomarker to confirm pathogenicity

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Introduction: Autosomal dominant macrothrombocytopenia due to abnormality of α -actinin-1 (ACTN1) has recently been described; but confirming the pathogenicity of a genetic change remains a diagnostic challenge.

Aim: To assess the pathogenicity of *ACTN1* genetic variants in Australian macrothrombocytopenic patients using an *in vitro* cytoskeletal model. Informed consent was obtained and the study was approved by relevant ethics committee.

Methods: Targeted gene sequencing of 47 genes important for platelet formation and function was performed in 221 individuals from 162 families; 47 (21.3%) had macrothrombocytopenia. To determine the pathogenetic role of identified *ACTN1* variants, CHO cells were transfected with Myc-tagged wild-type or "mutant" *ACTN1* and spread onto fibronectin coated slides before being fixed, permeabilized, and stained with fluorescent anti-c-Myc antibody, phalloidin and DAPI for imaging.

Results: Three novel heterozygous *ACTN1* missense variants were identified by targeted sequencing and confirmed by Sanger sequencing. Two variants (c.127T>A,p.Ser43Thr; c.384G>T,p.Trp128Cys) were located within the actin-binding domain (ABD), and one variant (c.2108A>G,p.Asn703Ser) was located in the spectrin-like repeats region.

By immunofluorescence, CHO cells transfected with wild-type *ACTN1* or 703Ser variant showed well-organized, finely stretched actin filaments with high level of ACTN1 colocalisation. By contrast, CHO cells expressing *ACTN1* ABD variants (43Thr and 128Cys) showed shorter and thicker filaments consistent with disorganisation of the actin filament network by the abnormal ACTN1 molecules.

Conclusion: Using immunofluorescence in an *in vitro* model as a diagnostic biomarker, we concluded that the 703Ser variant, located outside of the functional domains of ACTN1, was likely benign. By contrast, the two variants in the ACTN1-ABD domain impaired the actin filament organization, suggesting those variants are likely pathogenic and responsible for the macrothrombocytopenia. The individuals carrying those two variants are the first cases of ACTN1-related macrothrombocytopenia identified in an Australian population.

009. Fibrinolysis and Innate Immunity at play: Complement C5a receptor inhibition reduces tissue plasminogen activator (t-PA) and plasminogen (Plg)-induced blood brain barrier (BBB) opening *in vitro*

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Aim

The relationship between fibrinolysis and innate immunity is evident in the increased BBB permeability induced by t-PA and Plg, which can trigger CNS infiltration by immune cells. Although Rho-Kinase 2 (ROCK-2) signalling plays an important role here, the pro-inflammatory properties of plasmin, including C3 and C5 convertase activity, led us to hypothesise that plasmin mediated BBB permeation may in part be driven by complement activation. We aimed to characterise the effects of targeted complement inhibition on this phenomenon using *in vitro* BBB models. Synergy experiments evaluated added effects of antifibrinolytic, Tranexamic acid (TXA), and selective ROCK-2 inhibitor (KD025).

Methods

In vitro models of the BBB were assembled on porous membranes of Transwell inserts either as a monolayer of human brain endothelial cells (hBECs) (Model 1) or in co-culture with SVG human immortalised astrocytes (on abluminal membrane surface; Model 2) (Fig. 1). The *in vitro* BBB was stimulated with t-PA+Plg in the presence or absence of complement fragment 5a receptor 1 inhibitor (PMX205). BBB permeability was assessed 4hr post-stimulation by evaluating fluorescent tracer passage from luminal to abluminal chambers over 1hr. Permeability changes were calculated relative to a control model without stimulation.

Results

PMX205 blocked permeability increases in stimulated hBECs monocultures, most notably at 100µM ($p < 0.01$). PMX205 effect was comparable to KD025, which served as a positive inhibition control ($p < 0.01$) (Fig. 2). Greater BBB protection by PMX205 and synergistic action with TXA were observed in the co-culture system, suggesting a central role of astrocytes in BBB sensitivity to complement.

Conclusion

tPA and plasmin mediated increased BBB permeability is partly driven by C5a receptor activation. Inhibition of this alone, or with antifibrinolytics or ROCK-2 inhibitors may result in synergistic BBB protection. This has therapeutic implications in traumatic brain injury and stroke thrombolysis, where either endogenous or administered tPA, can compromise the BBB causing secondary insults.

Fig 1: *In vitro* BBB Models

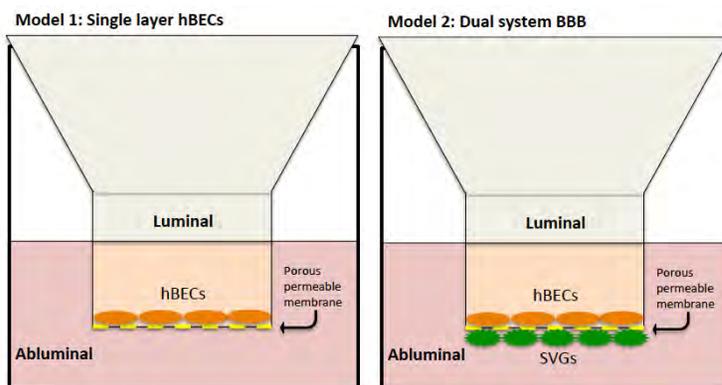
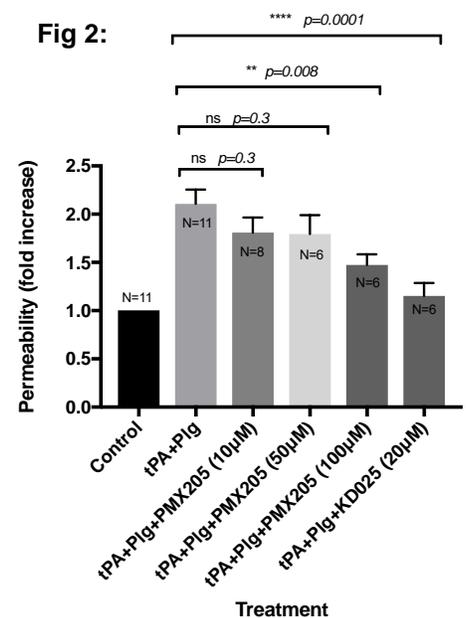


Fig 2:



010. Neuraminidase 1 and 2 are important for GPIIb/IIIa integrin activation

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Background

The platelet adhesion receptor glycoprotein Iba (GPIIb) contains many branched glycans capped by sialic acid. Sialic acid is cleaved (desialylation) by neuraminidases (NEU), which has been implicated in platelet clearance. So far NEU1-4 have been identified however, their role in platelet function has not been studied.

Aim

To investigate the role of NEU1 and NEU2 in platelet signalling.

Methods

Platelet-attached glycans and NEU1 and NEU2 membrane expression were measured in washed platelets following activation with ADP, arachidonic acid (AA), U46619, or collagen, using flow cytometry. GPIIb was activated by stimulation with von Willebrand Factor (vWF) + ristocetin in the presence of various signalling inhibitors prior to measuring NEU1 and NEU2. Platelet function was studied by fibrinogen-binding and static adhesion on a fibrinogen-coated surface, with or without the neuraminidase-inhibitor, 2-deoxy-2,3-didehydro-N-acetylneuraminic acid (DANA). Cellular localisation of NEU1 and NEU2 was studied using fluorescence microscopy.

Results

Sialic acid was highly cleaved only following specific activation of GPIIb. In resting platelets, little NEU1 was membrane bound, whereas vWF stimulation induced a 5-fold increase (n=4, p<0.05). Similarly, membrane associated NEU2 was increased by 8-fold following activation of GPIIb (n=4, p<0.05).

Inhibition of GPIIb reduced the majority of membrane-associated NEU1 and NEU2 (p<0.05), while addition of fibrinogen triggered an increase. Surprisingly, calcium, ADP-release and TXA2 formation were inversely correlated with membrane expression of NEU2.

Platelet adhesion to fibrinogen was unaffected by pre-incubation with DANA, while fibrinogen-binding was inhibited by 50%, but only when platelets were activated by vWF (n=3, p<0.05). vWF-mediated agglutination was increased in the presence of DANA. Microscopy revealed that NEU1 and NEU2 translocated to the membrane following vWF-activation.

Conclusion

These findings show a previously unrecognised role for NEU1 and NEU2 in GPIIb-mediated platelet signalling and consequent activation of GPIIb/IIIa-integrin.

011. Efficacy of upfront Prothrombinex in cytoreductive surgery with potential massive transfusion: a randomised controlled trial

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Aim

To assess the benefit and safety of early administration of Prothrombinex-VF in patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) with potential massive transfusion.

Methods

In St. George Hospital, eighty patients with peritoneal cancer index (PCI) of >10 at laparotomy undergoing CRS/HIPEC were randomised to either the early use of Prothrombinex-VF (n=40) or standard care (n=40). There were no significant differences in baseline demographic characteristics, PCI, duration of surgery, intensive care or total hospital stay between the two arms. Intraoperative and postoperative data were collected and analysed using unpaired t-tests and Chi-squared tests.

Results

Unpaired t-tests showed that early use of Prothrombinex-VF resulted in a lower incidence of intraoperative haemorrhage with reduction in packed red cell usage (mean 7.08 units vs 4.70 units; p=0.07). Postoperatively Chi-squared tests showed a 12% absolute risk reduction in major cardiac and infectious adverse events, without an increase in thrombotic events.

Conclusion

The early use of Prothrombinex-VF in patients undergoing CRS/HIPEC was haemostatically efficacious, safe, and resulted in reduction of blood product usage.

012. Extending the Post-Thaw Viability of Cryoprecipitate

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Aim

One of the difficulties encountered when using cryoprecipitate is the current recommendations regarding its storage post-thawing. Once thawed, cryoprecipitate should be maintained at 20-24°C until transfusion and used within 6hours.

The aim of the current study was to assess the stability of FVIII and fibrinogen levels from 6-hours until 120hours post-thawing when stored at two different temperatures (2-6°C and room temperature [RT]).

Method

Twenty expired cryoprecipitate batches were collected for analysis. Thawed units were sampled at the 6hour expiration mark and then stored at either 2-6°C or RT for 120hours and sampled every 24hours. One bag from each batch was sent for microscopy, sensitivity and culture at 120hours post-thawing to assess for bacterial contamination.

FVIII and fibrinogen were measured using standard coagulation assays and functional fibrinogen using ROTEM FibTEM.

Results

Whilst Factor VIII levels declined in cryoprecipitate-units at 120hours post-thawing, they declined at similar rates when stored at either RT or 2-6°C. Factor VIII levels at 120-hours post-storage, despite falling from 6 hours, still met Australian standards for FVIII content in cryoprecipitate regardless of storage temperature.

Fibrinogen levels degraded very little over 120hours and were also consistently present in levels that meet Australian standards for cryoprecipitate when stored at either temperature. ROTEM testing confirmed that fibrinogen function was not compromised at 120hours post-thawing.

There was no documented bacterial contamination of cryoprecipitate when stored for 120hours post-thawing.

Conclusion

Our study is the first that reports results of 2-6°C storage over 120hours. Our findings suggest that extending the storage time of cryoprecipitate post-thawing for 120hours is possible whilst still maintaining required fibrinogen and FVIII content. Storage at 2-6°C holds the advantage of a reduced risk of bacterial contamination. Limitations of our study include small numbers and no control for blood group discrepancies.

013. Transfusion modulates leucocyte populations in cardiac surgery patients

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Coronary artery bypass grafting (CABG) is a complex procedure which triggers a systemic inflammatory response which has been associated with modulation of leucocyte subsets. Transfusion can be used to support CABG. Understanding how CABG impacts leucocyte populations and whether transfusion results in any further modulation is limited.

Aim

To assess changes in leucocyte subsets following CABG and assess whether transfusion further impacted leucocyte populations

Method

Blood was collected from CABG patients (n=49) at 5 time-points (admission, intra-operative, ICU, day3 (D3), day5 (D5)). The absolute count (Trucount, BD Biosciences) of B-cells (CD20⁺), NK-cells (CD56⁺), monocytes (CD14⁺), T-cell subsets (CD3⁺; helper CD4⁺; cytotoxic CD8⁺, regulatory CD25⁺CD127⁺) and dendritic cell (DC) subsets (myeloid [mDC] Lin-HLA-DR⁺CD11c⁺ and plasmacytoid [pDC] Lin-HLA-DR⁺CD11c⁻CD123⁺) was determined. Changes in cell counts were compared to admission (repeated-measures one-way ANOVA with Dunnett's post-test; P<0.05). In addition, we further assessed whether transfusion resulted in further modulation of patient leucocyte populations (unpaired t-test cf. non-transfused patients; n=7).

Result

CABG resulted in significant modulation of multiple leucocyte subsets. The absolute cell counts of monocytes and B-cells were elevated from the ICU and D3 post-operative period (both P<0.001). CABG resulted in decreased numbers of cytotoxic, helper and regulatory T-cells from the ICU period (all P<0.001). Total mDCs and the number of activated mDCs were also decreased (both P<0.001) indicating an immature DC phenotype. pDC numbers spiked during CABG followed by a decrease post-operatively (P<0.001). Compared to non-transfused patients, transfusion recipients had significantly increased numbers of circulating NK-cells (P=0.046) and T-regulatory cells (P=0.033).

Conclusion

Our data demonstrates significant perturbation of multiple leucocyte subsets following CABG. Decreased numbers of these leucocyte subsets may contribute to increased infection risk. Increased NK-cells and T-regulatory cells evident in transfused patients suggests that transfusion impacts downstream regulatory processes.

014. Investigation of variability in the use of blood products across eight hospitals in NSW

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Aim

To employ rigorous data analytics methods to measure the levels of variation in blood product usage across hospitals and assess the appropriateness (based on evidence-based guidelines) of current blood transfusion practices.

Method

A retrospective observational study of patients admitted between 1st January 2014 to 31st October 2017 across eight hospitals in NSW. The linkage of hospital inpatient data with pathology laboratory and blood bank data was undertaken using a non-identifiable patient medical record number common to all datasets.

Results

This study included 388,175 patients with 878,476 admissions. A total 127,424 units of blood products were transfused to 21,877 patients during 31,266 admissions. Red blood cells represented 60% of all units transfused, followed by fresh frozen plasma (16%), platelets (12%), cryoprecipitate (11%) and cryodepleted plasma (1%). Patients aged between 60 and 89 years were the most frequent recipients of blood transfusions (61%). Overall, 36 transfusions occurred for every 1000 admissions (ranging from 11 to 51 per 1000 admissions across study hospitals). For RBC transfusions, 16% recorded pre-transfusion haemoglobin levels below 70 g/L, 72% between 70 – 100 g/L and 12% above 100 g/L. For fresh frozen plasma transfusions, 73% recorded pre-transfusion INR levels below 2.0, ranging from 46% to 83% across study hospitals. For platelets transfusions, 60% recorded pre-transfusion platelet counts below 50 x 10⁹/L, 12% between 50 – 100 x 10⁹/L, and 28% above 100 x 10⁹/L.

Conclusion

Variations in demographics and usage of blood products across hospitals identified by this research can be used to inform strategies that: a) facilitate the use of best practice evidence-based guidelines; and b) enhance the value and effectiveness of blood product usage, ultimately contributing to improved quality of care.

016. Genomics and red cell genotyping in transfusion medicine

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Blood group antigens are classically tested through hemagglutination techniques. However, those methods sometimes show limitations that may be overcome by RBC genotyping. The major indications of molecular testing are: blood typing in recently transfused patients; prediction of blood types in patients/donors when antisera are in short supply or unavailable; blood typing in patients with a positive direct antiglobulin test; optimization of RBC antibody screening/identification panels; detection of weakly expressed RBC antigens; distinction between auto and alloantibodies; investigation of blood type discrepancies; mass screening for rare donors. The International Society of Blood Transfusion now recognizes 360 RBC antigens, included in 36 blood group systems (322 antigens), 5 collections (14 antigens), the 700 series (17 antigens) and 901 series (7 antigens). The characterization of the 40 genes (and 2 associated genes) encoding the blood group systems has made possible the use of molecular testing to predict blood types. Many molecular mechanisms are at the origin of blood group diversity, but the great majority arise from a "single nucleotide polymorphism". Several techniques are available for genotyping. Microarray DNA-chips and mass spectrometry are medium- to high-throughput techniques implemented in the mid to late 2000s that allowed for standardization and computerized data interpretation. Sanger sequencing on genomic DNA is a second-line approach and complementary DNA investigation is used for most complex cases. More recently, Next Generation Sequencing, especially whole or targeted exome sequencing, has been developed for blood gene investigation. Despite some continuing limitations for paralog genes (e.g. *RHD/RHCE*), this approach is highly promising, notably for patients with sickle cell disease who demonstrate many potential clinically significant variant alleles (concept of "allele matching" or "dry matching"). Genomics is a routine and essential adjunct tool to complex serological case solving in reference laboratories worldwide, and now fully considered part of the decision-making process in clinical immunohematology.

017. Thrombophilia - is it ever helpful to test for it?

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Inherited and acquired thrombophilia increases the risk of venous thromboembolism (VTE) and are also associated with complications during pregnancy, such as recurrent miscarriage and preeclampsia.

Thrombophilia can be identified in many patients presenting with VTE. Whether the results of such tests help in the clinical management of patients has not been settled.

In this lecture, Saskia Middeldorp will review the potential testing scenarios. For inherited thrombophilia, the pros and cons of testing patients with VTE or their asymptomatic relatives will be discussed. Knowledge of absolute risks is essential to help clinicians as well as patients make an informed decision in which patient's preferences can be taken into account. Diagnosing antiphospholipid syndrome in patients with VTE and in women with recurrent miscarriage often leads to a change in patient management, although the evidence to support this is limited.

018. Inherited bone marrow failure in children and adults

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This session will discuss clinical and scientific advances in inherited bone marrow failure. An overview of the inherited bone marrow failure disorders will be presented. Clues to an underlying genetic bone marrow failure syndrome will be explored. The role of germline and somatic genetic testing in diagnosis and management is rapidly evolving. Diagnosis of inherited bone marrow failure informs treatment decisions and surveillance strategies.

019. Transfusion strategies in older adults

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Aim

Transfusion thresholds recommended in adult patient blood management guidelines do not take patient age into account. Several meta-analyses, randomised controlled trials and observational studies have reported better outcomes with higher haemoglobin thresholds for transfusion in older adults. This study investigates age-related changes that impact anaemia tolerance and haemoglobin thresholds in older adults.

Method

Using established physiology principles, a model of oxygen delivery potential at different ages and haemoglobin levels was developed. Recent normative cardiac output data in healthy adults was used to support calculation of oxygen delivery potential. Comparative data was generated for three adult age groups (18 to 40, 41 to 60, and >60 years of age) with normal and anaemic haemoglobin concentrations (Hb range 50 to 130 g/l).

Result

The oxygen delivery potential for older adults is negatively impacted by changes in cardiovascular and pulmonary function that occur with age.

Conclusion

Older adults have a reduced capacity to cope with adverse metabolic conditions, and this pre-condition is exacerbated by anaemia and ill health. This modelling provides strong support for the first and second pillars of patient blood management in older adults (optimisation of physiology and minimisation of blood loss). The third pillar, harnessing tolerance of anaemia, is impacted as older adults require higher haemoglobin concentrations to maintain their physiological reserve with respect to oxygen delivery.

020. Bleeding and clotting in neonates: Does anything make sense?

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Birth is a traumatic ordeal for mothers and babies alike. The risks of bleeding and clotting are high. However, neonatal coagulation is arguably the most rapidly changing homeostatic system. Coagulation measurements on cord blood do not reflect status in the baby's blood, which changes with each passing day. The impact of maternal and placental circulations is largely unknown. Add further variables such as gestational age and weight, and it is not hard to believe that any interventions are pure guesswork. How do we unravel this puzzle? This presentation will focus on the known changes that occur in neonatal coagulation in the early days of life and the implications of those changes for our clinical management of bleeding and clotting complications in this important age group.

021. Naive T cell depletion in allogeneic hematopoietic stem cell transplant

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Depletion of all T cells (TCD) from the stem cell graft can reduce the incidence of graft versus host disease (GVHD) but is complicated by infections due to delayed immune reconstitution post-HCT. Preclinical studies in murine models demonstrate that GVHD is largely the result of naïve T cells (T_N) in the stem cell graft rather than memory T cells (T_M), which are important for reconstituting protective immune responses to prevent infectious complications. We reported a first-in-human single arm clinical trial in which the G-CSF mobilized PBSC graft was comprised of positively selected $CD34^+$ cells and depleted of $CD45RA^+$ T_N cells. Forty-one patients with acute leukemia were treated with a myeloablative conditioning regimen and received matched related donor PBSC containing a defined dose of T_M and purged of T_N followed by single agent tacrolimus. The incidence of grade 3-4 acute GVHD was 9% and NIH-defined chronic GVHD at 1 year was 9%. T_M in the graft resulted in rapid T cell recovery and transfer of protective virus-specific immunity. The overall survival and GVHD and relapse free survival (GRFS) were 78% and 57% at two years. We have since tested T_N depletion in a reduced intensity conditioning setting, and with stem cells from unrelated donors demonstrated this to be safe and effective for establishing donor hematopoiesis. These studies show that graft manipulations based on defined subsets of T cells markedly reduce the incidence of chronic GVHD after allogeneic stem cell transplant without an increase in relapse or opportunistic infections.

022. Up-front treatment of multiple myeloma eligible for stem cell transplantation

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Since the introduction of novel agents and autologous stem cell transplantation (ASCT) for the treatment of multiple myeloma (MM) the capacity to increase the number of cases obtaining MRD negative states has increased dramatically. This has altered the therapeutic paradigm for MM to the extent that one of the major aims of current approaches is to maximize MRD negativity with the expectation that these states are associated with both prolonged progression free survival (PFS), overall survival (OS), and an increase in the number of patients who achieve 10 year OS and operational cure. These approaches rely upon selecting the optimum therapeutic combination for any individual patient and getting the maximum therapeutic benefit from it. Such combinations are given in the context of ASCT as induction, consolidation, and maintenance blocks of therapy. This strategy is based on the results of a number of recent studies that have compared ASCT with conventional dose treatment where all seem to favor transplantation. Further, a recent population based study has shown that receiving an ASCT is one of the most important prognostic variables for a patient. Thus, at this point it is logical to maximize the outcome of ASCT by integrating the use of novel agents around it. Induction regimens using combinations of IMiDs and proteasome inhibitors give some of the best results and lenalidamide and carfilzomib being potentially the optimum combination. Little formal work on consolidation therapy has been done but the EMN trial group has shown that even a limited number of cycles of MPV seem to improve outcome. Optimizing post transplant consolidation using immunologic approaches with daratumumab offers an exciting way to improve outcomes. It is now clear that maintenance therapy improves both PFS and OS with a number of studies and a meta analysis being consistent with this statement. Going forward this paradigm for treatment of younger patients is likely to be widely taken up even within the current regulatory settings. The important and outstanding question will be how CAR-T and bi-specific antibody therapy can be integrated into such a pathway with the aim of pursuing increased cure rates.

024. Addressing Acute Traumatic Coagulopathy in the austere environment

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While acidemia, dilution of clotting factors by fluid resuscitation and hypothermia were traditionally considered the main causes of coagulopathy in major trauma, it is clear that rewarming, correction of pH with bicarbonate, and “haemostatic resuscitation” with clotting-factor-containing fluids is insufficient to prevent or correct coagulopathy in many patients. The explanation is an endogenous entity, acute traumatic coagulopathy (ATC), which arises as a direct consequence of tissue damage and hypoperfusion. Mechanisms are thought to include disruption of the endothelial glycocalyx, exposure of thrombomodulin (and consequent sequestration of thrombin), activation of protein C, platelet inhibition, and consumption of Plasminogen Activator Inhibitor (PAI-1) leading to fibrinolysis. Understanding these mechanisms presents several attractive therapeutic targets, some of which are particularly applicable to the prehospital or austere surgical (e.g. military or remote hospital) environment. These include:

- Measures to prevent heat loss and preserve perfusion of undamaged tissue, serving to avoid the initiation of the ATC process;
- Avoiding infusion of resuscitation fluids, at least for a time. The optimal time has not been defined and will vary with the degree of shock, but a military consensus group recently recommended “permissive hypotension” for up to one hour;
- Maintaining the circulating blood volume with resuscitation fluids that preserve rather than destroy the endothelial glycocalyx. Extending the shelf-life of plasma to 5 days, or using whole blood, appears to achieve this aim, but there are promising experimental approaches to modified non-blood fluids that might have the same effect;
- Transfusing platelets early. This has typically been challenging outside large hospitals, as platelets stored at room temperature have a shelf-life of only 5-7 days. However, cold-storage extends shelf-life to 14 days, and cryopreservation to at least 2 years, potentially with added haemostatic benefits;
- Reducing fibrinolysis using tranexamic acid, noting the overwhelming evidence in the non-trauma context but also the equipoise underlying current trials in trauma; and
- Using clotting factor concentrates, especially fibrinogen, as more easily transported and stored alternatives to blood components, ideally guided by rapid point-of-care clotting analysis.

Theoretically attractive options in the prehospital environment, such as factor concentrates and novel artificial substitutes for platelets and red cells, should nonetheless be evaluated in adequately-powered clinical trials. The overriding priority in the most severely injured patients is rapid diagnosis (ideally by prehospital imaging), appropriate triage and transport, and (where required) effective damage control surgery. Telementoring of non-specialist surgeons and physicians to facilitate early surgery may offer a greater potential to reduce preventable mortality than any novel resuscitation strategy.

026. Clonal evolution in Acute Myeloid Leukaemia (AML)

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AML is a genetically heterogeneous malignancy, which has a dismal prognosis. With the development of next-generation sequencing techniques, we have gained a much clearer picture of the complex landscape of genetic changes in AML. The high relapse rate in AML is one of the reasons for its poor prognosis. One of the causes of relapse appears to be clonal evolution, which changes a disease responsive to therapy to a disease that exhibits increasing resistance to standard chemotherapy. The exact mechanisms of clonal evolution in AML are poorly understood. Using genetic techniques, like whole exome sequencing, comparing primary and relapsed samples from the same patient, one can observe the emergence of new mutations, the disappearance of certain mutations and also the persistence of mutations. These observations can be explained by several, probably not mutually exclusive, mechanisms: 1) the selection and emergence of pre-existing minor resistant subclones; 2) the emergence of new mutations and the selection of clones with these mutations; 3) an increased genetic instability of the leukaemic clone; 4) the existence of epigenetically different subclones with the same mutations. An understanding of clonal evolution is also clinically important. For example, it can help to select the most useful markers for minimal residual disease monitoring. Furthermore, certain patterns of clonal evolution have been shown to be of prognostic significance. To develop models to study clonal evolution in acute leukaemia, we established two murine bone marrow transplantation leukaemia models using the CALM/AF10 and the RUNX1/RUNX1T1-9a fusion genes. Using serial transplantation experiments in these models, we observed clonal evolution patterns similar to those seen in human AML. These models will be helpful in studying the mechanisms driving clonal evolution and to develop improved therapeutic strategies for leukaemia.

027. In-vivo evolution and clonal dynamics of Npm1-mutant acute myeloid leukaemia

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Acute Myeloid Leukaemia (AML) is an aggressive haematological malignancy of immature myeloid cells that usually presents suddenly in individuals without previous haematological abnormalities, making the study of the preclinical evolution of AML challenging. The identification of the phenomenon of clonal haematopoiesis (CH) has revealed that the establishment of the earliest clonal ancestors of AML and of other myeloid cancers is a common event that becomes ubiquitous with advancing age. More recently, it was also demonstrated that characteristics of CH such as a greater clonal size and complexity, are associated with an increased risk of progression to AML. This raises for the first time the prospect of developing genetic tests to identify those at risk. However, the timing and clonal dynamics of progression from CH to full blown AML remain poorly understood. This is exemplified by the most common subtype of AML characterised by mutations in the NPM1 gene, which almost invariably presents without any clinical antecedent. Here we used a faithful mouse model of mutant NPM1 combined with insertional mutagenesis to understand the dynamics of this progression. We first use common integration site analysis to identify the genes most commonly involved in the leukaemic progression and use semi-quantitative transposon integration mapping to reveal extensive subclonal complexity of developing leukaemias, confirmed by onward transplantation into recipient mice. We then use serial blood sampling to show that the cellular clones that eventually become AML are present for several weeks to months prior to disease development, but that leukaemic transformation happens very rapidly after acquisition of transforming mutations and without detectable antecedent changes in blood counts. Our findings propose that onward progression towards AML after acquisition of NPM1 mutations is an explosive process that is unlikely to be amenable to preventive screening.

028. Finding new direct targets of JAK-STAT signalling which underpin normal blood cell production and myeloproliferative neoplasms

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Myeloproliferative neoplasms (MPNs) are a group of chronic blood cancers characterised by excess production of mature blood cells accompanied by an increased risk of thrombosis and progression to marrow fibrosis (PMF) and acute myeloid leukaemia (AML). A mutation in the JAK2 tyrosine kinase (V617F) drives ~70% of MPNs. The remainder are driven by mutations in genes that encode proteins that mostly act within cytokine signalling pathways. Disease progression is often accompanied by the acquisition of additional mutations in genes that encode epigenetic regulators and/or RNA splicing factors. These have prognostic significance ¹. We developed a comprehensive NGS re-sequencing panel (86 genes) for diagnosis, prognosis and possible personalised treatment of MPNs which we are adapting to routine pathology practice ². We will present our updated data on the utility of this assay for diagnosis and management in >80 cases of MPNs of various subtypes.

In order to find direct targets of JAK2-STAT5 signalling in normal murine erythroid cells, we undertook ChIP-Seq for pSTAT5 and 4sU-labelling and RNA-seq following stimulation of J2E cells with EPO (5U/ml) ³. We found ~300 robust pSTAT5-occupied sites in promoters and enhancers of known and novel target genes including a novel intronic enhancer of the *Bcl2l1* gene, which encodes the pro-survival protein, BCL-XL.

We undertook pSTAT5 ChIP-seq in HEL and SET2 cell lines (which carry the JAK2-V617F mutation) to define direct targets of pSTAT5 in PV and ET in human cells. We also undertook RNA-seq following inhibition of JAK-STAT signalling with ruxolitinib and two STAT5 inhibitors in HEL and SET2. There was a marked overlap between JAK-STAT target genes in human MPN cell lines and EPO-induced genes in the mouse. Many of these genes encode for proteins not previously known to be important in MPNs. They encode for genes involved in cell survival, proliferation, RNA-splicing, epigenetic regulation and down regulation of cytokine signalling. This gene list provides new insights into the biology of MPNs, and provides a source of potential new biomarkers and drug targets. We have validated some of these novel target genes in primary samples from patients with PV and ET, and functionally validated some using gene editing in cell lines and mice.

References:

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029. Data mining in pathology - can it lead to best practice?

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Data mining is the practice of examining large pre-existing databases in order to generate new information. The new information arises either because different questions are being asked or different techniques are being used. Different questions may arise because our understanding of fundamental processes has changed and we are searching 'old' data to verify these processes. Different techniques may involve the use of greater computer power which can examine ever bigger data bases ('big data') or different statistical techniques that may be able to identify associations within data sets. Pathology data is a rich source of information which can supplant animal models in many cases. Every human disease has clinical and pathology data associated with it. Mining that data will tell us as much as an animal model.

There are problems with this data mining of human information. These include the heterogeneity of medical data, ethical, legal, and social issues of accessing this information. There are also statistical issues such as the following myths:

Myth 1. Big data is universally big

Myth 2. Big data means never having to say what your research question is

Myth 3. Big data means never having to say what your model is

Myth 4. Big Data means never having to consider sampling theory, a standard error, or a p-value

Myth 5. Big data means more valuable information

Myth 6. Big data means observational data can be used to measure causal relationships

Myth 7. Classical statistical methods are inadequate to deal with big data.

Practical examples of data mining include the following;

- Quality Control

 1. Reference Intervals and Critical Differences
 2. Relationships between analytes
 3. Modelling
 4. Predicting outcomes
 5. Detecting Poor Performance.

Some of these will be discussed in particular new evidence on red cell survival in the circulation and the role of RDW as an important biomarker.

030. Topic advances in laboratory haematology - NGS and personalised care

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The detection of genomic abnormalities is a central part of the diagnostic classification of haematological malignancy. In addition to contributing to diagnosis, the detection of genomic abnormalities contributes to accurate prognostication, identification of targetable lesions and identification of genomic mechanisms of resistance. Through these domains clinical care of the patient can be impacted upon. The diversity and quantity of sequence variants, copy number abnormalities and structural variants that need to be detected in order to comprehensively and accurately assess patients within these domains necessitates the use of flexible platforms such as massive parallel sequencing in order to provide this information in a timely and cost-efficient manner. This presentation will cover the personalisation of the treatment haematological malignancy through identification of genomic abnormalities by massive parallel sequencing and provide case examples of where this technology is most beneficial and impactful in today's clinic.

031. Digital morphology - where will this technology take us?

Williams C¹

¹Sullivan Nicolaides Pathology, Brisbane, Australia

Digital morphology is used widely throughout the world as a tool for reporting blood film morphology. Australia, however, has been relatively slow to take up this technology in medical laboratories. This presentation will review the use of automation for reporting blood film morphology, as well as present some morphological case studies captured digitally.

032. How I treat: High risk aggressive DLBCL

LaCasce A¹

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I will review the approach to the classification of aggressive DLBCL, using cell of origin and other molecular classifiers, including double/triple hit and double protein expresser lymphoma. I will then discuss therapeutic approaches, including novel therapies and immune based treatments.

034. Hodgkin lymphoma

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In recent years, several large PET-adapted randomised trials in limited and advanced stage classical Hodgkin lymphoma (HL) have been conducted. In limited stage HL, trials have examined the role of radiotherapy in addition to chemotherapy. In advanced stage disease, trials have examined the role of bleomycin, brentuximab vedotin, PET-adapted strategies for escalated BEACOPP and consolidative radiotherapy. This presentation will review recent randomised trials that have shaped current first line treatment practices.

036. Phase 1 Study of Gilteritinib Plus 7+3 Induction and HiDAC Consolidation Chemotherapy in Patients with Newly Diagnosed Acute Myeloid Leukemia

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Aim

To examine the safety/tolerability and antitumor effects of once-daily gilteritinib, an oral FLT3/AXL inhibitor, plus front-line intensive chemotherapy in patients with newly diagnosed AML.

Method

This open-label, dose-escalation/expansion phase 1 study (NCT02236013) assessed the safety/tolerability of gilteritinib plus 7+3 induction and high-dose cytarabine (HiDAC) consolidation, and as single-agent maintenance therapy in adults with newly diagnosed AML. Subjects (aged ≥ 18 years) received gilteritinib (40–120 mg/day) plus 7+3 induction (cytarabine 100 mg/m²/day, Days 1–7; plus idarubicin 12 mg/m²/day, Days 1–3) and HiDAC (1.5 g/m² q12h, Days 1, 3, 5) consolidation, and as single-agent maintenance therapy. During dose escalation, subjects received once-daily doses of 40, 80, or 120 mg gilteritinib. Subjects received ≤ 2 cycles of 7+3 chemotherapy plus gilteritinib (initially, Days 1–14; later, Days 4–17) induction. During consolidation, gilteritinib was administered (Days 1–14) for ≤ 3 cycles. Subjects subsequently received once-daily gilteritinib (28-day cycles) as maintenance therapy for ≥ 26 cycles.

Result

As of October 2017, 50 subjects (male, 67.3%; median age, 59 years) have been enrolled; 48 subjects had known *FLT3* mutation status. During dose escalation, two subjects who had received 40 mg/day gilteritinib on Days 1–14 experienced dose-limiting toxicities (DLTs; prolonged neutropenia/thrombocytopenia, decreased ejection fraction); no DLTs were observed in the 40 or 80 mg/day cohorts after changing the gilteritinib dosing schedule. The maximum tolerated dose was not reached; 120 mg/day was the chosen recommended expansion dose. The most common grade ≥ 3 adverse events were febrile neutropenia (65.3%), thrombocytopenia (20.4%), and neutropenia (16.3%). The composite complete remission (CRc) rate (n=44 evaluable subjects) was 79.5% (complete remission, 63.6%); CRc rates in *FLT3*^{Mut+} (n=21) and *FLT3* wild-type (n=23) groups were 100% and 60.9%, respectively.

Conclusion

Gilteritinib can be safely combined with front-line chemotherapy in patients with newly diagnosed AML; high antileukemic response rates were observed in *FLT3*^{Mut+} subjects.

037. Chemotherapy and Venetoclax in Elderly AML Trial (CAVEAT): Phase 1b dose-escalation study examining modified intensive chemotherapy in fit elderly patients

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Aim: Venetoclax (VEN) in combination with low-dose chemotherapy has shown promise in elderly AML patients unfit for intensive therapy.^{1,2} This study aims to evaluate the optimal dose, safety and efficacy of VEN in combination with modified intensive chemotherapy in fit elderly patients with AML.

Method: *Eligibility-* AML (except APL), ≥65years (≥60years if monosomal karyotype), ECOG≤1, adequate organ function. Prior HMA/LDAC permitted. *Treatment-* 1) dose escalation cohorts comprised VEN 50mg (Cohort A), 100mg (B), 200mg (C), 400mg (D) or 600mg (E); 2) a 7-day VEN pre-phase incorporating dose ramp-up to minimise TLS risk followed by a 7 day overlap with chemo (day -7 to +7); 3) attenuated induction chemotherapy with 5+2³ (cytarabine 100mg/m²/d IVI d1-5, staggered with idarubicin 12mg/m² IV d2-3). For patients in remission, 4 cycles of “continuation” therapy were given, comprising 14 days of VEN with cytarabine (100mg/m²/d IV d1-2) and idarubicin (12mg/m² IV d1), followed by 7 cycles of VEN monotherapy maintenance. The first patient was enrolled 17JUL2016.

Result: Data cut-off date was 11 MAY2018. 41 patients were enrolled (table 1). Median age was 72 (22% ≥75 years), 49% had secondary AML. Grade ≥3 non-haematological adverse events during induction (≥10%) were febrile neutropenia (56%), sepsis (32%), rapid atrial fibrillation (15%), diarrhoea (12%), nausea (10%) and localised infection (10%). No clinical TLS was observed. One haematologic dose-limiting toxicity was reported in cohort E. Treatment-related mortality was 7% in induction. CR/CRi rate was 71%. Median overall survival was 7.7 months. Prior HMA/LDAC exposure was associated with worse survival due to relapsed/refractory disease (3.8 vs 18.5 months, p=0.002).

Conclusion: To date, VEN up to 600mg in combination with 5+2 induction is tolerable in fit elderly patients with AML. The maximum tolerated dose has not been reached. CR/CRi rate was 71%. Analysis for response duration, survival and molecular correlate are ongoing.

Table 1. Baseline characteristics of each cohort.

*ECOG: Eastern Cooperative Oncology Group; HMA: hypomethylating agent; LDAC: low dose cytarabine; ELN: European LeukemiaNet; CR: complete remission; CRi: complete remission with incomplete count recovery.

References

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Venetoclax cohort	50mg (n=8)	100mg (n=8)	200mg (n=9)	400mg (n=8)	600mg (n=8)	Total (n=41)
Median age, years (range)	73 (68-80)	70 (65-77)	73 (63-80)	70 (64-78)	72 (67-75)	72 (63-80)
Males, n (%)	3 (38)	6 (75)	7 (78)	2 (25)	8 (100)	26 (63)
ECOG 1, n (%)	7 (88)	6 (75)	3 (33)	8 (100)	5 (63)	29 (71)
Secondary AML, n (%)	6 (75)	3 (38)	3 (33)	3 (38)	5 (63)	20 (49)
Prior HMA, n (%)	3 (38)	3 (38)	2 (22)	2 (25)	4 (57)	14/39 (36)
Prior LDAC, n (%)	-	1 (14)	-	-	1 (13)	2/39 (5)
ELN 2010 risk, n (%)						
Favorable	-	1 (13)	3 (33)	1 (13)	1 (13)	6 (15)
Intermediate-1	-	1 (13)	-	1 (13)	1 (13)	3 (7)
Intermediate-2	5 (62)	3 (38)	1 (11)	4 (50)	5 (62)	18 (44)
Adverse	3 (38)	3 (38)	5 (56)	2 (26)	1 (13)	14 (37)
CR/CRi, n (%)	5 (63)	6 (75)	9 (100)	5 (63)	4 (50)	29 (71)

038. Measurable Residual Disease (MRD) by 10-Colour Flow Cytometry (FACS) in acute myeloid leukaemia (AML) at end of consolidation predicts outcome

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Aim: MRD following chemotherapy is important for prognostication. We investigated prognostic significance of leukaemia-associated phenotypes (LAPs) by 3-tube, 10-colour FACS analysis in bone marrow of newly-diagnosed AML.

Method: Retrospective analysis of FACS MRD data on adults treated at our institution July 2012 to March 2018. Panel described in figure 1. At follow up, 250,000 events were acquired for sensitivity of level 0.1%. Level of <0.1% cells with LAP defined MRD-negativity. Statistical analysis performed in R version 3.5.

Results: 65 patients, 28 male (43%), median age 56 years (range 20-76 years). 20 favourable risk, 19 intermediate-I, 13 intermediate-II and 13 adverse. Of 63 evaluable at end-of-induction (EOI) 39 (62%) were MRD-negative. MRD-positive at EOI not predictive of overall survival (OS) (762 days vs NR, p=0.2), event free survival (EFS) (1365 vs 1249 days, p=0.91) or relapse free survival (RFS) (1365 vs 1249 days, p=0.91). Of 62 evaluable at end-of-consolidation (EOC) 77% were MRD-negative. MRD-positive at EOC was predictive of EFS (468 vs 1249 days, p=0.011) and RFS (468 vs 1249 days, p=0.008); trend for inferior OS (medians NR, p=0.054). 2-year EFS for EOC MRD-positive 28% vs 67% in MRD-negative, 2-year OS 64% vs 85%. 25 patients received CR1 transplant with trend to poorer EFS (263 vs 1365, p=0.06) and OS (541 vs 1417 days, p=0.053) in MRD-positive.

Cumulative risk of relapse in MRD positive was 57% vs 37% for MRD negative (p=0.06). In ELN Intermediate-I/Intermediate-II risk MRD positivity at EOC predicted disease relapse (83% vs 28%, p=0.02), but not in adverse (50% vs 50%, p=1) nor favourable risk (0% vs 25%, p=1). MRD at EOC was strongest predictor of EFS on multivariate-analysis.

Conclusion: MRD by 10-colour FACS predictive of EFS and RFS at EOC, particularly in intermediate-risk; allogeneic transplantation may not overcome impact of MRD-positivity. Further prospective validation warranted, particularly assessing impact of post-remission therapies.

Figure 1 – 10-colour flow cytometry panel

Tube	FITC	PE	ECD	PC5.5	PC7	APC	APCA700	APCA750	PB	KrOr
1	CD64	CD15	CD4	-	CD117	CD56	CD34	CD14	HLA-DR	CD45
2	CD2	CD71	CD13	-	CD117	CD11b	CD34	CD16	HLA-DR	CD45
3	CD38	CD123	CD13	CD19	CD117	CD7	CD34	CD33	HLA-DR	CD45

Figure 2 – EFS by MRD status at EOC

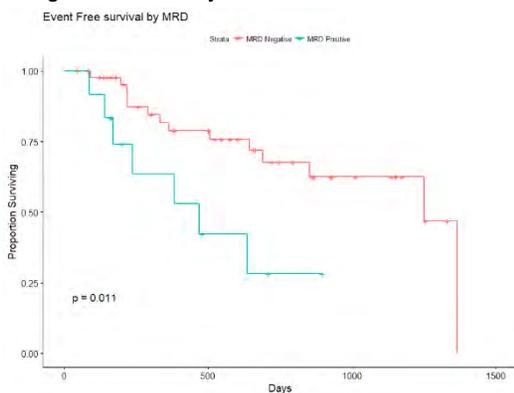
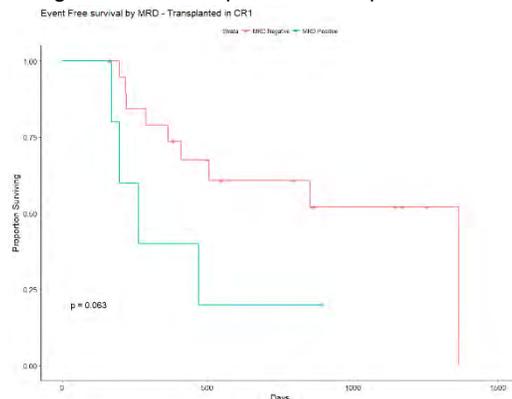


Figure 3 – EFS in patients transplanted in CR1



039. Effect of FLT3-ITD and NPM1 mutations on outcomes in 814 Western Australian Acute Myeloid Leukemia patients, a retrospective, multicentre study

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Aim

Prognosis attributed to molecular alleles of *FLT3* internal tandem repeats (*FLT3*-ITD) and *NPM1* in patients with Acute Myeloid Leukaemia may be due to co-inheritance or independent effect of these alleles.

Method

We retrospectively examined the contribution of these alleles on outcomes of 814 patients within the Western Australian AML cohort treated with intensive chemotherapy. We used Kaplan-Meier method to assess OS and PFS. Log rank test was used to determine difference in survival curves using SPSS 25. Continuous variables were compared using Student T-test. Non-random association between groups was compared using Fisher's exact test (2-sided). A p-value of <0.05 was considered statistically significant.

Result

Of the patients with molecular analysis (n=336), *FLT3*-ITD+ had poorer overall survival (OS), 26.6 mo versus 45.7 mo (p=0.019) compared with *FLT3*-ITD- patients with normal karyotype and 9.5 mo versus 33.9 mo in patients with aberrant cytogenetics. In the subgroup who received chemotherapy only, *FLT3*-ITD+ conferred poorer OS of 7.7 mo versus 23.2 mo, (p=0.023) compared with *FLT3*-ITD- patients which was abrogated by allogeneic haematopoietic stem cell transplantation (HSCT) on univariate analysis (p=0.0001). *FLT3*-ITD+ allele length also influenced outcomes. Patients with <45 repeats (n=21) were associated with longer OS of 34.2 mo versus 9.5 mo (p=0.031) in patients with >70 repeats (n=14). In the chemotherapy-only group, our data identifies 3 prognostic groups: favourable *FLT3*-ITD-/NPM1+ (n=39) with OS of 58 mo; intermediate *FLT3*-ITD-/NPM1- (n=88) and *FLT3*-ITD+/NPM1- (n=28) and poor *FLT3*-ITD+/NPM1+ (n=33) with OS of 16.2, 20.4 and 7.6 mo respectively. Progression free survival (PFS) was significantly influenced by *NPM1*+ only.

Conclusion

In conclusion, this study demonstrates that *FLT3*-ITD+ confers poor OS and can possibly negate the favourable outcome attributed by *NPM1*+. Early testing of *FLT3*-ITD, to enable incorporation of *FLT3* inhibitors during induction or consolidation with HSCT, is recommended.

040. Lineage switch from T-acute lymphoblastic leukaemia to acute myeloid leukaemia in a 21 year old male with primary refractory disease

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Background

Lineage switch is a rare, poorly-defined, prognostically dismal phenomenon rarely described outside childhood leukaemia. It most commonly involves lymphoblastic to myeloid/mixed phenotype switching and *KMT2A* rearrangements. We present a case of lineage switch from early T-cell precursor (ETP) acute lymphoblastic leukaemia (ALL) to acute myeloid leukemia (AML).

Case

A 21 year-old man presented with lymphadenopathy, splenomegaly and pleural/pericardial effusions. Excisional lymph node and bone marrow (BM) biopsy showed extensive infiltration with ETP lymphoblasts without MPO expression. The karyotype was normal, with no fluorescence in situ hybridisation (FISH) evidence of numerical aberrations, *TLX3*, *BCR-ABL1* or *KMT2A* rearrangements. Induction with UKALL-11 regimen B was undertaken with 4% blasts in BM, a partial nodal response and no change in splenomegaly post-treatment.

The patient underwent multiple sequential salvage regimens (CAZED, FLAG-Amsa, nelarabine) without meaningful response. *TP53*, *PHF6*, *EZH2* and *ASXL1* mutations were detected early in treatment with next generation sequencing. Brief flow cytometric minimal residual disease positive morphological remission was obtained in BM after MOpAD salvage, however nodal response remained poor. Despite two further cycles and pan-*NOTCH* inhibition, BM progression occurred. Blasts were immunophenotypically myeloid, lacked cytoplasmic CD3, and had complex karyotype including a derivative chromosome 9 with complex q rearrangement resulting in trisomy 9q34 by FISH. *TP53*, *PHF6*, *ASXL1* and *EZH2* mutation levels, alongside retrospective FISH evidence of trisomy 9q34 in early disease, linked the leukemic clones. No response to AML induction (HIDAC-3) or venetoclax was seen. Death from progressive disease occurred 12.5 months after original diagnosis.

Conclusion

Lineage switch in acute leukaemia is uncommon. Association with ETP-ALL has not been formally described, although rare case reports exist when diagnostic criteria are retrospectively applied. As ETP-ALL is known for mutational/transcriptional overlap with AML, this case provides further insight into its lineage plasticity and invites further study of leukemic stem cell biology.

041. Incidence, risk factors and morbidity of avascular necrosis in acute lymphoblastic leukaemia patients treated with the FRALLE-93 protocol

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Introduction

FRALLE-93 is a protocol used in treatment of acute lymphoblastic leukaemia (ALL) with a 3-year overall survival of 70% in adolescents and young adults. This favourable outcome highlights the need to assess long-term complications including avascular necrosis (AVN) of the bone, commonly linked to high cumulative corticosteroid doses. Rates of AVN are reported to be higher in older children, suggesting the adult patients treated with this regimen may be at particular risk.

Methods

An observational, retrospective, multi-centre analysis of incidence, risk factors and morbidity of AVN among ALL patients treated with the FRALLE-93 protocol was performed, across three tertiary centres between 2006-2017.

Results

Of 64 patients, 17 (27%) developed AVN, involving 42 joints. Median time to diagnosis following FRALLE-93 initiation was 14.6 months (range 1.9-36.3), with 14 patients diagnosed within 24 months. A majority (n=16) had symptoms preceding diagnosis, most frequently insidious pain in weight bearing joints. Diagnosis was confirmed on MRI (94%) and PET scan (6%). Multiple joints were involved in 14 patients (82%); 8 had multiple joints involved at initial presentation. Affected joints were the hip (n=11, 65% of patients), shoulder (n=4, 24%), knee (n=4, 24%), ankle/foot (n=3, 18%) and elbow (n=1, 6%). Treatment included observation (n=7, 41% of patients), hip decompressive surgery (n=4, 24%), joint replacement (n=4, 24%), arthroscopic knee repair (n=1, 6%) and ankle fusion (n=1, 6%). Long-term complications included chronic pain (n=8 patients) and impaired mobility (n=8). Table 1 shows patient demographics and possible AVN risk factors.

Characteristics	Confirmed AVN (n=17)	No AVN (n=47)	P-value
Age, median (range)	24 (17-57.8)	25 (17-52.7)	0.66
Sex (%)			
Male	8 (47)	30 (64)	0.23
Female	9 (53)	17 (36)	
BMI, median (range)	22.1 (16.2-34.6)	24 (14.5-42.5)	0.27
Smoking (%)			
Yes	2 (12)	7 (15)	0.83
No	13 (76)	38 (81)	
Unknown	2 (12)	2 (4)	
Vitamin D deficiency (%)			
Yes	4 (24)	12 (26)	0.85
No	5 (29)	13 (28)	
Unknown	8 (47)	22 (47)	
Allogenic Transplant (%)			
Yes	4 (24)	13 (28)	0.74
No	13 (76)	34 (72)	

Table 1: Categorical variables analysed with Chi-squared; continuous with Mann-Whitney U-test

Conclusion

AVN is a frequent complication of the FRALLE-93 protocol with significant morbidity. Our study demonstrated no statistically significant correlation of AVN with gender, BMI, smoking or vitamin D status. Steroid use remains crucial to this potentially curative regimen. A prospective study to identify at-risk patients may enable early intervention including bisphosphonates or decompressive surgery, to mitigate long-term morbidity.

042. A Phase I/II study of Pegylated-Interferon 2-alpha for relapsed haematological malignancy after allogeneic haematopoietic progenitor cell transplantation

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Background and Aim

Relapse after allogeneic hematopoietic progenitor cell transplantation (HPCT) reflects failure of immune graft-versus-malignancy (GVM) and manifests poor survival. Pre-clinical data shows type I Interferons regulate GVM and graft-versus-host disease (GVHD) (Robb R et al, Blood 2011). We tested safety and efficacy of pegylated-Interferon-2 α (peg-IFN2 α) added to therapy for relapse post HPCT.

Methods

Patients 18-70 years with haematological and minimal residual disease (MRD) relapse were eligible. Cessation of immune suppression (where applicable) was followed by Fludarabine and Cytarabine (FLAG). Weekly peg-IFN2 α commenced after count recovery and doses escalation over 6 months. Dose adjustment was based on toxicity. In absence of grade II-IV acute GVHD or progressive chronic GVHD patients could receive DLI. 29 patients were recruited and 2 year OS the primary endpoint.

Results

2 year OS is 30% (median follow-up 1089 days). Median DFS is 183 days (median follow-up 857 days). Peg-IFN2 α was tolerable; 11 patients (38%) had \geq grade 3 AE however only 4 were probably or likely related to peg-IFN2 α . 18 patients (62%) had acute (11%) or chronic (89%) GVHD, 11 (61%) after peg-IFN2 α alone. 7/11 (64%) patients receiving DLI developed GVHD. 7/12 (58%) patients without prior GVHD experienced GVHD after peg-IFN2 α . 8/13 (62%) of patients with MRD or mixed chimerism post FLAG responded to peg-IFN2 α , including 6 CR (75%). Immune profiling demonstrates persistence of cytolytically active Tc1 cells (Interferon γ secreting, granzyme B positive CD8+ T cells) in patients with GVHD versus those without.

Conclusion

30% 2 year OS represents significant improvement upon an institutional control cohort not receiving peg-IFN2 α (2 year OS 9% Curley C et al, Int J Lab Haematol 2014). Peg-IFN2 α caused expected and manageable toxicity. Our data supports addition of peg-IFN2 α post relapse to enhance GVM in patients with myeloid malignancies, where CAR based therapies are not available.

043. CD39+ T regulatory cells and CD39 genetic polymorphism in MS patients undergoing autologous HSCT

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Autologous HSCT (AHSCT) may induce remission in autoimmune diseases like Multiple Sclerosis (MS) by regenerating immune-regulatory cells, including antigen-specific CD39+ T regulatory cells (Tregs). CD39+ Tregs play a role in regulating inflammatory responses contributing to MS pathogenesis, and are defective in MS patients, but the role of these cells in AHSCT for MS is yet to be determined. Variable CD39 expression and Treg function has been attributed to polymorphism of the CD39 gene.

Aims and Methods: We aimed to determine whether AHSCT reconstitutes CD39+ Tregs (CD4+CD25^{hi}CD127^{lo}) by flow cytometry and to investigate CD39 genetic polymorphism using PCR-based genotyping assays in MS patients ($n=13$). Statistical analysis was performed using Mann-Whitney U and Wilcoxon's test.

Results: Before transplantation, we found a significant difference in CD39 antigen density (median fluorescence intensity [MFI]) of CD39+ Tregs in MS patients with different CD39 genotypes (mean MFI: 2152 vs 3347; $p<0.05$). CD39 MFI expression on CD39+ Tregs remained stable after transplantation in each genotype group for up to 12 months. Overall, a significant increase was detected in the proportions of CD39+ Tregs in the blood of MS patients at 3 ($p<0.0001$), 6 ($p<0.001$) and 12 months ($p<0.01$) post-transplantation compared to baseline. However, when grouped by CD39 genotype, the proportions of CD39+ Tregs were only significantly increased post-AHSCT in the patient cohort with lower CD39 MFI expression (baseline vs 3 [$p<0.05$], 6 [$p<0.01$] and 12 months [$p<0.01$]).

Conclusions: CD39 gene polymorphism is correlated with CD39 antigen density of CD39+ Tregs and may influence the reconstitution of CD39+ Tregs in MS patients post-AHSCT. Differences in CD39+ Treg reconstitution between patients with different CD39 genotypes may reflect different clinical responses towards AHSCT, suggesting CD39 genetic polymorphism to be a potential biomarker for aiding management of MS patients undergoing AHSCT.

044. DNA damage in haemopoietic stem cells impacts on neutrophil and platelet engraftment following autologous transplantation

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Background and Aim: Processing and cryopreservation is known to reduce the viability and absolute number of CD34⁺ haematopoietic stem cells (HSCs). DNA damage to stem cells may occur in the treatment of haematological malignancy. Cell death during the freeze/thaw process may result plasma membrane damage and generation of reactive oxygen species (ROS). We investigated whether the degree of DNA damage in cryopreserved HSCs product correlates with time to neutrophil and platelet engraftment in patients following autologous HSCs transplantation.

Methods: Cryopreserved HSC samples from 51 patients who underwent autologous transplantation were studied. HSC's were defined as CD45⁺/CD34⁺. DNA damage and intracellular ROS levels were assessed in the HSC population using an antibody against the phosphorylated form of histone H₂Ax (γ-H₂Ax) and 2',7'-dichlorodihydrofluorescein diacetate (H₂DCFDA), respectively. Data acquisition and analysis were performed by flow cytometry.

Results: A proportion of HSCs in each sample expressed elevated levels of ROS and γH₂Ax. The median percentages of ROS and γH₂Ax expressing CD34⁺ cells were 88.6 (range 40.8-100) and 54.6 (range 3.4-98.4), respectively. We observed a strong correlation between ROS and γH₂Ax levels in terms of the dose of cells/kg infused ($p < 0.0001$, $r = 0.83$). γH₂Ax expression was associated with delayed neutrophil engraftment; the γH₂Ax% expressing cells were 35.3% (range 3.7-95.5) vs. 59.1% (range 3.4-98.4) ($p = 0.046$) in patients achieving an absolute neutrophil count (ANC) of >0.5 in ≤ 12 and >12 days respectively. Modest but significant correlations between γH₂Ax expression and time to plt20 ($r = 0.3$, $p = 0.02$) and plt50 ($r = 0.3$, $p = 0.02$) were seen. A similar correlation was observed when the dose of γH₂Ax⁺ HSCs infused was considered. Median time to plt20 was 20 days (range 10-55) for $>1.5 \times 10^6$ /kg γH₂Ax⁺ HSC infused vs 17 days (range 11-30) for doses $\leq 1.5 \times 10^6$ /kg ($p = 0.04$).

There is no correlation between the dose of CD34⁺ HSCs delivered and neutrophil or platelet engraftment.

Conclusion: Our data suggest that the degree of DNA damage in CD34⁺ as assessed by γ-H₂Ax expression may have an impact on engraftment capacity of cryopreserved PBSC product following autologous transplantation.

045. Fludarabine, Melphalan, Carmustine: retrospective review of a reduced intensity conditioning regimen for allogeneic transplant and comparison with Fludarabine, Melphalan

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Background

Reduced intensity (RI) regimens for allogeneic transplant (HCT) have extended the curative benefit of HCT to a wider patient population by reducing transplant related mortality compared to myeloablative regimens. Previous comparisons between Fludarabine, busulphan and Fludarabine, melphalan for AML/MDS have found higher relapse rates for the former however there have been no direct comparisons between various Fludarabine, melphalan based RI regimens.

Aim

To report Overall Survival (OS), Non-relapse mortality (NRM) and Relapse Rate (RR) for Fludarabine, Melphalan, Carmustine (FMB) and compare outcomes to Fludarabine, Melphalan (FM) conditioning.

Methods

We conducted a retrospective review at Westmead Hospital of data from matched sibling and unrelated donor transplants receiving (FMB) and (FM) from 2011 to 2016. FMB regimen was changed to FM from 2015 according to standard institutional practice.

Results

There were 132 transplants performed for Acute Leukaemias (FMB=67, FM=11), Lymphomas (FMB=27, FM=3), MDS/MPN (FMB=16, FM=4), Myeloma (FMB=2, FM=2) and donors were unrelated (FMB=76, FM=10) and related (FMB=36, FM=10). Median recipient age was similar for FMB (61) and FM (58). OS at one year for FMB was 64% (95%CI: 56-74) and for FM was 95% (95% CI: 86-100) (p=0.012). The 100 day/1 year cumulative incidence of NRM for FMB and FM were 15%/26% and 5%/5% respectively, calculated with relapse as a competing risk. The one year RR for FMB/FM conditioning was 14%/5%(FM:2 events). Multivariate analysis to follow.

Conclusion

Our results indicate that FMB RI achieves acceptable outcomes. Our small cohort of FM RI appears to have better outcomes perhaps due to differences in other factors such as GVHD prophylaxis. An Australasian Bone Marrow Transplant Registry analysis has shown the effectiveness of FM conditioning. Our results need to be validated in a larger prospective analysis and could form the basis of a randomised trial comparing the addition of active agents to the standard regimen of FM.

046. Characteristics and outcomes of patients receiving second allogeneic haematopoietic cell infusion for graft failure or dysfunction

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Background/Aim: Graft failure (GF) or dysfunction (GD) following allogeneic blood or marrow transplant (alloBMT) are associated with poor outcomes. Salvage strategies may include a second infusion of allogeneic cell product with or without conditioning (Allo2). We seek to characterise this group and their outcomes in a single transplant centre.

Methods: We retrospectively reviewed records for all patients undergoing Allo2 for GF or GD at the Royal Melbourne Hospital between 1998-2018. Survival was calculated using the Kaplan-Meier method. Univariable comparisons were made using Fisher's exact test for discrete outcome variables and log-rank test for survival outcomes.

Results: Twenty Allo2 were performed for GF (n=12 [8 primary; 4 secondary]) or GD (n=8 [all secondary]), out of 1172 total alloBMT, during the study period. The table describes patient, disease and transplant characteristics. Platelet and neutrophil engraftment occurred in 45% with no significant difference in engraftment rate between GF or GD patients (P=0.36). Median times to neutrophil & platelet engraftment were 12.5 (range 0-69) & 30 (7-125) days respectively. Death before day +28 occurred in 4 GF patients. Median overall survival (OS) was 3.32 months. Five patients were alive at time of analysis (median follow-up 120 months [1.1–182 months]); estimated 2yr OS was 21%. Relapse occurred in one patient. Acute GvHD occurred in 30% patients and was grade III/IV in 25% patients. Deaths occurred due to infection (55%), organ dysfunction (15%) and GvHD (5%). Both neutrophil and platelet engraftment were mandatory for long-term survival - median OS in engrafters and non-engrafters was 93.2 and 1.4 months respectively (HR 0.24; 0.085–0.68, p=0.006). No other variables significantly predicted OS or engraftment, though patients >50yrs demonstrated a trend toward inferior survival (HR 2.4, 95% CI 0.87–6.63; p=0.09).

Conclusion: GD and GF can be successfully salvaged by Allo2, though long-term survival is limited by high rates of non-engraftment and early death.

	All (n=20)	GF (n=12)	GD (n=8)		All (n=20)	GF (n=12)	GD (n=8)
Age [yrs], median	52.5	53	36	Graft Source (Allo1)			
Disease				PB	15	9	6
SAA	3	0	3	BM	5	3	2
Myeloma	3	2	1	CD34 count (Allo2) (x10⁵/kg), median	3.9	4.00	3.80
AML	4	3	1	Donor type (Allo2)			
PMF	2	2	0	MSD	6	5	1
CML	3	2	1	MUD	13	6	7
MDS	2	1	1	Haplo	1	1	0
B-ALL	2	2	0	Donor change	1	1	0
CLL	1	0	1	ABO match			
Conditioning (Allo2)				Matched	10	6	4
MAC	0	0	0	Minor mismatch	5	4	1
RIC	2	1	1	Major mismatch	1	0	1
NMA	8	5	3	Bidirectional	3	2	1
None	10	6	4	Unknown	1	0	1
ATG (Allo1)	13	6	7				
ATG (Allo2)	4	3	1				

Table. Patient and transplant characteristics

047. Outcomes of severe aplastic anaemia post allogeneic stem cell transplant

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Background

Severe aplastic anaemia (SAA) is a rare life-threatening disease for which haematopoietic stem cell transplant (HSCT) is the treatment of choice in patients ≤ 40 yrs with a matched sibling donor, as well as in patients ≤ 60 yrs with a matched unrelated donor who have failed prior immunosuppressive therapy (IST).

Method

We retrospectively analysed the outcome of 21 adults with SAA undergoing HSCT. At time of HSCT, 76% of patients had failed prior IST, and 24% were untreated. Conditioning regimens included cyclophosphamide/ATGAM for matched sibling HSCT (sHSCT), or cyclophosphamide/ATGAM/2Gy total body irradiation for unrelated matched donor HSCT (uHSCT).

Results

With a median follow up of 3.5 yrs, OS was 90% for sHSCT and 71% for uHSCT recipients. TRM in uHSCT patients occurred secondary to infection in the setting of primary graft failure (D33), and acute gut graft versus host disease (GVHD) (D102). Death in a sHSCT 49yr old patient occurred prior to engraftment and was secondary to cardiomyopathy in the setting of sepsis (D27).

Median time to neutrophil and platelet engraftment was 18 and 30 days respectively for sHSCT recipients, and 20 and 24 days respectively for uHSCT recipients.

Acute GVHD occurred in 40% and 30% of sHSCT and uHSCT recipients respectively. Chronic GVHD (cGVHD) occurred in only 10% sHSCT recipients. However, 55% uHSCT recipients had cGVHD, and 33% had extensive cGVHD.

Age < 40 was the only favourable prognostic factor predicting a longer survival (HR 14.74; 95% CI 1.519-143.1; $p=0.02$). Patient sex, interval from diagnosis to transplant, prior IST, female donor-to-male recipient, ABO mismatch, CMV positive donor-to-CMV negative recipient, and number of donor CD34 cells were not prognostic.

Conclusion

Local outcomes remain comparable to published literature, with excellent results in young, previously untreated patients with a matched sibling. However, uHSCT recipients have comparatively inferior engraftment, response rates and survival, and a significantly increased risk of chronic GVHD. Larger studies are required to assess the potential impact that conditioning may have on engraftment and mortality in uHSCT.

048. Integrating multimodal genomic data for diffuse large B-cell lymphoma cell of origin sub-classification

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Aim

Diffuse large B cell lymphoma (DLBCL) is a genomically heterogeneous disease. Recent large-scale studies have demonstrated the value of comprehensive genetic characterisation to improve disease classification and inform outcomes. We aimed to evaluate the use of such an approach in the diagnostic pathology laboratory where accurate DLBCL sub-classification using histological approaches can be challenging.

Method

RNA and DNA was extracted from FFPE samples of patients with histologically defined DLBCL at the Peter MacCallum Cancer Centre (PMCC). Germinal centre (GC) versus non-GC was assigned by expert pathology review using the Hans classification. Gene expression profiling (GEP) was performed with the Nanostring Human Immunology v2 gene panel (594 genes) and sequence variant, whole genome copy number and structural variant detection was performed using the PMCC PanHaem hybridisation based NGS panel.

Results

Using combined RNA-GEP and DNA-based data we developed a unique DLBCL cell of origin (COO) classifier using random forests ensemble machine learning techniques. Integrated genomic subtyping was concordant with histological classification in 79% (30/38) of samples. Review of the 8 discordant cases resulted in pathologist reclassification of 2 cases. The remaining 6 cases were considered difficult/borderline cases after histopathology review.

In addition to COO classification, Nanostring GEP data demonstrated heterogeneity of expression of immunotherapy targets (PD1, LAG3, CTLA-4), heterogeneity of expression of antibody-drug targets (CD79B, CD30) and heterogeneity of relative expression of BH3-mimetic targets (BCL2, MCL1) over the cohort.

Conclusion

We have performed integrated genomic analysis of multimodal genomic data using machine learning techniques to improve COO classification in DLBCL. This was achieved using genomic data that is able to be generated within the diagnostic laboratory. In addition, this approach provides data on expression of therapeutic targets to inform treatment choice in DLBCL.

049. A review of 65 patients with mycosis fungoides/Sézary syndrome treated with extracorporeal photopheresis: our experience at Peter MacCallum Cancer Centre

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Extracorporeal photopheresis (ECP) has demonstrated therapeutic benefit in patients with cutaneous lymphoma, particularly Sézary Syndrome (SS)¹. The aim of this study is to review patients with mycosis fungoides (MF) and SS who were treated with ECP at our institute.

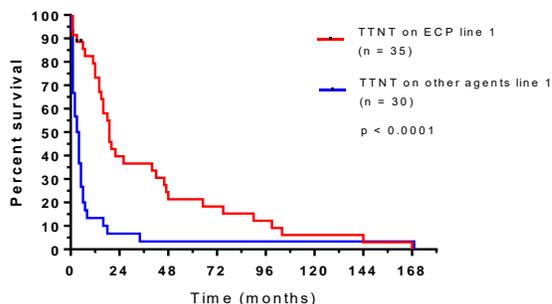
Note: Peter Mac is the only centre in Australia that currently offers ECP for patients with MF/SS.

We identified a cohort of 65 patients with a diagnosis of MF/SS who were treated with ECP at our institute. Patients with MF were required to have blood involvement. Of note, 58/65 (89%) of these patients had advanced stage disease (Stage IIB – IVB). Patient outcomes were examined using overall survival (OS) and time to next treatment (TTNT) as the study endpoints.

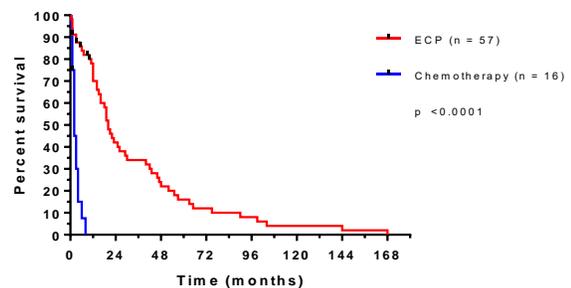
Analysis of the data showed a median OS of 61 months across the entire cohort, which compares favourably to previous studies of a similar cohort². 88% of patients commenced ECP at treatment lines 1 – 3, either as a monotherapy or in conjunction with other systemic agents. Our data showed that the use of ECP increases TTNT when compared to other agents, particularly when given at treatment line 1 ($p < 0.0001$). ECP also demonstrated significantly better TTNT outcomes as a first-line agent compared to traditional chemotherapy ($p < 0.0001$), suggesting that chemotherapy has limited benefit as an early-line treatment in advanced MF/SS³. ECP monotherapy was found to have the longest overall median TTNT of any treatment regimen (11 months) and was also shown to prolong TTNT when used in combination with other systemic agents. Furthermore, no patients ceased treatment due to side effects relating to ECP, highlighting its excellent tolerability.

The results of our study demonstrate that ECP is highly effective in treating patients with advanced MF/SS and is one of the optimum therapies for patients with SS and erythrodermic MF with blood involvement.

TTNT comparison of patients treated with ECP vs other agents at Line 1 (n = 65)



TTNT comparison of patients treated with ECP vs Chemotherapy across Rx lines 1 - 3



1. Edelson R, Berger C, Gasparro F, et al. Treatment of Cutaneous T-Cell Lymphoma by Extracorporeal Photochemotherapy. *New England Journal of Medicine*. 1987;316(6):297-303.
2. Kim YH, Liu HL, Mraz-Gernhard S, Varghese A, Hoppe RT. Long-term outcome of 525 patients with mycosis fungoides and sézary syndrome: Clinical prognostic factors and risk for disease progression. *Archives of Dermatology*. 2003;139(7):857-866.
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050. Genetic analysis of Diffuse Large B-cell Lymphoma occurring in cases with antecedent Waldenström Macroglobulinaemia reveals different patterns of clonal evolution

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Background and Aims

Diffuse large B-cell lymphoma (DLBCL) occurs in 2-10% of cases with antecedent Waldenström Macroglobulinaemia (WM) but there is lack of understanding of the clonal relationship between the two lymphomas. We aimed to use easily applicable genetic analysis on paired samples to determine the clonal relationship of the two lymphomas.

Methods

We extracted DNA from and performed MYD88 L265P and immunoglobulin heavy chain (IgHv) PCR and sequencing on WM and subsequent DLBCL samples of 4 patients. Patients received no treatment (patient 3), nucleoside analogues (patient 4), alkylating agents (Patient 2) and Ibrutinib (patient 1) for WM. The minimal amount of brain tissue on Patient 1 was subjected to laser-capture microdissection, IgHv PCR and cloning before sequencing.

Results

MYD88 L265P mutation was detected in all 4 cases at WM diagnosis, and in 3 cases at occurrence of DLBCL. Patient 3 with wtMYD88 DLBCL had variable IgHv to the treatment naïve WM, indicating independent clonal origin. Patients 2 and 4 had the same IgHV, indicating clonal evolution from the antecedent WM. IgHv on patient 1 was inconclusive despite laser microdissection.

Conclusion

IgHv and MYD88 mutation analysis from archived bone marrow and secondary lymphoma tissue can help determine if the DLBCL has arisen from the original WM clone or is a de-novo lymphoma. This information is important for prognosis as de-novo DLBCL has a better prognosis than transformed lymphoma. We also report the first case of a WM patient compliant with and responding to Ibrutinib developing DLBCL within the CNS despite retention of the MYD88 mutation.

051. High dose methotrexate toxicities and glucarpidase use

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Introduction: We conducted a retrospective audit on toxicities attributable to high dose methotrexate (HD MTX) in an adult population undergoing treatment of a haematological malignancy. An additional objective of the study was to assess adherence to published guidelines on the use of glucarpidase for delayed methotrexate clearance.

Method: Patients who received HD MTX between 1/1/2013 to 31/12/2017 were identified using the chemotherapy pharmacy database. Adult patients who received a dose of methotrexate $\geq 1\text{g/m}^2$ were included. Combination chemotherapy regimens were excluded. Delayed methotrexate clearance was defined as a serum methotrexate level $> 0.05\mu\text{mol/L}$ more than four days post completion of the methotrexate infusion. Toxicities were graded according to the CTCAEv5. A literature review was performed to identify guidelines for the use of glucarpidase.

Results and Discussion:

	No. of Patients	No. of cycles of HD MTX	Average Age (years)	No. of days to clear MTX	Average LOS* (days)	No. of cycles with delayed MTX clearance
ALL	36	62	60.3 (25 – 83)	4.2	6.8	11
3g/m ²	30	51	57.7	4.6	7.3	11
< 3g/m ²	6	11	71.7	3	5.3	0

*Length of stay (ie. duration of inpatient admission)

All patients had normal renal function (serum CrCl $>60\text{ml/min}$) prior to methotrexate. All patients received adequate hydration, urinary alkalinisation and leucovorin. Review of medication histories found that two (3.2%) patients received medications known to interfere with methotrexate clearance.

	No. of cycles complicated by toxicity (%)
Acute kidney Injury (\square Grade 3)	10 (16.1%)
Anaemia (\square Grade 3)	6 (9.6%)
Neutropenia (\square Grade 3)	7 (11.2%)
Neutropenic Sepsis	3 (4.8%)
Mucositis (\square Grade 3)	7 (11.2%)
Acute Liver Injury (\square Grade 3)	2 (3.2%)
Admission to Intensive Care	2 (3.2%)
Death	0 (0%)

Toxicities were attributable to delayed methotrexate clearance in all patients. The average length of stay for patients with delayed methotrexate clearance was 15.6 days. The incidence of acute kidney injury was similar to that reported in the literature (9.1%) for adult lymphoma patients. One of the 11 patients with delayed methotrexate clearance received glucarpidase. A retrospective review found that 5 of these 11 patients met criteria for glucarpidase based on recently published guidelines.

Conclusion: Despite optimal supportive care, toxicity attributable to delayed methotrexate clearance remains a significant cause of morbidity for patients with haematological malignancies. Glucarpidase is an under-utilised treatment. Local guidelines on the criteria for glucarpidase are required as well as studies to assess the longer term clinical impact of its use.

052. Nivolumab for relapsed or residual haematological malignancies after allogeneic haematopoietic stem cell transplantation (NIVALLO)

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Aim

To evaluate the safety and efficacy of nivolumab for the treatment of relapsed or residual haematological malignancies after allogeneic stem cell transplantation (alloSCT).

Background

T-cell inhibition mediated by PD-1/PD-L1 interactions may contribute to relapse of haematological malignancies after alloSCT. Nivolumab inhibits PD-1 signalling and warrants investigation to treat post-transplant relapse.

Method

This is an investigator-initiated clinical trial. Patients with relapsed haematological malignancies following alloSCT are eligible. Patients with current GVHD or prior grade ≥ 2 acute GVHD or chronic GVHD are excluded. Patients receive nivolumab 3mg/kg fortnightly for up to 48 weeks.

Results

Six participants have received at least one dose of nivolumab. Primary haematological malignancies included Hodgkin lymphoma (HL, 2 patients), acute myeloid leukaemia (AML, 2), transformed chronic lymphocytic leukaemia (tCLL, 1) and mantle cell lymphoma (MCL, 1). Two participants developed grade 3 acute GVHD following the first dose of nivolumab. Complete or partial responses were observed in 3 participants (50%). Two participants with HL achieved complete responses. One participant with MCL had a complete nodal response with small volume persistent bone marrow disease. One participant with AML achieved initial blast reduction however subsequently developed progressive AML. Prior to nivolumab treatment a high proportion of CD8+ T cells expressed PD-1 and T-cell immunoglobulin and mucin domain 3 (TIM-3) consistent with T-cell exhaustion. Following treatment with nivolumab there was an increase in TNF α production by CD8+ T-cells at day 7 post nivolumab. Despite continued nivolumab treatment TNF α production declined and correlated with loss of clinical response. TIM-3 expression was further upregulated at post-nivolumab progression suggesting this inhibitory checkpoint receptor may have contributed to nivolumab resistance.

Conclusion

Nivolumab treatment after alloSCT results in potent immune stimulation with a high rate of clinical responses, albeit with a risk of GVHD. Acquired resistance to nivolumab may develop via upregulation of alternative inhibitory checkpoints.

053. Outcomes of primary central nervous system lymphoma treated with R-MPV +/- whole-brain radiotherapy: A single centre experience

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Aim: Tolerability of planned high dose chemoradiotherapy for primary central nervous system lymphoma (PCNSL) remains poor for many patients and leads to poor outcomes, particularly for the elderly. We undertook this study to assess the outcomes and tolerability of the R-MPV protocol in a real-world population.

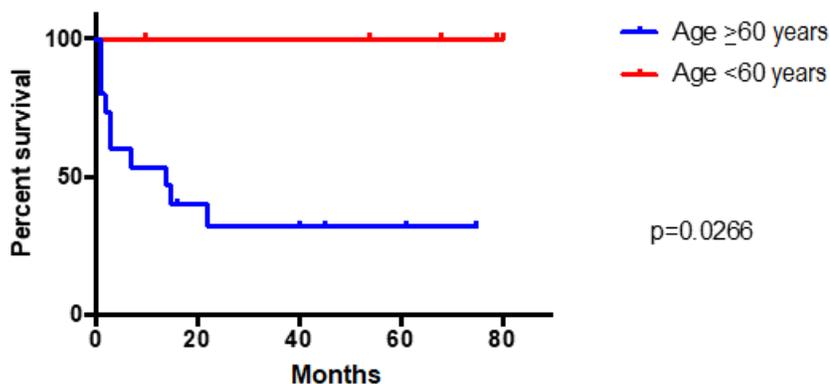
Methods: We performed a retrospective analysis of medical records of patients with PCNSL treated with R-MPV +/- whole-brain radiotherapy (WBRT) between 2010 and 2017 at the Royal Brisbane and Women's Hospital (RBWH) from an institutional database. Baseline patient and disease demographics were identified and outcomes including overall survival (OS), progression-free survival (PFS), best response, tolerability and toxicity were recorded. Kaplan-Meier survival curves were compared by log-rank test.

Results: 20 patients received R-MPV for PCNSL during the study period. The median age was 66 years (range, 21-78 years), 9 patients had ECOG >2, and majority had IELSG intermediate (n=12) or high (n=6) risk disease. The median number of cycles delivered was 5 (range, 1-7), and 8 patients required dose reductions for toxicity. 11 patients attained a complete response (CR) to R-MPV, 8 proceeded to WBRT (23.4Gy) and 11 patients proceeded onto cytarabine consolidation. There were no treatment-related deaths. With median follow-up of 61 months, the 5-year OS and PFS were 48% and 42% respectively. Age ≥ 60 years and less than CR to R-MPV were the only factors associated with an inferior OS (HR=4.72, p=0.0266 and HR=23.15, p<0.0001). 1 patient relapsed at 55 months, was salvaged with ASCT and remained in remission at 24 months. Consolidative WBRT was not associated with improved OS or PFS. Dose reductions were not associated with inferior OS.

Conclusion: R-MPV is well tolerated and associated with excellent outcomes for younger patients. However, patients over the age of 60 years have high rates of early progression and poor long-term survival.

Figure 1

OS based on age ≥ 60 years of patients treated with R-MPV



054. Optimizing Therapy for Myeloma Patients – Lessons Learnt from the UK Myeloma XI Study

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Aim

The optimum IMiD induction and maintenance regimen for myeloma are unknown and may depend on patient age and cytogenetic risk.

Methods

Myeloma XI, a randomized controlled trial for newly diagnosed patients (ISRCTN49407852) addressed a comparison of Len vs Thal plus cyclophosphamide and dexamethasone (CRD vs CTD) for induction continued for a minimum of 4-6 cycles followed by ASCT for younger patients. A maintenance randomization compared Len until disease progression vs observation. 3894 patients underwent the induction randomization, and 1971 the maintenance randomization. Co-primary endpoints were PFS and OS with pre-specified subgroup analyses by cytogenetic risk.

Results

CRD induction was associated with longer median PFS compared to CTD (25m vs 24m, HR 0.91, p=0.0175). Significantly improved PFS was seen in transplant-eligible patients (CRD 36m vs CTD 33m, HR 0.85, p=0.0116) and was associated with improved 3-year OS (50% vs 45%, HR 0.77, p=0.0072). There was no significant difference in PFS /OS for non-transplanted patients.

Len maintenance was associated with a 54% reduction in the risk of progression/death (Len 39m vs observation 20m, HR 0.46; p<0.0001). PFS was significantly improved in transplant-eligible patients (57m vs 30m, HR 0.48, p<0.0001) and transplant-non-eligible patients (26m vs 11m, HR 0.44, p<0.0001). Significantly longer OS was seen in Len maintained transplanted patients (3-year OS Len 87.5% vs observation 80.2% HR 0.69; p=0.0140). Survival benefits were consistent across all patient subgroups, including patients with high-risk features.

An exploratory analysis of transplanted patients showed that CRD induction with Len maintenance was optimum: 5-year PFS CRD-R 50.2%, CTD-R 39.1%, CRD-obs 18.5%, CTD-obs 23.4%.

Conclusion

CRD was associated with deeper responses than CTD and with a PFS/OS benefit in transplant-eligible patients. Len maintenance improved PFS/OS. The best outcomes were associated with Len induction plus Len maintenance. Our findings support continuing Len therapy through induction until disease progression.

055. Single Arm Multicentre study of Carfilzomib Thalidomide Dexamethasone for Relapsed/Refractory Multiple Myeloma: A preliminary analysis of the ALLG MM18/AMN003 study

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Introduction

Combination of immunomodulatory drugs (IMiD), proteasome inhibitors, and dexamethasone has proven effective treatment of multiple myeloma (MM). Carfilzomib, lenalidomide and dexamethasone is proven effective in the ASPIRE study. Thalidomide, a first generation IMiD, is more affordable than lenalidomide. We aim to assess the safety and efficacy of combination carfilzomib, thalidomide and dexamethasone (KTd) in patients with Relapsed Refractory Multiple Myeloma (RRMM).

Method

56 of the planned 100 patients were enrolled and received combination KTd: carfilzomib [20mg/m² IV C1D1,2, 56mg/m² (36 for patients age ≥75 years) from C1D8 onwards], thalidomide (100mg po nocte) and dexamethasone [40mg (20mg for patients age ≥75 years) weekly], in a 28-day cycle. After 12 cycles of KTd, 6 further cycles of Kd [carfilzomib 56mg/m² (36 for patients age ≥75 years) and dexamethasone 40mg (20mg for patients age ≥75 years) on D1 and 15 every 28-days, were given.

Results

Of the 54 patients (50% male, median age 66 years) who received ≥1 cycle of treatment, 38 patients had evaluable response after median follow up of 4.9 months (1.0 to 13.7 months). Of these, ORR (≥PR) was 92% (≥VGPR 68%). No patients with ≥MR have relapsed. Median TTP is not reached. All grade and grade ≥3 AEs occurred in 99% and 56%, respectively. The most common grade ≥3 AEs were peripheral sensory neuropathy (13%), dyspnoea (13%) and infections (7%). VTE occurred in 4% patients. All grade dyspnoea, cardiac complications, systemic-hypertension and pulmonary-hypertension occurred in 27, 5, 9 and 1.9% of patients respectively, however very few were grade ≥3. Three patients have died on study from disease complications, haemorrhage, and primary cardiac ischaemic event.

Conclusion

Combination KTd appears effective for the treatment of RRMM, inducing deep, durable responses albeit with short follow up in this analysis. So far, treatment is safe and tolerable. Accrual is ongoing.

056. Overall survival of RRMM patients treated with carfilzomib/dexamethasone (Kd56) vs bortezomib/dexamethasone (Vd) by age: results from the ENDEAVOR study

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Background

Mature overall survival (OS) data has recently been reported from ENDEAVOR, showing that Kd56 resulted in a statistically and clinically significant improvement in OS compared with Vd in the intention-to-treat (ITT) population. We report a subgroup analysis from ENDEAVOR to evaluate OS and updated safety outcomes by age.

Methods

Full details of the study design have been reported elsewhere. OS was compared between treatment arms in patients grouped according to age (i.e., <65, 65–74, and ≥75 years of age) using an unstratified Cox proportional hazards model.

Results

The ITT population included 929 patients enrolled in the study. OS was improved with Kd56 vs Vd within each age subgroup (Table). In the safety population (n=919), the median duration of treatment was longer with Kd56 than with Vd within each age subgroup (<65 years: median, 49.0 weeks vs 27.0 weeks; 65–74 years: 49.9 weeks vs 27.6 weeks; ≥75 years: 43.3 weeks vs 20.6 weeks). Rates of any-grade adverse events (AEs) and grade ≥3 AEs of interest are shown in the Table. Grade ≥3 hypertension, dyspnoea, cardiac failure, and acute renal failure were more common with Kd56 vs Vd within each age subgroup, whereas grade ≥3 peripheral neuropathy occurred more often with Vd vs Kd56 within each subgroup (Table). AEs were not adjusted for exposure.

Conclusions

Clinically meaningful improvements in OS were observed with Kd56 compared with Vd across all age groups examined, including patients aged ≥75 years. The safety results were comparable to those reported in the age subgroup analysis of the PFS interim results for ENDEAVOR. Overall, these data support the favourable benefit-risk profile of Kd56 in patients with RRMM, regardless of age.

057. Weekly carfilzomib, lenalidomide, and dexamethasone (KRd) in relapsed or refractory multiple myeloma (RRMM): a phase 1B study

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Background

Under the approved KRd regimen, carfilzomib is given twice weekly (20/27mg/m²; 10-min IV infusion). We present updated results from a dose-finding study assessing weekly KRd.

Methods

This study consisted of a dose-evaluation component and a dose-expansion component in both RRMM and newly diagnosed MM. Results for RRMM patients are presented. Two dose levels were evaluated: carfilzomib 56mg/m² and 70mg/m². All patients received carfilzomib (30-min IV infusion on days [D] 1, 8, and 15; 20mg/m² on C1D1), lenalidomide 25mg (D1–21), and dexamethasone 40mg (D1, 8, 15, and 22) on a 28-day cycle (dexamethasone was not given on D22 for cycles 9+). Patients in the expansion arm received the selected KRd regimen on the same schedule used for dose evaluation.

Results

Twenty-two RRMM patients were enrolled in the dose-evaluation part and received study drug (56mg/m², n=10; 70mg/m², n=12). The MTD of carfilzomib was not reached; 70mg/m² was selected for dose expansion and 34 additional RRMM patients received this dose. Results are presented for patients who received 56mg/m² during dose evaluation (n=10; median 2 prior regimens [range 1-3]) and for patients who received 70mg/m² during dose evaluation or expansion (n=46; median 1 prior regimen [range 1-5]). Median (mean) average carfilzomib dose was 53.2 (52.8)mg/m² (56mg/m² group) and 62.4 (61.3)mg/m² (70mg/m² group). Patient incidence of grade ≥3 AEs was 70.0% (56mg/m²) and 71.7% (70mg/m²). Patient incidence of carfilzomib discontinuation due to AEs was 20.0% (56mg/m²) and 17.4% (70mg/m²). There were three deaths in the 70mg/m² group (one each: cardiac arrest, cardiac disorder, progressive disease). Overall response rates were 90.0% (56mg/m²) and 89.1% (70mg/m²); 20.0% (56mg/m²) and 30.4% (70mg/m²) of patients achieved a CR or sCR.

Conclusions

Both regimens tested in this once-weekly KRd study were effective, with manageable toxicity in patients with RRMM. As weekly carfilzomib could offer patients greater convenience, these results support further clinical evaluation.

058. Impact of baseline renal function on efficacy and safety of daratumumab plus bortezomib-melphalan-prednisone in transplant-ineligible newly diagnosed multiple myeloma (ALCYONE)

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Aim: We conducted a subgroup analysis of D-VMP vs VMP according to baseline creatinine clearance (CrCl; ≤60 mL/min [moderately impaired] and >60 mL/min).

Methods: Randomized patients were ineligible for high-dose chemotherapy with ASCT and had baseline CrCl ≥40 mL/min. Up to nine 6-week VMP cycles (V 1.3 mg/m² SC twice weekly during Cycle 1 and QW during Cycles 2-9; M 9 mg/m² PO and P 60 mg/m² PO on Days 1-4 during Cycles 1-9) ± daratumumab (16 mg/kg IV QW for Cycle 1, Q3W for Cycles 2-9, and Q4W for cycles 10+) were received.

Results: The study enrolled 295 (150 D-VMP; 145 VMP) patients with baseline CrCl ≤60 mL/min and 411 (200 D-VMP; 211 VMP) patients with baseline CrCl >60 mL/min. D-VMP prolonged PFS vs VMP in ≤60 mL/min (median not reached [NR] vs 16.9 months; HR 0.36; 95% CI 0.24-0.56) and >60 mL/min (median NR vs 18.3 months; HR 0.63; 95% CI 0.45-0.88) subgroups after median follow-up of 16.5 months. ORR benefit was maintained for D-VMP vs VMP in the ≤60 mL/min (89% vs 73%; ≥CR: 43% vs 24%) and >60 mL/min (92% vs 74%; ≥CR: 43% vs 25%) subgroups. Similar findings were observed with minimal residual disease-negative rates in the ≤60 mL/min (25% vs 8%) and >60 mL/min (20% vs 5%) subgroups. Safety findings for D-VMP vs VMP are summarized in **Table 1**.

Conclusions: Daratumumab plus VMP prolongs PFS, induces deep responses, and demonstrates acceptable tolerability regardless of baseline CrCl.

	CrCl ≤60 mL/min		CrCl >60 mL/min	
	D-VMP	VMP	D-VMP	VMP
Grade 3/4, %				
Most common (≥10%) TEAEs				
Neutropenia	47	38	35	39
Thrombocytopenia	43	42	28	34
Anemia	21	29	12	13
Pneumonia	15	6	9	2
Peripheral sensory neuropathy	2	4	1	4

059. Increased bortezomib discontinuations in transplant-ineligible newly diagnosed multiple myeloma patients correspond to the point of reapplication for continuing therapy

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Background

Bortezomib-based therapy is available through the Pharmaceutical Benefits Scheme (PBS) for transplant-ineligible newly diagnosed multiple myeloma (TI/NDMM) patients, who can access up to 52 doses under PBS subsidy. However, patients are required to demonstrate response and physicians need to reapply for continuing therapy at the 32nd dose.

Objective

To describe the longitudinal patterns of bortezomib use in TI/NDMM patients.

Methods

A retrospective analysis of TI/NDMM patients receiving bortezomib-based frontline therapy between October/2012–December/2017 using PBS 10% sample data was performed. Kaplan-Meier methods were used to estimate persistence between scripts (doses) 32-33. Persistence was defined by the absolute or relative difference in the percentage of patients who filled consecutive scripts.

Results

3710 TI/NDMM patients received bortezomib for a median of 29.4 scripts. The majority were aged >70 (61.7%) and male (56.6%). While 44.2% of patients received a 32nd dose, only 34.0% received the 33rd dose (absolute persistence difference=10.2%, relative drop=23.1%). The median absolute difference in persistence between all consecutive scripts (i.e., 1 to 52) was 1.20%, with median relative drop of 2.60%. Larger relative drops between doses 32-33 were seen for women vs men (27.9% vs 18.8%), VIC vs NSW (28.0% vs 16.1%) and later years of treatment initiation: 2016 (26.5%), 2015 (35.3%), 2014 (19.1%).

Conclusions

Discontinuations were considerably higher between the 32nd and 33rd bortezomib scripts in TI/NDMM patients. These were more pronounced for some subgroups and corresponded to the time point for reapplication of PBS continuing therapy. We hypothesize that this drop is a consequence of patients having obtained their best confirmed response to treatment, or to administrative requirements to continue treatment beyond the 32nd dose. Given that the VISTA trial demonstrated that higher bortezomib cumulative doses achieved through a treatment duration up to 52 doses are associated with improved outcomes, factors decreasing treatment persistence should be stringently evaluated.

061. Genetic and molecular pathogenesis of myeloid leukaemia predisposition

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Germline genetic etiologies are increasingly identified in a growing subset of seemingly sporadic MDS or AML. This session will focus on germline genetic predisposition to myeloid malignancies. Mechanistic insights of clonal evolution gleaned from the study of these germline genetic disorders will be explored. Clinical implications of genetic predisposition to myeloid malignancies will be discussed.

062. What's new in AML in 2018?

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The therapeutic landscape for AML stagnated for over 40 years. Since April 2017, unprecedented progress has been made with 5 new drugs for the treatment of AML approved by the FDA. Three of these are molecularly targeted therapies approved for patients with specific gene mutations. Hopes are high that this heralds the dawn of a new era, in which several decades of molecular pathogenesis research comes to fruition translating into therapeutic paradigm shifts with associated improvements in outcomes for AML patients. The multi-kinase inhibitor Midostaurin was the first targeted therapy to be approved for FLT3-mutated AML. Clinical development of a number of more potent and specific inhibitors targeting FLT3 is ongoing. Enasidenib, a mutant IDH2 inhibitor, has provided a unique therapeutic option for IDH2-mutated AML patients and is associated with a specific toxicity profile related to its mechanism of action. The mutant IDH1 inhibitor Ivosidenib is the most recent approval providing a treatment option for another molecularly defined subset of patients. Vyxeos, a novel liposomal formulation of standard AML drugs in a fixed ratio combination, is the first treatment to improve outcomes for specific subtypes of AML, usually associated with a poor prognosis. The re-approval of the first immunotherapy for AML, Gemtuzumab Ozogamicin, an anti-CD33 antibody-drug conjugate, after its withdrawal in 2010, has provided another important agent in the therapeutic armamentarium for AML. Greater understanding of mechanisms of disease pathogenesis and treatment resistance has yielded other promising novel agents including Venetoclax and Uproleselan with registration studies underway. Novel targeted immunotherapeutic strategies are also under investigation and showing early promise. The technology to sensitively monitor molecular targets through therapy has facilitated the increasing use of minimal residual disease endpoints in clinical decision making and drug efficacy evaluation. The future of AML therapeutics has never been brighter with exciting opportunities for strategically directed research efforts to translate into meaningful clinical advances and patient benefit.

064. Dealing with MRD / transplant / cure / cost / CART

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The treatment landscape is rapidly changing for patients diagnosed with multiple myeloma. Several new drugs have been approved the past few years. Using the best available combination therapies in newly diagnosed patients, high rates of patients become minimal residual disease (MRD) negative, which translates into longer progression-free survival and overall survival. Even in patients with relapsed myeloma newer combination therapies are showing high rates of MRD negative patients. Beyond these successes, the development pipeline looks promising. For example, bi-specific monoclonal antibodies, antibody drug conjugates, novel small molecules, and CAR T cell therapies are already far along in clinical trials. What are the unmet needs, where is the field going, how to manage all these new opportunities in the clinic?

066. Bone marrow failure and MDS

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Identification of genetic causes of bone marrow failure (BMF) and MDS informs precision medicine approaches to medical management and treatment. Accurate diagnosis of genetic BMF/MDS disorders enables risk stratification, leukemia surveillance, and attention to associated co-morbidities. The rapidly expanding genetic testing options for the evaluation of BMF and MDS has led to exciting advances but also raises new questions. This case-based session will explore challenges to diagnosis and management of BMF and MDS in the genomic era.

067. Myeloma

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With modern combination therapies a high proportion of patients achieve non detectable disease (MRD negativity) before collection of stem cells. In parts of the world, newly diagnosed patients are asking about the role of default autologous stem cell transplant up-front. What combination therapies are most promising in the newly diagnosed setting? In other malignancies, such as acute leukemia, MRD-driven therapy already has been established. Will MRD-driven therapy become the new standard in myeloma care?

With the ability to detect low levels of disease, conversion from MRD negativity to MRD positivity is an emerging situation in the clinic. Monitoring of patients who converted over to MRD positivity show patterns of clinical progression over time. Yet, the guidelines recommend continued monitoring and start of relapse therapy when the patient develops symptoms and/or other labs start to drift off. Some patients are asking about earlier initiation of therapy; will future guidelines recommend start of therapy at the time of confirmed MRD positivity?

For patients who start combination therapy for relapsed myeloma, most protocols recommend continued therapy. However, for relapsed patients who achieve MRD negativity, similar to newly diagnosed patients, can they transition over to maintenance therapy?

070. Immunotherapy in lymphoma

LaCasce A¹

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I will discuss the biologic characteristics of Hodgkin lymphoma and subsets of B-cell non-Hodgkin lymphoma which make these diseases amenable to checkpoint inhibition and other immunotherapeutic approaches (excluding CAR-T cells). I will then review the data for approved drugs and combinations, as well as immunotherapy agents and combinations in clinical trials.

071. Improving the efficacy and safety of CAR T cells in hematologic malignancies

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Advances in synthetic biology and adoptive T cell transfer are making inroads in cancer therapy. Therapy with genetically modified T cells that express synthetic chimeric antigen receptors (CARs) targeting CD19 has resulted in remarkable responses in patients with advanced refractory B cell malignancies. The underpinnings of this approach have been derived empirically, and the principles for designing synthetic receptors and utilizing a patient's own T cells for therapy are still being revealed. Our lab conducted the first clinical trials in which the CD4 and CD8 T cell composition of the CAR-T cell product is uniform in all patients. This approach identified CAR-T cell dose/response and dose/toxicity relationships that were not apparent in prior studies, and improved the therapeutic index. Complete durable responses were achieved in a significant fraction of patients with advanced chemotherapy refractory acute lymphoblastic leukemia (ALL), Non Hodgkin lymphoma (NHL), and chronic lymphocytic leukemia (CLL) treated with CD19 CAR T cells. Relapse with CD19 negative disease is a mechanism of failure, and targeting additional lineage specific B cell markers is a potential strategy to improve outcomes. The adoptive transfer of B-Cell Maturation Antigen (BCMA) chimeric antigen receptor (CAR) T cells is also demonstrating early promise in MM. However, BCMA is cleaved by gamma-secretase, releasing a soluble BCMA fragment that could bind to CAR T cells, and lower ligand density for CAR T cell recognition, enabling escape of tumor cells from CAR T cells. We found that MM patient bone marrow may contain levels of soluble BCMA (sBCMA) sufficient to inhibit CAR T cell recognition of tumor cells. Treatment with a small molecule gamma-secretase inhibitor (GSI) rapidly and reversibly increases surface BCMA levels on MM cell lines and patient samples in a dose dependent fashion, and decreases sBCMA. When GSI was combined with BCMA CAR T cells in preclinical models, antitumor efficacy and progression free survival were improved. The concurrent administration of a GSI is a rational approach to improve BCMA targeted therapies, and we have obtained FDA approval to combine GSI with BCMA CAR T cells in a clinical trial.

072. Latest development in T cell non Hodgkin Lymphoma

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The key developments in T cell NHL over the last few years have included:

- Major advances in our understanding of the genomic and epigenetic landscape of T cell lymphomas which have allowed us to better define the various entities within this heterogeneous group of diseases.
- The development of novel systemic therapies for both peripheral T cell lymphoma and cutaneous T cell lymphoma including histone deacetylase inhibitors (vorinostat, romidepsin), brentuximab vedotin and mogamulizumab. Novel agents in advanced development include the monoclonal antibody IPH4102, duvelisib, and the new modified formulation of denileukin diftitox.
- The recognition of new entities such as breast implant associated anaplastic large cell lymphoma
- Most recently, germline predispositions have been identified as risk factors for T-cell lymphoma such as those found in patients with subcutaneous panniculitis T cell lymphoma

The above will be discussed using examples of various T-NHL subtypes.

073. Comprehensive genomic evaluation in bone marrow failure syndromes - results of the Melbourne Genomics Health Alliance Bone Marrow Failure Flagship

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¹Victorian Comprehensive Cancer Centre, Melbourne, Australia, ²Royal Children's Hospital, Melbourne, Australia, ³Monash University, Clayton, Australia, ⁴Austin Hospital, Heidelberg, Australia, ⁵Melbourne Genomics Health Alliance, Melbourne, Australia

Background and Aims

The detection of sequence variants and copy number changes can improve diagnosis, inform prognosis and guide treatment in patients with inherited bone marrow failure syndromes and aplastic anaemia. We aimed to prospectively assess the impact of comprehensive genomic evaluation on clinical outcomes in patients with genomically uncharacterised bone marrow failure syndromes.

Methods

In this multi-institute collaborative study supported by the Melbourne Genomics Health Alliance, all patients underwent both whole exome sequencing and accredited targeted panel sequencing using an 84-gene subset of the Peter MacCallum Cancer Centre PanHaem panel (Agilent SureSelect hybridisation based next generation sequencing panel). Sequence variants and whole genome copy number changes were assessed. Results were reviewed in multidisciplinary case conferences with treating clinicians present.

Results

100 patients were enrolled. Median age was 24 years (range 3 months - 80 years); 44% were under 18 years. The genomic findings confirmed, contributed to, or altered the established diagnosis of the patient in 66% of cases. The established clinical diagnosis was altered in multiple cases and previously undetected disease defining mutations were detected in *SAMD9L*, *FANCM*, *RPS19*, *HAX1*, *RPL35A*, *SBDS*, *TERT* and *RAD51C*. Genomic data impacted clinical decision-making in all cases where a pathogenic mutation was identified. Acquired mutations were detected predominantly in the adult cohort, with diagnoses of aplastic anaemia, paroxysmal nocturnal haemoglobinuria and hypoplastic myelodysplastic syndrome, including *PIGA*, *TET2*, *IDH2*, *SF3B1*, *U2AF1*, *TP53*, *RUNX1* and *ASXL1*, providing a molecular marker to be used for longitudinal monitoring and as a basis for assessment of clonal evolution.

Conclusion

Genomic characterisation is of significant clinical utility in patients with genetically uncharacterised bone marrow failure and can significantly influence diagnostic categorisation and subsequent clinical decision-making and healthcare utilisation.

074. Real world bortezomib use for multiple myeloma (MM): Data from the Australian/New Zealand (ANZ) Myeloma and Related Diseases Registry (MRDR)

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Background: Bortezomib is the standard of care for newly diagnosed (ND) MM. In ANZ the reimbursement of bortezomib for NDMM is based on data from clinical trials including the VISTA trial which included up to 48 bortezomib doses.

Methods: We reviewed NDMM patients treated with bortezomib registered from 01/06/2012-12/10/2017 on the MRDR, a prospectively maintained, "real-world" database from ANZ (30 sites). Baseline characteristics, therapies and outcome data were reviewed. Chi-square tests were used for analysis of categorical variables, rank sum tests for continuous variables and Kaplan-Meier analysis to estimate survival durations.

Results: 432 NDMM patients were available for analysis, of whom 311 (72%) received upfront ASCT. Disease response to bortezomib did not differ between patients who did and did not proceed to an ASCT (□PR 89.7% vs 84.7%, p=0.18). ASCT patients were younger (58.9y (52.8-64.2) vs 64.7y (59.3-68.5), p<0.001); received fewer bortezomib cycles (median 4 vs 5.5, p<0.001); and, were more likely to have received bortezomib via a 21-day cycle (40.7% vs 25%, respectively, p=0.008). There was no difference in disease response by cycle length (p=0.5) or route of bortezomib administration (IV or SC, p=0.28). Importantly, however, a better disease response was correlated with longer duration of bortezomib treatment (□PR, median 16 doses vs <PR, median 13 doses; p=0.002). Patients achieving □PR showed no differences in age (p=0.26), ECOG (p=0.8), ISS or R-ISS stage (p=0.65 and 0.91 respectively) or renal function (eGFR: 80 vs 76.5, p=0.5) when compared with those achieving <PR. Achieving □PR post-bortezomib induction therapy was associated with both improved progression free and overall survival (30.5m vs 20.5m, p=0.007 and not reached vs 60.9m, p=0.09, respectively.)

Conclusion: The underutilisation of available bortezomib may contribute to the shorter than expected survival of some NDMM patients in ANZ.

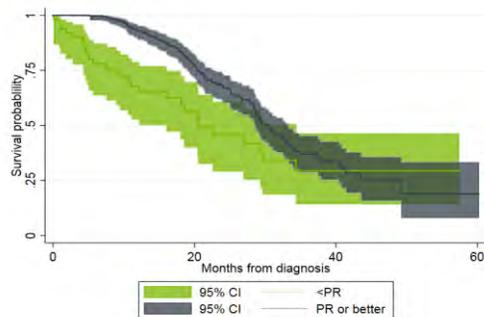


Figure 1. Progression-free survival by response to induction bortezomib

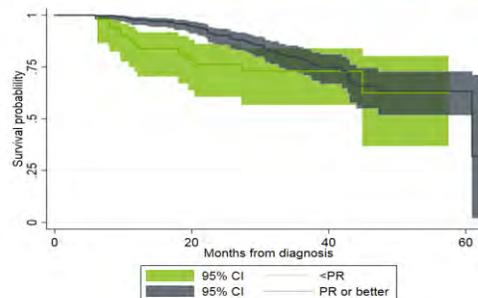


Figure 2. Overall survival by response to induction bortezomib

075. Identification of genetic pathways controlling resistance to standard combination chemotherapy in acute myeloid leukaemia

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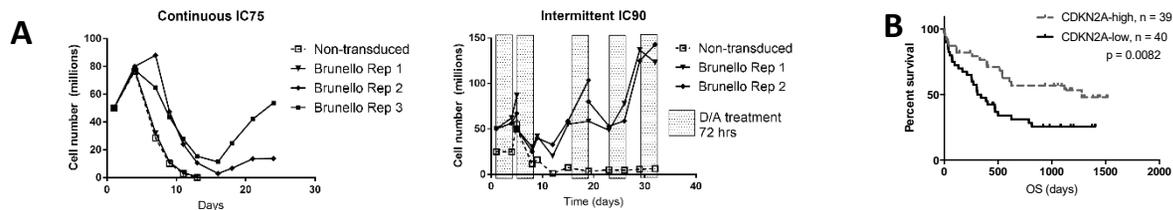
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Background and Aim: Resistance to chemotherapy, manifesting as refractory or relapsed disease, remains the largest cause of mortality in AML. Clonal evolution, through acquisition of new mutations or selection of resistant clones, is often responsible for relapse. We used a genome-wide CRISPR-Cas9 loss-of-function screen to identify deleted genes mediating resistance to Cytarabine (AraC) and anthracycline, Doxorubicin (Dox) in AML.

Methods: Dose response was defined using MTS viability assays, with synergism determined using the Chou-Talalay method. For the screen, Cas9-expressing OCI-AML3 cells were transduced with the Brunello whole genome gRNA library¹ and treated with either continuous, intermediate-dose or intermittent, high-dose AraC/Dox (A/D). gRNA representation was measured before and after treatment using next-generation sequencing. Enriched genomic targets were validated using individual gRNAs in independent cell lines and *in silico* using human clinical datasets.

Results: AraC and Dox were synergistic at ratios 10:1, 20:1 and 40:1; the most synergistic ratio (40:1) was used. By 12 days, both dosing regimens eliminated non-transduced controls and the bulk of library-transduced cells, however a resistant population emerged by 20 days, mimicking dynamics of relapsed or refractory disease (Figure A). Deoxycytidine kinase (DCK) and cyclin-dependent kinase inhibitor 2a (CDKN2A) were the top hits identified. DCK is essential for converting AraC to its active form and accordingly, AML cells with DCK deletion were resistant to AraC, but also to A/D, demonstrating that resistance to a single agent may result in therapeutic failure of combination regimens. CDKN2A encodes tumour suppressors, p14^{ARF} and p16^{INK4A}, and regulates cell cycle and apoptosis. In 3 independent AML patient cohorts²⁻⁴ (ref. 2 in Figure B), low CDKN2A expression conferred inferior survival. Functionally, CDKN2A knockout caused chemoresistance through enhanced proliferation and prevention of cell cycle arrest.

Conclusion: This study demonstrates the utility of genome-wide CRISPR screens to functionally capture genetic heterogeneity and evolution through chemotherapy in AML. This approach can identify clinically relevant gene mutations and therapeutic vulnerabilities.



References: ¹Doench, et al. 2016, *Nat Biotech*, ²Metzeler, et al. 2016, *Blood*, ³Wouters, et al. 2009, *Blood*, ⁴Bullinger unpublished.

076. Novel combination therapy targeting rDNA transcription and histone deacetylation provides effective treatment for multiple myeloma, and synergises in bortezomib-resistant MM

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Background: Multiple myeloma (MM) requires combination drug therapy to delay acquired drug resistance and clinical relapse. We co-developed CX-5461, a small molecule inhibitor of RNA polymerase I-mediated transcription⁽¹⁾, currently in phase I trials for relapsed haematological malignancies (PMCC). CX-5461 produces a nucleolar-localised DNA damage response (DDR), triggering a nucleolar stress response and killing malignant cells without inhibiting normal haematopoiesis^(2,3). Single-agent CX-5461 provides an impressive survival benefit in mouse models of B-cell lymphoma, acute myeloid leukaemia and now MM^(2,4,5). However, drug resistance eventually occurs, confirming the need for combination therapies.

Aim: To test the efficacy of CX-5461 in combination with the deacetylase inhibitor panobinostat, (prioritised from a boutique high-throughput screen of anti-myeloma agents), with a focus on the setting of resistance to proteasome-inhibitors (PIs).

Methods: We assessed the impact of CX-5461 and panobinostat on overall survival in 2 mouse models of MM, then surveyed the effects on cellular response and molecular markers of DDR. We developed bortezomib-resistant cell lines and an *in vivo* model of bortezomib-resistance to test this combination in the setting of PI-resistance.

Results: CX-5461 with panobinostat provides a significant survival advantage in the tvk*MYC and 5T33/KaLwRij models, with minimal bone marrow toxicity. The combination showed increased anti-proliferative effects and cell death. Interestingly, while both drugs are on-target, the downstream CX-5461-elicited DDR response is only moderately increased by the addition of panobinostat. Global transcriptome analyses to further explore the mechanism of synergy are underway. Importantly, the combination remains effective *in vitro* in the setting of PI-resistance and is currently being tested *in vivo*.

Conclusion: The rDNA transcription inhibitor CX-5461 synergises *in vitro* and *in vivo* with panobinostat, with retained efficacy in the setting of bortezomib-resistant cell lines.

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077. Assessment of Pneumococcal vaccination response in multiple myeloma

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Background

Patients with myeloma are at increased risk of infective complications and current international guidelines recommend immunization against *S. pneumoniae*, *H. influenzae* and influenza. Prior studies in the non-IMiD/proteasome inhibitor era assessing response to influenza vaccine have demonstrated poor seroconversion. We sought to assess the rate of seroconversion in patients with myeloma receiving modern treatment regimens.

Methods

Prospectively recruited, consenting patients had pneumococcal antibody titres performed pre- and six weeks post vaccination with Prevenar23. Patients were grouped based on whether they were newly diagnosed, or currently on (or within three months of ceasing) either PI or IMiD based therapy. A response was defined as a four-fold increase in antibody concentrations or an absolute value increase of >1.3 ug/mL and optimal response as response in >75% of tested.

Results

63 patients were enrolled, median age was 67 (range 43-89), and 42 were male. There was a difference between weekly dexamethasone dose (49mg vs 17.5mg vs 30.7mg, $p<0.001$), lines of therapy (0 vs 1.9 vs 0.89, $p=0.002$), paraprotein size (32 vs 5.5 vs 14.6g/L $p<0.001$) and level of residual gamma globulins (3 vs 5.4 vs 4.1g/L, $p=0.003$). Baseline anti-Pneumococcal IgG antibody geometric mean concentrations (GMCs) were 0.12, 0.21, 0.16, 0.47, 0.20, 0.34 and 0.20 respectively for serotypes 4, 6B, 9V, 14, 18C, 19F and 23F. One-way ANOVA demonstrated significant increases in antibody concentration with serotypes 14 and 18. 41 (80%) patients responded to at least one serotype. 18 (35%) had an optimal response to vaccination. There was one case of Pneumococcal infection following vaccination. Two-way ANOVA demonstrated a difference in response between serotypes ($p<0.001$) but not treatment group ($p=0.36$).

Conclusions

Baseline levels of pneumococcal immunity in this population are low. Although most patients are capable of seroconverting to at least one serotype, the rates of protective post-vaccination antibody concentrations remain low. Choice of therapy does not appear to influence seroconversion rates however this may be confounded by other clinical and disease related factors.

078. Discovery of MBD4 as a novel familial AML predisposition gene with implications beyond leukaemia

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Aims

We sought to understand the biological basis of AML with exceptionally high mutational burden (33-fold higher than is typical for AML) in 3 young patients (<35 years old), two of whom were siblings. Having identified *MBD4*, encoding a thymine glycosylase involved in repairing cytosine to thymine mutations, as the candidate gene, we investigated how germline *MBD4* loss predisposes to AML.

Methods

Next-generation sequencing was performed on patient samples from multiple treatment time-points. Functional loss of *MBD4* was confirmed using a glycosylase assay. The 10,683 cancers in TCGA were interrogated for *MBD4* mutations to define its broader role in cancer risk. *MBD4* was pursued in model systems, including a murine knockout model.

Results

The AMLs' mutational profile was highly distinct, with >95% cytosine to thymine mutations in CG dinucleotides (CG>TG). All patients had germline mutations causing complete loss of *MBD4* function. Methylation profiling indicated the mutations occurred at methylated cytosines.

While no AMLs in TCGA had *MBD4* loss, a uveal melanoma and a glioblastoma with inactivated *MBD4* were identified and these cancers exhibited the identical mutational profile. Whole genome sequencing of single myeloid progenitor colonies from *Mbd4*-null and wild-type mice confirmed the causal role of *MBD4* loss for the mutational signature.

The three AML patients harboured preleukaemic clones, all with monoallelic *DNMT3A* mutations, a finding typical of age-related clonal haematopoiesis in much older people. The emergent leukaemic clones carried biallelic *DNMT3A* mutations and either *IDH1* or *IDH2* mutations, a relatively uncommon combination observed in <3% of TCGA AMLs. All these driver mutations were CG>TG.

Conclusions

MBD4 loss results in a unique mutational signature from a failure to repair DNA damage at sites of methylated cytosines. Germline *MBD4* loss predisposes to AML via a conserved path involving *DNMT3A* and *IDH*. These results highlight the link between methylation damage and AML pathogenesis.

079. Hyperferritinaemia and the validation of an alternate Magnetic Resonance Imaging modality in assessment of Liver Iron Concentration

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Hyperferritinaemia is a common diagnostic problem and can be associated with increased overall iron body stores or may simply be a factor of an underlying inflammatory process. Determining whether a raised serum ferritin is indicative of an iron overload state can be problematic.

MRI (Ferriscan® R2) has generally replaced liver biopsy for assessment of liver iron concentration (LIC) and is the validated reference standard.(1, 2) However, due to long scan time and licensing restrictions this technique is expensive. R2* Relaxometry (R2*) is emerging as an inexpensive alternative. (3-7) The purpose of this study was to confirm an acceptable correlation between the reference standard R2 and R2* values and to assess the impact on clinical decision making.

Methods

Patient with 2 elevated serum ferritin levels (> 500 µg/L) underwent both MR imaging modalities. Clinician interpretation of R2* and R2 results were recorded, as well as patient management based on these results. Pearson's correlations, linear regression analyses, and receiver operator characteristic (ROC) curves were also calculated.

Results

Thirty-one patients were recruited (Table 1). Median serum ferritin at enrolment was 875 µg/L (506-3361 µg/L). A high degree of correlation between mean R2* and R2 was observed (slope ± SE of 43.6 ± 1.74 Hz mg/g; 95 % CI 40.05 to 47.22; P < 0.001) and with a Pearson correlation coefficient of r = 0.96 (95% CI 0.89 to 0.99; p <0.001, two tailed). As a tool to guide clinical assessment of hyperferritinaemia, clinical decision making was amended in 10/31 patients following the disclosure of R2* results. Clinically relevant iron overload was satisfactorily excluded in 10/31 patients using only R2* results. ROC curve analysis revealed a 92.3% sensitivity and 100% specificity for R2* values >86.55.

Conclusion

R2* MRI is a rapid and inexpensive alternative to R2 for assessment of hyperferritinaemia and estimation of LIC.

080. Individualized management plans for outpatients on anticoagulants undergoing invasive procedure or surgery: a single hospital experience

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Aim

Perioperative management of patients on Warfarin and direct oral anticoagulants (DOACs) can be complex, based on thrombotic risk, surgical procedure and bleeding risk. These patients require careful assessment and clear planning. This prospective analysis assessed the efficacy and safety of individualized management plans. This analysis includes all patients including patients with metallic heart valves.

Methodology

600 consecutive patients referred to our service for peri-operative anticoagulation management between May 2015 - February 2017 were included in the analysis.

Patient's on Warfarin were seen pre-procedure, counselled and given a copy of their individualised treatment plan. After two missed doses, the INR was checked and low molecular weight heparin (LMWH) was commenced if required. The patient received reminder phone calls at key time points prior to the procedure and on discharge, clear instructions on bridging doses of LMWH and timing of warfarin recommencement was provided. Care was then transferred back to primary care once re-stabilised on warfarin.

DOAC patients were not bridged, but had anticoagulation stopped at a time point dictated by their renal function and the planned procedure. Treatment was restarted 24 hours post operatively for low bleeding risk procedures, and at 48-72 hours for higher risk procedures.

Results

A total of 600 patients were referred, 519 of whom underwent a surgical procedure necessitating an anticoagulation management plan. 235 Were on Dabigatran and 333 on Warfarin. 1.3% experienced a thrombotic event, while major bleeding events were seen in 2%.

Conclusion

Our study showed lower thrombotic and bleeding complications compared to previously report bridging studies. Implementing evidence based individualised management plans, not only reduces complications, but also has positive effects on patient satisfaction, compliance and safety. Their use, in conjunction with existing clinical guidelines, should become an integral part of any thrombosis service.

081. Antenatal haemoglobinopathy screening. Correlation of phenotype and genotype. Time for a National Consensus Guideline

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Aim

Antenatal haemoglobinopathy screening is not standardised throughout Australia, with variation in access and practice, and increasing ethnic diversity of the Australian population. We aimed to correlate genotype and phenotype, in order to determine the optimal screening approach.

Method

An audit of molecular genetic haemoglobinopathy investigations at NSWHP Genetics and Haematology Randwick was performed between 1st Jan 2015 and 31st Dec 2017. Alpha gene MLPA and beta gene sequencing results were correlated with red cell indices and HbEPG/HPLC.

Results

In the 348 individuals undergoing *HBA* analysis, 152 variant alleles were observed. 13.5% carried a 2 gene deletion *in cis* and 7.2% carried a 2 gene deletion *in trans*. 4.9% had a 3 gene deletion. Mean MCV for 3 gene deletions was 61.8fl (50.4-75.6fl), 2 genes *in cis* was 67.2fl (58.1-83.9), 2 genes *in trans* was 70.4fl (46.7-76.0fl) and single genes was 76.3fl (58.0-86.0fl). There was excellent correlation between MCV and MCH ($R^2=0.9032$).

In the 163 individuals undergoing *HBB* analysis, 109 variants were detected including β^0 (33%), β^+ (25%), HbS (16%) and HbE (10%). The average HbA₂ for individuals with β^+ variants was 4.7% (2.4-6.0%) and β^0 variants 5.3% (3.3-6.2%). HbA₂ results in the 'non-diagnostic' range (3.2-3.9%) were observed in 7 *HBB* variants (3.2-3.9%) and 4 sequence-variant negative (3.4-3.7%). One silent β^+ was detected.

6% of individuals carried variants in both *HBA* and *HBB* genes. HbH/ICT testing resulted in 8 false positives (5%) and 3 false negatives.

Conclusion

In Sydney, the 2 alpha gene deletion *in cis* is the predominant 2 alpha gene mutation with the potential for Barts Hydrops Fetalis in offspring. The FBC parameters are useful for indicating the presence of the 2 gene deletion, but are unreliable for indicating a 1 gene deletion. HbA₂ results between 3.2%-3.9% require molecular testing to diagnose beta thalassaemia trait.

Next steps will be discussed, including collection of data nationally and development of an antenatal haemoglobinopathy screening guideline.

082. Final safety and efficacy data of long-term open-label weekly dosing of subcutaneous (SC) romiplostim in children with Immune Thrombocytopenia (ITP)

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Background: Children with ITP for ≥ 6 months who completed a romiplostim phase 1/2 or 3 study were eligible; final data are presented.

Methods: Initial dose was the parent study final dose/1 μ g/kg for those previously receiving placebo, adjusted weekly by 1 μ g/kg/week from 1–10 μ g/kg to target platelet counts of 50–200 $\times 10^9$ /L. Primary endpoint: incidence of AEs.

Results: Sixty-six patients entered the extension; 65 received romiplostim for ≤ 7 years. All 65 patients received their doses per-protocol $>90\%$ of the time; 37 patients received romiplostim until study end. Fifty-four SAEs occurred in 19 patients but were treatment-related in only 1 patient (concurrent G4 thrombocytopenia, G3 epistaxis, G2 anaemia). Bleeding AEs occurred in 57 patients; 3 AEs were deemed treatment-related. The most frequent bleeding AEs were contusion (51%), epistaxis (49%), petechiae (31%), and gingival bleeding (20%). No thrombotic events were reported. From week 2, median platelet counts remained $>50 \times 10^9$ /L; median platelet counts were generally $>100 \times 10^9$ /L from weeks 24–260. 61/65 patients had ≥ 1 platelet response. The median (Q1, Q3) % months responding was 93% (68%, 100%); the median (Q1, Q3) number of months responding was 30 (13, 43). 47/65 patients had a platelet response $\geq 75\%$ of the time and 38/65 had a platelet response $\geq 90\%$ of the time. Twenty-three patients received rescue medications; usage was highest in the first few months. Fifteen patients had treatment-free periods of platelet counts $\geq 50 \times 10^9$ /L for ≥ 24 weeks (remission; Table). Younger age at first dose ($p=0.0012$) and platelets counts reaching $\geq 200 \times 10^9$ /L in the first 4 weeks ($p=0.0035$) were predictive of developing treatment-free periods ≥ 24 weeks in a multivariate model.

Conclusion: Seven years of data show that $>90\%$ of children achieved a platelet response with romiplostim, most responding $\geq 75\%$ of the time. Romiplostim was mostly well tolerated. 23% of patients with longstanding ITP (median 3.5 years) discontinued all ITP medications for ≥ 6 months.

Patient number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Age at study end, years	17	8	12	9	6	13	19	8	8	9	5	5	7	15	15
Race	W	B	W	W	W	W	W	W	B	A	W	B	H	W	W
ITP Rx, #, prior to studies	3	6	4	2	2	3	4	5	2	1	2	1	4	4	3
Baseline platelet count ($\times 10^9$ /L) [†]	10	7	5	19	7	82	17	22	26	29	30	1	11	10	7
Romiplostim, years [‡]	6	4.4	4.2	0.7	2.1	3.9	3.5	1.6	0.8	0.9	0.7	0.9	2.3	2.3	1.1
Maximum dose, μ g/kg	10	8	9	5	10	2	2	1	3	1	2	1	9	4	10
ITP, years [‡]	7.1	5.5	5.1	1.3	4.3	11	13	2.6	1.4	2.3	2.9	3.5	3.5	5.1	2.6
ITP remission, years	1.1	2.1	1.1	1.6	1.0	0.8	0.9	1.7	2.1	1.1	0.6*	0.6	0.8	0.6	0.4 [‡]

A, Asian; B, Black; H, Hispanic/Latino; Rx, therapy; W, white. [†]At start of parent study (not extension). [‡]At remission start. *Remission ended before study end.

[‡]This patient met remission criteria for 0.4 years on study and 20.5 years post study.

083. Paroxysmal nocturnal haemoglobinuria (PNH) in Australia: results from the PNH Registry 7-years following eculizumab reimbursement

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Paroxysmal nocturnal haemoglobinuria (PNH) is a rare haemopoietic stem cell disorder characterised by chronic, complement-mediated haemolysis and life-threatening thrombosis¹. Eculizumab, a complement C5 inhibitor, has been demonstrated to reduce both intravascular haemolysis and thrombosis, and to improve survival in PNH patients². We present updated data from Australian patients enrolled in the International PNH Registry 7 years following reimbursement of eculizumab.

As of January 2018, 111 Australian patients from 22 sites were enrolled in the PNH Registry. 70 patients were eculizumab-treated (ET) and 41 patients were eculizumab-naive (NT). At enrolment 80 patients (72%) were aged <50 years and 31 patients (28%) ≥50 years. In the ET cohort the mean age at diagnosis was 32 years, median granulocyte PNH clone size was 87.5% and eculizumab was commenced a mean of 8.0 years from diagnosis. The NT cohort was older with a mean age at diagnosis of 41 years.

Mean follow-up for the ET cohort was 5.1 years. In evaluable patients of this cohort at last follow-up, there was a marked improvement in LDH ratio from a median of 4.2 to 1.1 x ULN with median increases in haemoglobin of 5.5 g/L and in granulocyte PNH clone size of 5.6%. Of the 27 evaluable transfusion-dependent patients, 16 became transfusion-independent. Improvements in physician-reported PNH symptoms of abdominal pain, dysphagia and fatigue were observed but not erectile dysfunction. 5 patients developed physician-reported renal dysfunction. Additionally, 3 patients had thrombotic events, 2 patients developed a bone marrow disorder (1 myelodysplasia, 1 'other'), 2 patients had pregnancies, and 3 deaths were reported.

Data from the Australian PNH Registry cohort reveals that eculizumab treatment results in a sustained improvement in LDH, PNH symptoms and transfusion-independence, and compared to historical cohorts a reduction in the incidence of thrombotic complications.

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084. Anthocyanin supplementation improves blood glucose, lipid profile and inflammation in a population with high risk of thrombosis

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Background

Anthocyanins as a potential antioxidant have been shown atheroprotective effect on thrombotic formation.

Objective

This study aimed to investigate the antithrombotic effect berry-derived anthocyanin supplements on thrombosis risk factors in a population with high risk atherosclerosis.

Design

A total of 52 participants in two groups of normal healthy and at risk (age 25-75y) were given 320 mg anthocyanin twice daily for 4 weeks in a blinded randomized controlled trial.

Results

Anthocyanin consumption for four weeks, significantly decreased fasting blood glucose (FBG) concentration 11.51 % in at risk group. Similarly, it was observed a significant reduction on triglyceride and low density lipoprotein (LDL) levels with 24.86% and 25.7% respectively in the at risk group compared with normal control group ($p < 0.05$). Moreover, anthocyanin supplementation reduced high sensitivity C- reactive protein (hs-CRP) as inflammatory biomarker (18%, $p < 0.05$) with no change in normal group. The positive correlation also established in the at risk group between decreased hs-CRP values and the levels of LDL-C and FBG ($p < 0.05$).

Conclusion

Anthocyanin supplementation in at risk population of atherosclerosis improves lipid profile, inflammatory biomarker and blood glucose concentrations and enhance cholesterol efflux to serum.

Keywords

Anthocyanin, thrombosis, platelets activation markers, at risk population.

085. Synergy between IBL-202 and venetoclax overcomes TP53-induced drug resistance under conditions that mimic the chronic lymphocytic leukemia (CLL) tumour microenvironment

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Background

TP53 mutations are associated with shorter TFS and OS in patients with CLL after frontline therapy with fludarabine-based regimens (1). Novel agents such as ibrutinib and venetoclax, which inhibit Btk and Bcl-2 respectively, are important treatment options in CLL, particularly for patients with *TP53* loss or mutation, where early access to these agents is advocated (2). In spite of good evidence of response to these agents there is no evidence these are curative and *TP53* lesions remain an indication of poor outcome (3).

IBL-202 (Inflection Biosciences Ltd) is a dual inhibitor of the P13K and PI3-kinases, which we have recently shown to be effective against CLL cells cultured under *in vitro* models that recapitulate the CLL tumour microenvironment (4). Here, we demonstrate synergy between IBL-202 and Venetoclax against CLL cells and show that this drug combination is particularly effective against CLL cells with defective *TP53* signaling.

Methods

Stable genetic knock-out of *TP53* in the OSU-CLL cell line (OSU-CLL-*TP53ko*) was achieved using the CRISPR-Cas9 system. Primary CLL cells, OSU-CLL, OSU-CLL-*TP53ko* and CD40L-expressing fibroblasts were cultured in RPMI + 10% FCS at 37°C. Cell viability was assessed using the mitochondrial membrane potential dye, DiIC5, propidium iodide and flow cytometry.

Results

IBL-202 in combination with Venetoclax was significantly more effective than Venetoclax alone when tested against primary CLL cells in a stromal co-culture model. *TP53* knock-out significantly reduced the sensitivity of OSU-CLL cells to both IBL-202 and Venetoclax. IBL-202 combined with Venetoclax was significantly more effective than either agent alone against both the OSU-CLL (p=0.006) and OSU-CLL-*TP53ko* (p=0.008) lines.

Conclusion

IBL-202 in combination with Venetoclax is effective against CLL cells *in vitro* under conditions that mimic the tumour microenvironment and against *TP53-ko* cells. Our data suggest that the combination may represent an effective treatment strategy particularly for patients with *TP53* lesions.

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086. More than a BTK inhibitor: Ibrutinib impairs cytotoxic T cell responses

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Aim: Ibrutinib is increasingly being incorporated into the clinical management of B cell malignancies. This study aimed to determine if ibrutinib and more selective BTK inhibitors impact the cytotoxic capacity of T cells. Ibrutinib inhibits all Tec family kinases including ITK at clinically meaningful concentrations and may exert a Th1 selective pressure whilst sparing Th1 and CD8 T cell function¹. However this has not been shown in patients². More selective BTK inhibitors have also been developed including zanubrutinib and acalabrutinib. However the impact of ibrutinib or other BTK inhibitors on T cell function remains unclear.

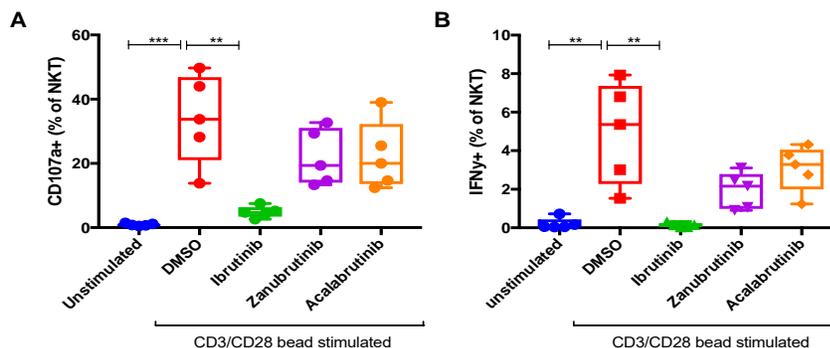
Method: PBMC were isolated from six treatment-naïve CLL patients at the Royal Melbourne Hospital. Healthy donor NKT cells were FACS sorted from PBMC and ex vivo expanded. Cells were treated in vitro with 1µM ibrutinib, zanubrutinib or acalabrutinib. CD8 T cell and NKT cell response to CD3/CD28 stimulation and NKT response to α-Galactosylceramide loaded CLL cells was assessed by flow cytometry (CD107a, Granzyme B and IFN γ). Statistical analysis was performed using GraphPad Prism. Differences between drug treatments was assessed by Friedman ANOVA with Dunn's multiple comparisons test.

Result: Ibrutinib, but not zanubrutinib abrogates CD8 T cell degranulation and IFN γ production in response to CD3/CD28 stimulation ($p < 0.01$). Similarly, NKT cells treated with Ibrutinib, but not zanubrutinib or acalabrutinib did not degranulate (Figure 1a) or produce IFN γ (Figure 1b) in response to either CD3/CD28 bead stimulation or α-Galactosylceramide loaded CLL cells.

Conclusion: The off-target inhibition of ITK and other members of the Tec family profoundly inhibits T and NKT cell cytotoxic responses. Understanding how BTK inhibitors alter the function of cytotoxic cells is essential to the combination of these therapies with immunotherapies and may inform the use of these therapies in the context of stem cell transplants and adoptive cell therapies.

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Figure 1



087. Maintenance dosing of Ibrutinib for Chronic Lymphocytic Leukaemia (CLL) / Small Lymphocytic Lymphoma (SLL) patients

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Aim

It has been established that treatment with ibrutinib is often discontinued due to intolerance rather than disease progression and strategies such as reduced dosing or cycling of dose have been proposed, but not explored. We aim to consider the effects of reduced frequency ibrutinib dosing in terms of tolerance and efficacy in CLL/SLL patients.

Method

A retrospective data audit was conducted on all patients who had received ibrutinib maintenance dosing (280 – 420 mg second daily) at Southern Sydney Haematology. These patients had all achieved CR or VGPR and been stable on ibrutinib for 12-24 months. Criteria being assessed included total time on therapy, time on maintenance dosing, effects of maintenance dosing on any side effects, evidence of relapse, and basic demographic data.

Result

Out of 40 patients treated with ibrutinib, a total of 15 patients (9 males and 6 females) had commenced maintenance dosing. Age range 63 – 77. Total time on therapy ranged 34-39 months. Time on maintenance dosing ranged 9-27 months. One patient developed new onset atrial fibrillation seven months after commencing maintenance dosing that was effectively medication controlled. Seven patients had developed various side effects on full dose therapy but none of these side effects recurred on maintenance dosing. Time to onset of side effects varied greatly. No patients have relapsed on maintenance dosing and the entire cohort remain on maintenance therapy at time of writing.

Conclusion

Based on findings from this cohort, maintenance dosing of ibrutinib (280 – 420 mg second daily) for patients who have achieved CR or VGPR and been stable on therapy for at least 12-24 months would appear to be sufficient to maintain remission, and a good way for managing some side effects that impact on quality of life and medication compliance. Further studies are warranted to better assess maintenance dose protocol effectiveness.

088. High-grade transformation of marginal zone lymphoma: a clinico-genomic description

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Aim

Marginal zone lymphoma (MZL) is an uncommon, indolent, B-cell non-Hodgkin lymphoma capable of high-grade transformation (tMZL). We aimed to describe the clinical features, outcomes and genomic aberrations of a large cohort of tMZL.

Method

Cases of tMZL managed at the Peter MacCallum Cancer Centre (PMCC) during 2002-2017 were included. DNA extracted from formalin-fixed, paraffin-embedded archival tissue was sequenced using the PMCC PanHaem hybridisation capture panel which detects gene variants, low-coverage whole-genome copy number variations and *IGH* gene translocations.

Result

Twenty seven patients were included (16 males). MZL subtypes were: 8 splenic, 10 nodal and 9 MALT. Fifteen patients had tMZL at first presentation – the median time to transformation in the remainder was 54.5 months.

The median age at transformation was 65 years. Most transformations were to DLBCL alone (89%, 24/27) and were usually of advanced stage (81%, 22/27). Where cell of origin was assessed this was usually of non-GCB type (73%, 11/15).

First-line treatment was with anthracycline-containing chemo-immunotherapy in the majority of cases (74%, 20/27). 44% (12/27) of patients underwent autologous stem cell transplantation (ASCT) during first response. The CR rate post first-line treatment was 85% (23/27) – relapse occurred in 48% (13/27). Median PFS and OS were 37 and 74 months respectively.

Genomic analysis was performed in 10 cases: recurrent aberrations primarily affected genes involved in cell cycle regulation (e.g. *CDKN2A*, *CCND1* and *CCND3*), epigenetic regulation (e.g. *ARID1A*, *EP300* and *KMT2C*), lymphocyte development and signalling (e.g. *CD79B*, *BRAF* and *PIM1*), *MYC* and *TP53*. Concurrent *MYC* and *BCL2* translocations were detected by FISH and/or sequencing in 9% (1/11) of cases.

Conclusion

We have characterised a large cohort of tMZL. In the absence of randomised trial data the favourable CR rate, PFS and OS support the use of anthracycline-containing chemo-immunotherapy and ASCT where appropriate as first-line therapy. The significant relapse rate indicates a need for effective second-line therapies. Dysregulation of the cell cycle, epigenetic processes, lymphocyte development and signalling, *MYC* and *TP53* were implicated in the pathophysiology of tMZL.

089. The outcomes of stage I and II follicular lymphoma in the era of 18F-FDG PET-CT staging: An international collaborative study from the Australian Lymphoma Alliance

Tobin J¹, Cheah C², Rule G², Kridel R³, Ratnasingam S⁴, Dunduru C⁴, Janowski W⁵, Simpson J⁵, Morris K⁶, Galikanokus J⁶, Kansara R⁷, Johnstone A⁸, Tan X⁸, Opat S⁹, Talaulikar D¹⁰, Hodges G¹¹, Hawkes E¹², Campbell R¹², Abro E¹³, Tneh S¹³, Tam C¹⁴, Cochrane T¹⁵, Darch J¹⁵, Gilbertson M¹⁶, Wong J¹⁶, Villa D¹⁷, Hapgood G¹

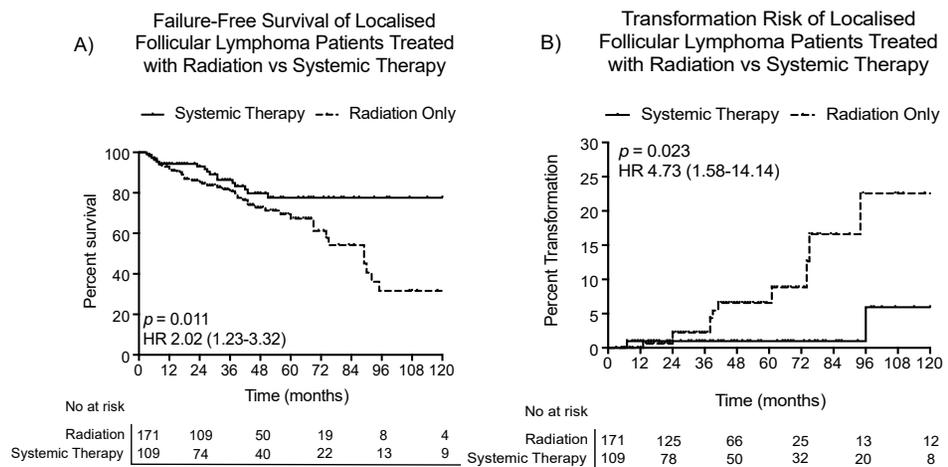
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Background: Localised follicular lymphoma (FL) is considered potentially curative when treated with radiotherapy (RT). Despite this, 50-60% of patients relapse by 10 years and 1-2% of patients annually transform to aggressive lymphoma with a guarded prognosis. A recent randomised-controlled trial (NHL-LOW5) demonstrated the addition of chemoimmunotherapy to RT improved progression-free survival in localised FL; however, only half were staged with a PET/CT. Compared with CT, 20-60% of cases are up-staged using PET/CT imaging. Consequently, this trial has been criticised regarding its applicability to modern cohorts. The aim of our study was to compare real-world treatment outcomes in rigorously-staged localised FL patients treated with radiation alone or systemic therapy.

Aims & Methods: We conducted an international, multicentre retrospective study of stage I and II FL patients staged with a bone marrow biopsy and PET/CT. Eligible patients were >18 years, with newly-diagnosed grade 1-3A FL, ≥ 3 months follow-up and no prior therapy. The primary outcome measures were Failure-Free Survival (FFS) and risk of transformation.

Results: A total of 388 patients treated at 16 centres in Australia and Canada between 2005-2017 were studied. Median follow up was 45 months (range 3.1 – 164.0). 5-year FFS and OS was 73.5% (95% CI 66.0-78.5) and 94.4% (95% CI 89.4-93.6) respectively. Generally, high-risk features were enriched in the systemic therapy group. Compared with RT alone, systemic therapy demonstrated significantly improved FFS (10-year FFS 78.3% vs 32.1% (HR 2.02, $P=0.011$) and a lower risk of transformation (HR 5.03, $P=0.018$) (Figure 1). The addition of maintenance rituximab to systemic therapy further improved FFS (HR 3.96; $P=0.02$).

Conclusion: Patients treated with systemic chemoimmunotherapy demonstrated a superior FFS and lower risk of transformation compared to RT alone. This is consistent with the NHL-LOW5 trial and suggests systemic therapy is effective first-line treatment in stage I and II FL.



090. Median 3.5-year follow-up of ibrutinib treatment in patients with relapsed/refractory mantle cell lymphoma (MCL): a pooled analysis

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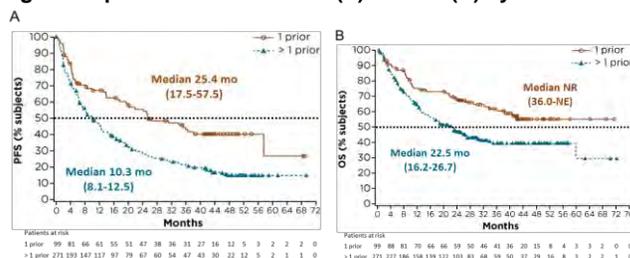
Aim: We previously reported a pooled analysis of 370 ibrutinib-treated patients with relapsed/refractory MCL in the PCYC-1104 (n=111), SPARK (n=120), and RAY (n=139) studies (median follow-up 24 months). Here, we present median 3.5-year follow-up, including additional follow-up of 87 patients rolled over to the long-term access study CAN3001. **Methods:** Patients in SPARK, RAY, and PCYC-1104 received ibrutinib 560 mg po QD until progression or unacceptable toxicity. Analysis excluded patients who crossed over to ibrutinib from the comparator arm. Investigator-assessed tumor response, PFS, and OS, plus grade ≥ 3 treatment-emergent adverse events (TEAEs) were evaluated. **Results:** Median duration of follow-up (N=370) and treatment exposure was 41.1 (95% CI, 37.3-42.5) and 11.1 (range, 0.03-72.1) months, respectively, with median 2 (range, 1-9) prior lines of therapy (LOT) before ibrutinib. 83 and 40 patients had ibrutinib exposure ≥ 3 and ≥ 4 years, respectively. 54/87 (62.1%) patients in CAN3001 remain on ibrutinib. Median PFS and OS in the overall population, and in subgroups by prior LOT and best response, are shown in the Table and Figure. At 2 and 3 years, respectively, 36% (95% CI, 0.31-0.42) and 26% (0.20-0.32) of patients were progression free, and 53% (0.47-0.58) and 45% (0.39-0.50) were alive. CR rate increased to 26.5% with 41 months' follow-up. DOR was 55.7 months in complete responders and 2 times longer with 1 versus >1 prior LOT (Table). Grade ≥ 3 TEAEs occurred in 295 (79.7%) patients; events decreased over time after Year 1. Cumulative incidence of any major hemorrhage was 7.3%; grade ≥ 3 atrial fibrillation incidence was 5.9% and led to dose reductions in 2 (0.5%) patients and no discontinuations. Treatment-emergent serious AEs (SAE) occurred in 229 (61.9%) patients; SAEs decreased over time. **Conclusions:** Clinical outcomes were best for patients achieving a CR or treated with ibrutinib at first relapse/progression. Grade ≥ 3 AEs/SAEs decreased over time.

Table. PFS, OS, Clinical Response, and DOR for Pooled Analysis including CAN3001

End point	Overall (N=370)	Prior lines of therapy		Best response	
		1 (n=99)	>1 (n=271)	CR (n=98)	PR (n=160)
PFS - months, median (95% CI)	12.5 (9.8-16.6)	25.4 (17.5-57.5)	10.3 (8.1-12.4)	57.5 (42.8-NE)	12.9 (10.4-16.8)
OS - months, median (95% CI)	26.7 (22.5-38.4)	NR (36.0-NE)	22.5 (16.2-26.7)	NR (59.9-NE)	26.2 (21.6-34.7)
ORR, n (%)	258 (69.7)	77 (77.8)	181 (66.8)		
CR	98 (26.5)	36 (36.4)	62 (22.9)	--	--
PR	160 (43.2)	41 (41.4)	119 (43.9)		
SD	43 (11.6)	11 (11.1)	32 (11.8)		
DOR ^a - months, median (95% CI)					
All responders	21.8 (17.2-26.4)	35.6 (23.2-NE)	16.6 (12.9-21.3)	--	--
CR	55.7 (40.7-NE)	55.7 (35.6-NE)	NR (39.9-NE)		
PR	10.6 (7.7-14.9)	22.3 (12.1-34.4)	8.5 (6.2-12.5)		

CI, confidence interval; CR, complete response; DOR, duration of response; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response, SD, stable disease. ^aKaplan-Meier estimate.

Figure. Kaplan-Meier Plot of PFS (A) and OS (B) by Prior LOT



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091. Tissue engineering of an orthotopic humanised bone-organ as a platform for preclinical multiple myeloma research

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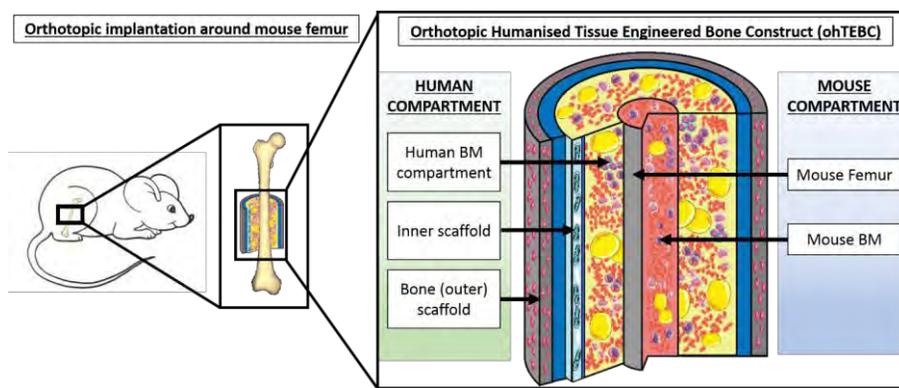
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Multiple Myeloma (MM) is a B cell neoplasm that remains largely incurable. Despite numerous efforts to develop new therapeutic strategies for MM, most drugs fail clinical trials, mainly due to the lack of clinically predictable animal models. There is an unmet need to develop a model that mimics key aspects of MM, such as tumour-microenvironment interactions. We sought to address the current lack of reliable preclinical platforms that feature a humanised immune system together with a humanised tumour microenvironment and primary MM cells in order to test immunotherapeutic strategies.

Here we developed a fully personalised MM animal model that is able to engraft patient cancerous cells into an orthotopic humanised tissue-engineered bone construct (ohTEBC) to create a fully functional humanised bone marrow (hBM) niche and a human haematopoietic system.

The ohTEBC was generated from melt electrospun medical-grade polycaprolactone tubular scaffolds and seeded with human bone osteoprogenitor cells, while the hBM niche was engineered with the MM patient's own BM cells in a hydrogel. This ohTEBC also contained human haematopoietic stem cells that contributed to form a humanised immune system. 8 weeks after orthotopic implantation around the right femur of NSG mice, the ohTEBC formed an organ bone containing a cortical shell infiltrated with human BM that was composed of human cells and extracellular matrix components. hCD45⁺ cells derived from the implanted hCD34⁺ were found in mouse BM, human BM compartment, spleen and peripheral blood, reaching levels of as high as 62% by week 7. Interestingly, part of the construct underwent endochondral ossification, forming new mineralised tissue. hCD45⁺ cells were also recruited towards the newly formed bone, suggesting the development of new BM tissue.

We demonstrated that this tissue-engineered MM model holds the potential as a unique and patient-specific drug testing platform, not only for common drugs but also for immunotherapy.



092. Beyond a marker: a novel role of CD45 in myeloma metastasis

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Aim

In multiple myeloma (MM) loss of CD45 expression has been correlated with earlier disease progression and inferior treatment outcomes. Our previous *in vitro* studies demonstrated a 'metastatic' phenotype for CD45 negative MM, but the underlying mechanism(s) remain unknown. Proline-rich kinase (Pyk2) and downstream target of CD45, Src family kinases (SFKs), are associated with cell migration in many malignancies. Here we utilise CRISPR-Cas9 system to knockout (KO) CD45 from HMCLs to evaluate the role of CD45/SFKs/PYK2 in metastasis.

Method

CRISPR-Cas9 mediated PTPRC knockout (KO) in a HMCL, OCI-MY1, was used to investigate the role of CD45/SFKs/Pyk2. Phenotypic and transcriptional changes were identified by immunoblotting, modified Boyden chamber assays and RNA sequencing. SFK inhibitor (Saracatinib), PYK2 inhibitor (PF573228) and siRNAs were used to validate the role of SFKs and PYK2 in migration.

Result

The inhibitory phosphorylation on Lyn p-Y507 (the predominate member of SFKs in MM) was significantly enhanced in the absence of CD45 phosphatase activity in the OCI-MY1 CD45^{KO} cells, leading to the subsequent inactivation at Y416. Pyk2 activity was also dysregulated. These cells demonstrated a significant reduction in homing capacity towards healthy and malignant bone marrow stromal cells (reduced to 11.5% and 2.7%, p<0.0001, respectively) compared with the WT cells. Saracatinib-treated and PF573228-treated WT cells showed 47.3% (p<0.0001) and 71.3% (p<0.01) reduction in homing capacity. Also, silencing Lyn and Fyn with siRNAs in WT cells demonstrated similar effects (76%, p<0.01 and 55%, p<0.001 respectively), confirming the reduction in homing potential of CD45^{KO} cells was due to their lower SFK activity. RNA sequencing identified differentially expressed migration-related genes in the CD45^{KO} cell. Further *in vivo* studies illustrating metastatic pattern are in progress.

Conclusion

Our data demonstrated CD45/SFK/Pyk2 play an important role in regulating MM homing towards bone marrow, providing a novel approach for early detection and intervention of metastatic myeloma.

093. Autologous stem cell transplant causes permanent defects in CD4+ T cells in patients with multiple myeloma

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Aim

Patients with multiple myeloma (MM) acquire immune paresis due a combination of the effects of cumulative chemotherapies, autologous stem cell transplant (ASCT) and an ageing T cell population in a chronically inflammatory environment. In our laboratory, we have previously analysed T cell populations in newly diagnosed multiple myeloma (NDMM) and relapsed/refractory multiple myeloma (RRMM) patients. We found that there is a significant decline in circulating CD4⁺ T cells and loss of naïve T cells (with a reciprocal increase in the proportion of CD8⁺ T cells and antigen-experienced T cells) in RRMM patients compared to NDMM and age-matched controls¹. We hypothesized that ASCT and corticosteroid exposure play a role in accelerating the reduction in CD4:8 ratio and the loss of circulating naïve T cells in MM patients.

Method

Using flow cytometry, we analysed T cell subsets from NDMM patients treated with lenalidomide and dexamethasone (len/dex) at serial timepoints: after 4 cycles of len/dex induction ($n=21$), 6 months post-ASCT with ongoing len/dex therapy ($n=21$), and at last follow-up ≥ 12 months post-ASCT ($n=21$). We compared with RRMM patients treated with 6-9 cycles of len/dex ($n=13$) and age-matched normal donors ($n=10$). Statistical significance was determined using the Mann-Whitney test or, for grouped analysis, the student's t test using the Holm-Sidak method.

Result

We confirmed that these T cell changes occur post-ASCT and do not recover, suggesting that this treatment has an irreversible effect on the T cell pool. Furthermore, PD1 expression is upregulated post-ASCT and remains elevated in CD4⁺ T cells (but not CD8⁺ T cells) 12 months post-ASCT, perhaps explaining their inability to undergo effective homeostatic proliferation².

Conclusion

ASCT remains a backbone of myeloma treatment in medically fit patients. However, this leads to significant permanent defects in the T cell repertoire, which may have unintended adverse outcomes.

094. The impact of a specialised exercise intervention on quality of life in people with blood cancer

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'Fit to Thrive' (FTT) is an individualised, participant-focussed exercise program available to people with blood cancer who are clinically able to carry out exercise. This study aimed to assess the effect of FTT on health-related quality of life (HRQoL) in people with blood cancer.

The 12-week FTT program utilises progressive aerobic and resistance training, supervised by an Accredited Exercise Physiologist, and delivered in two, 1-hour group sessions and three home-based sessions per week, with associated psychosocial and peer support. HRQoL was measured using the 36-item Short Form Survey Instrument (SF-36) and the Functional Assessment of Cancer Therapy General (FACT-G) at baseline, immediately post-intervention and, for a subset of participants, at 3 months post-intervention. Minimally important differences (MID) involved a change of 2 points for the SF-36 and 3 points for the FACT-G.

Participants (n=106) who attended the FTT program between 2014 and 2016 were included in this analysis, with 36 participants followed up 3 months post-intervention. The SF-36 physical component summary (PCS) significantly increased (+4.99 [95% CI 3.29-6.68] p<0.001) immediately following the intervention, with 68% (n=72) of participants achieving the MID. Whilst all mental health domains significantly increased, the improvement in the SF-36 mental component summary did not achieve statistical significance (+2.36 [95% CI -0.06-4.78] p=0.06), with 51% (n=54) achieving the MID. FACT-G scores improved significantly from pre- to post-intervention (+5.90 [95%CI 2.52-8.47], p<0.001) with 58% (n=62) of participants meeting the MID. MID improvements in PCS and FACT-G were maintained in 77% (n=20/26) and 95% (n=19/20) of participants 3 months following completion of the program.

The FTT program is effective in improving and maintaining HRQoL. An individually-prescribed exercise program supervised by an Accredited Exercise Physiologist should be considered as part of standard care to improve HRQoL in patients with stable blood-borne cancer.

095. The "Comenzo" split-melphalan conditioning protocol facilitates the use of autologous stem cell transplantation in systemic AL amyloidosis treatment

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Introduction

Autologous stem cell transplant (ASCT) in systemic AL amyloidosis (AL) is effective, however often limited by cardiac involvement. The "Comenzo" protocol, utilising melphalan conditioning split over two days, is used in many amyloidosis centres to mitigate toxicity without compromising response.

Method

We conducted a single-centre, retrospective, observational study of clonal and organ response rates, survival and toxicity of ASCT in AL patients using the "Comenzo" protocol between September 2014 and May 2018.

Result

Twelve patients (male:female 11:1) were identified. Median age was 64 (range 44-71). Revised Mayo Staging I-IV was 4, 3, 3, and 2 respectively. Ten had plasma cells >10% on diagnostic bone marrow biopsy. Amyloid organ involvement included cardiac (n=8), renal (n=4), nodal (n=2), nerve (n=1), hepatic (n=1) and gastrointestinal (n=1).

Induction therapy was VCD (n=11), RCD (n=1). All achieved a PR or greater, pre-ASCT. Eleven received "Comenzo" split-dose melphalan 200mg/m² (total), one received 140mg/m² (total) since age >70 years.

Median engraftment time was 18 days (range 13-25). Six (50%) experienced major complications including ICU admission (n=4), arrhythmias (n=4), kidney injury (n=4; two temporary haemofiltration), and grade >2 mucositis (n=2). Fluid overload and diarrhoea were universal (n=12). One patient with cardiac amyloidosis died, day +9, from decompensated heart failure and septicaemia despite inotrope support.

Four were in CR pre-ASCT. Six improved clonal responses with ASCT (1 PR to CR, 3 PR to VGPR, 2 VGPR to CR).

Median follow-up is 16 months (range 6-31). Cardiac responses (>30% NTproBNP decrease) occurred in 5, renal responses (>50% proteinuria decrease) in 1. The patient with neuropathy reported improvement. One patient developed clonal and organ progression at 23 months.

Conclusion

The ASCT "Comenzo" protocol in AL confers excellent clonal and end-organ responses, with tolerable toxicity and engraftment timeframes. This, together with careful fluid management, facilitates ASCT in AL patients with low-grade cardiac disease.

096. Velcade, Cyclophosphamide and Dexamethasone (VCD) as front-line treatment for Systemic AL-Amyloidosis (AL): a “real-world” experience at a single centre

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Introduction: “VCD” as first-line treatment for AL is reported to have excellent clonal responses (Venner et al, 2012; Mikael et al, 2012). We sought to undertake a “real-world” local analysis of VCD in this setting.

Methods: We conducted a single-centre, retrospective, observational study of response rates and overall survival (OS) for patients undergoing VCD frontline treatment for AL September 2014 and May 2018.

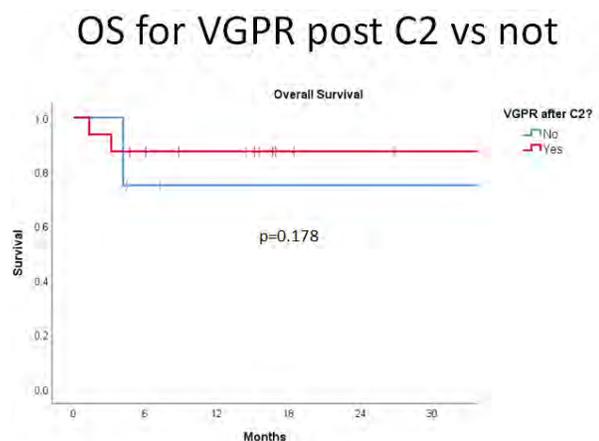
Results: 30 patients (male 16, female 14) were identified. Median age was 64 (range 44-83). Revised Mayo Staging I-IV was 3 (10%), 7 (23.3%), 11 (36.7%), and 9 (30%) respectively. Amyloid organ involvement included cardiac in 24 (80%), renal in 15 (50%), peripheral neuropathy in 8 (26.6%), and autonomic neuropathy in 4 (13.3%).

Overall haematological response (PR or better) was observed in 28 (93%), VGPR or better in 22 (73%), and CR in 11 (37%). 23 (77%) achieved PR after completing one cycle of VCD, 20 (67%) achieved VGPR after completing two cycles.

Median follow-up was 14 months (range 1-43 months). Twelve month OS is 75% (15/20 assessable patients). 5 patients died - 2 were non-responders, none achieved CR. Median NTproBNP concentrations were 848pmol/L (range 188-2095) and 393pmol/L (range 11.5-4130) respectively in deceased versus alive cohorts.

Cardiac responses (>30% NTproBNP decrease) occurred in 10 (66.7%) of 15 patients with available serial NTproBNP. 7 patients underwent ASCT consolidation. Twelve month OS for patients who achieved a VGPR by cycle 2 was 88% (14/16) vs 50% (2/4) for those who did not (p=0.178).

Conclusion: Our study confirms that in the “real-world” setting, VCD is excellent treatment for AL with encouraging clonal and organ responses. With limited follow-up, our study suggests that patients with brisk, deep clonal responses and less advanced cardiac disease have improved outcomes. The ANDROMEDA trial, adding daratumumab to VCD to hopefully improve OS, is currently underway.



098. Treatment of patients with relapsed/refractory myeloma

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The past few years, several new combination therapies have become available for relapsed and refractory myeloma. When should particular combinations be considered? Are there optimal sequences? Driven by all treatment advances myeloma patients are living longer and longer, reflected in a skyrocketing prevalence of myeloma. Due to the lack of established curative treatment, most patients will continue to relapse. Consequently, in myeloma care, the unmet needs are greater than ever. Many new combinations are in development. Where is the field going?

099. An update in amyloidosis

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Amyloidosis is a rare but devastating condition caused by deposition of misfolded proteins as aggregates in the extracellular tissues of the body, leading to impairment of organ function. High clinical suspicion is required to facilitate early diagnosis. Correct identification of the causal amyloid protein and extent of organ involvement is absolutely crucial for clinical management in order to avoid misdiagnosis and inappropriate, potentially harmful treatment, to assess prognosis and to offer genetic counselling if relevant. Improved diagnostic techniques, particularly in the assessment of cardiac amyloidosis, have entered mainstream clinical practice in Australia. Therapeutic advances including anti-sense oligonucleotide or chemotherapy mediated knockdown of the amyloidogenic protein, protein stabilisers and disrupters, and anti-amyloid fibril monoclonal antibodies have completed phase 3 clinical trials and will alter the therapeutic landscape of amyloidosis. The Australasian Amyloidosis Network has formed to promote education and research and to improve the diagnosis and management of all types of amyloidosis. This update will highlight recent developments in the field for clinical and laboratory haematologists.

100. Adult morphology cases

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In this session the QAP morphology cases sent out in the RCPA September survey will be reviewed by deputy chair of the RCPA-QAP (Dr Archana Sharma) followed by presentation of paediatric morphology cases (Dr Sally Campbell) and the adult morphology cases (Dr Surender Juneja).

The last 30 minutes of this session will include a new feature this year which is the presentation of highlights of Transfusion QAP programme by Mr Arthur Joyce.

101. CML - treatment free remission

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Multiple clinical trials over the past decade have enrolled more than 2000 CML patients with sustained deep molecular response in studies of tyrosine kinase inhibitor (TKI) discontinuation. The overall results are remarkably consistent with around 40-60% of patients remaining in treatment-free remission (TFR), despite differences in the defined depth of molecular response and cut-off for molecular relapse, and differences in the TKI being used.

The EuroSKI TFR registry has recently published an interim analysis involving 755 patients. With large numbers of imatinib-treated patients having variable durations of TKI treatment and deep molecular response it was possible to show that each additional year of MR4.0 (BCR-ABL $\leq 0.01\%$) prior to stopping imatinib increased the probability of TFR by 2-3%. Similar data for second-generation TKIs are not yet available. Among patients treated second-line with nilotinib or dasatinib there is conflicting evidence on the effect of response to first-line imatinib treatment, with some studies reporting higher relapse rates for patients with resistance to imatinib, and others reporting no significant effect.

Patients who experience a molecular relapse after discontinuation are typically re-treated with the same TKI and within several months regain a deep molecular response. The prospects for these patients to have a second discontinuation attempt have recently been explored. Simply prolonging the duration of TKI treatment may result in a successful second TFR attempt for some patients (35% at 3 years in the RE-STIM study). The development of more effective strategies should be driven by an understanding of the biological factors that determine TFR outcome.

Based on experience in the allogeneic transplant setting it has long been known that CML can be responsive to immunological therapy. Higher numbers of NK cells prior to stopping have been reported in several studies to be associated with a higher probability of TFR, as have certain other immunological parameters. None of these observations has yet been translated into a therapeutic strategy, but there is interest in the potential of immunomodulatory drugs, such as interferon or nivolumab, to improve the probability of TFR.

The achievement of TFR is increasingly important as a goal for patients with CML, and clinicians who treat CML should be aware of current recommendations for patient selection and molecular monitoring.

102. State of the art management of MPN in the Australian context

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Over the last 15 years there have been considerable advances in our understanding and management of the Philadelphia chromosome-negative myeloproliferative neoplasms (MPN). The discovery of the 3 driver mutations, testing for which has now been incorporated into routine clinical practice, has revolutionised our understanding of pathogenic mechanisms and the clinical heterogeneity of these diseases. Clinical, morphological and molecular genetic features have been utilised in the 2016 WHO classification to improve disease definitions (in particular for polycythaemia vera and prefibrotic primary myelofibrosis) enabling optimal prognostication and therapy for our patients. The role of molecular abnormalities in clinical behaviour and prognostication is reflected by the incorporation of mutation status into recently validated prognostic scores (e.g. IPSET, MIPSS70).

The identification of the JAK-STAT pathway as the key signalling cascade in MPNs led to the development of JAK inhibitors, which were incorporated into clinical practice almost 7 years ago. The impact of interferon therapy on mutation burden has fuelled a resurgence of interest in interferon therapy and is reflected by the recent PBS-funding of pegylated-interferon in Australia. Despite the improvement in our therapeutic armamentarium for MPNs there are many unmet needs for our patients including normalisation of lifespan, reduction of cardiovascular complications, prevention of haematological progression and improved quality of life.

104. Future perspectives for CAR T cells in hematologic malignancies

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The ability to harness a patient's immune system to target malignant cells is now transforming the treatment of many cancers, including hematologic malignancies. The adoptive transfer of T cells selected for tumor reactivity, or engineered with natural or synthetic receptors has emerged as an effective modality, even for patients with tumors that are refractory to conventional therapies. The most notable example of adoptive cell therapy is with T cells engineered to express synthetic chimeric antigen receptors (CARs) that reprogram their specificity to target CD19 and BCMA. CAR T cells targeted to these molecules have shown remarkable antitumor activity in patients with refractory ALL, NHL, CLL and myeloma. Ongoing research is focused on understanding the mechanisms of incomplete tumor elimination, reducing toxicities, preventing antigen escape, and identifying suitable targets. Strategies based on established and emerging principles of synthetic biology are extending this approach to other hematologic malignancies. This talk will review the current status, challenges, and potential future applications of CAR T cell therapy in hematologic malignancies.

107. 18F-FDG-PET/CT in multiple myeloma reveals additional myelomatous lesions and changes clinical management

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Background: Internationally, ¹⁸F-FDG-PET/CT is the preferred functional imaging modality to distinguish metabolically active from inactive multiple myeloma (MM)⁽¹⁾, with normalisation of PET-avidity pre-transplant being associated with improved survival⁽²⁾. In Australia, there is no Medicare rebate for PET/CT in MM, resulting in use restricted to centres who fund it internally or through clinical trials.

Aim: to assess ¹⁸F-FDG-PET/CT use in MM at PMCC, focusing on clinically-relevant information gained.

Method: a 5-year retrospective audit of patients receiving an autologous stem cell transplant (AuSCT) for MM at PMCC (2012-2016), compared with data from the Myeloma and Related Diseases Registry (MRDR)⁽³⁾. Data includes demographics, indication for imaging, additional information gained, and changes in clinical management.

Results: of patients undergoing AuSCT at PMCC, 99/201 (49%) had a PET/CT, with 248 PET/CTs performed in total. Of the 72 patients managed at PMCC from diagnosis, 74% undertook at least 1 PET/CT, including 54% at diagnosis. This compares with 22/546 (4%) at diagnosis of those on the MRDR who underwent AuSCT.

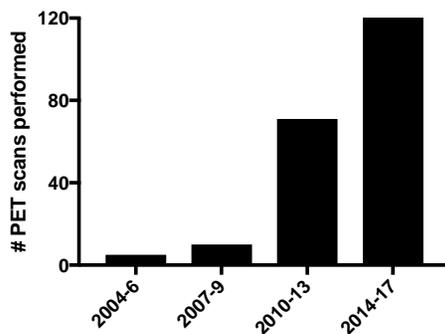


Figure 1. There was increased utilisation of PET/CT at PMCC over time, suggesting that clinicians are finding the imaging modality useful.

The most common indications were suspected progressive disease (105/248, 42%), diagnostic staging (40/248, 16%), infection (23/248, 9%), and another malignancy (19/248, 8%). 11 (4%) were for performed for pre-transplant

for pre-transplant assessment, 16 (6%) post-transplant, and 17 (7%) for restaging post-salvage-treatment. 46 PET/CTs were for screening or reassessment on clinical trials.

There were 76 scans performed contemporaneous with another modality, of which 38/76 (50%) revealed additional FDG-avid MM lesions. Changes in clinical management directly resulting from PET-CT findings was difficult to determine retrospectively but was documented in 6/38 cases (16%).

Conclusion: There was higher utilisation of ¹⁸F-FDG-PET/CT at PMCC compared to other Australian institutions, and our data show it often provides additional clinically-relevant information. Utilisation, however, remains lower than international consensus recommendations. In order to replace skeletal survey with PET/CT, broadening of Medicare reimbursement to enable patient access is required.

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- The Myeloma and Related Diseases Registry, www.mrd.net.au

108. High rates of early treatment failure in diffuse large B-cell lymphoma: early results from the Lymphoma and Related Diseases Registry

Dickinson M¹, Hawkes E², Berkahn L³, Cheah C⁴, Gandhi M⁵, Giri P⁶, Johnston A⁷, Keane C⁸, McQuilten Z^{9,10}, Rowsell L⁹, Shortt J¹⁰, Talaulikar D¹¹, Trotman J¹², Wood E^{9,10}, Opat S¹⁰

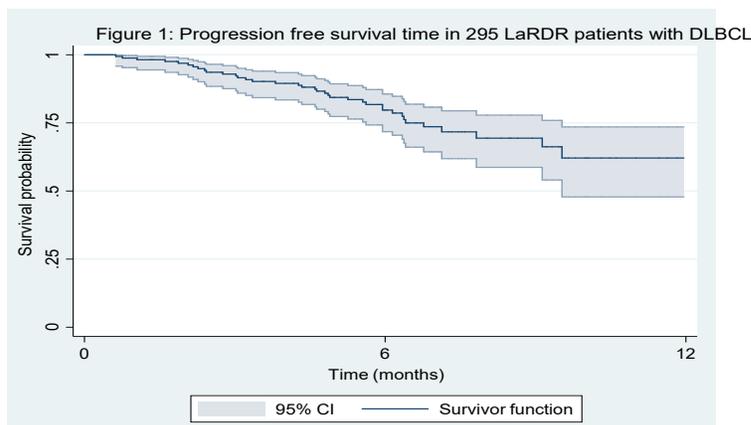
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Background: Clinical trial data in lymphoma patients are often criticised for not reflecting real-world populations, due to strict eligibility criteria. Registry data can help identify if this is the case.

Aim: To report PFS in a real-world cohort of DLBCL patients from the Australian Lymphoma and Related Diseases Registry (LaRDR).

Method: All patients with newly diagnosed DLBCL offered active therapy registered from January 2016 until June 2018 at 11 active sites were included in this analysis. Progression free survival was defined as time from diagnosis until disease progression or death from any cause.

Results: 295/298 patients with DLBCL offered active treatment were included (44% of B-cell lymphomas on the registry). The median age was 69 years (range 19-99); 209/295 (71%) were age>60, 75/295 (25%) were age>75 and 180/295 (61%) were male. One quarter (55/224) had IPI score 4-5, 84% (227/271) had ECOG 0-1 and 73% (195/268) stage III/IV disease. Review at 6 months post diagnosis and response to first line treatment were available for 145 (49%) and 137 (46%) patients, respectively. Median days from diagnosis to first line treatment commencement was 14 (IQR 7, 24). 131 (90%) patients with first line of treatment assessed received curative chemotherapy, with 121 (83%) receiving anthracycline-based regimes. Of patients with any follow-up, 39/211 (19%) had experienced disease progression (Figure 1) and 17/210 (8%) had died.



Conclusion: This preliminary analysis from a national registry indicate 20% (95%CI 14 to 27%) of patients experience treatment failure within 6 months of diagnosis, lower than published trial data¹. The inferior outcomes in these registry patients suggests data derived from prospective clinical trials poorly reflect outcomes in patients treated at Australian tertiary hospitals. This observation highlights the importance of clinical registries to monitor treatment outcomes practice outside of clinical trials.

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109. Predictors of early mortality in multiple myeloma: Results from the Australian and New Zealand Myeloma and Related Diseases Registry (MRDR)

McQuilten Z¹, Wellard C¹, Moore E¹, Augustson B², Bergin K³, Blacklock H⁴, Harrison S⁵, Horvath N⁶, King T⁷, Ho J⁷, McNeil J¹, Mollee P⁸, Quach H⁹, Reid C¹, Rosengarten B¹⁰, Walker P¹¹, Wood E¹, Spencer A³

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Early mortality in newly diagnosed multiple myeloma (NDMM) patients is infrequent in clinical trials, however rates appear higher in population-level studies. Identification of risk factors may inform strategies to improve outcomes.

Aim

To describe early mortality in a real-world cohort of NDMM and explore factors predictive of early mortality.

Methods

We included all NDMM patients in the MRDR from Jan 2013-May 2017. Early mortality was defined as death from any cause within the first 12 months of diagnosis. Associations between early mortality and patient characteristics (age, gender, co-morbidities), year of diagnosis, country, disease characteristics (international staging system [ISS], cytogenetics, lactate dehydrogenase [LDH], beta-2 microglobulin [B2MG], albumin), baseline renal function, blood count and EQ5D were assessed. Multivariable logistic regression models were developed using backward and forward stepwise selection.

Results

966 NDMM patients were included. Median age was 66.5y (IQR 58.2, 74.1). Early mortality was reported in 83 (8.5%) patients. Cause of death was disease in 47 (57%), infection 4 (5%), non-disease related 20 (24%) and unknown 12 (14%). Factors associated with early mortality were age, ISS, estimated glomerular filtration rate (eGFR), moderate to severe cardiac and moderate to severe pulmonary disease, ECOG performance status, platelet count, calcium, LDH, lower albumin, B2MG, and EQ5D (all $p < 0.05$). Independent predictors of early mortality in the final model were age $>75y$ (OR 2.75, 95%CI 1.31-5.71, $p=0.0007$), albumin (OR 0.93, 95%CI 0.89-0.99, $p=0.025$), ISS (OR 1.97, 95%CI 1.08-3.58, $p=0.026$) LDH >300 (OR 3.13, 95%CI 1.36-7.19, $p=0.007$), cardiac (OR 2.86, 95%CI 1.25-6.51, $p=0.012$) and pulmonary disease (OR 3.22, 95%CI 1.19-8.74, $p=0.022$). ROC area under the curve was 0.82.

Conclusion

In a large cohort of NDMM patients, early mortality occurred in 8.5% with disease accounting for more than half of all deaths. Age $>75y$, ISS, lower albumin, cardiac and pulmonary disease were independent predictors of early mortality.

110. A retrospective analysis of patients with co-existent primary cutaneous anaplastic large cell lymphoma and mycosis fungoides from the Australian Cutaneous Lymphoma Network database

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It can be difficult to distinguish between lesions of primary cutaneous anaplastic large cell lymphoma (pcALCL) versus mycosis fungoides (MF) with CD30+ transformed tumour-lesions. The purpose of this study was to review patients with pcALCL, pcALCL and co-existent MF, and those with MF large-cell transformation (LCT) and compare their overall survival (OS).

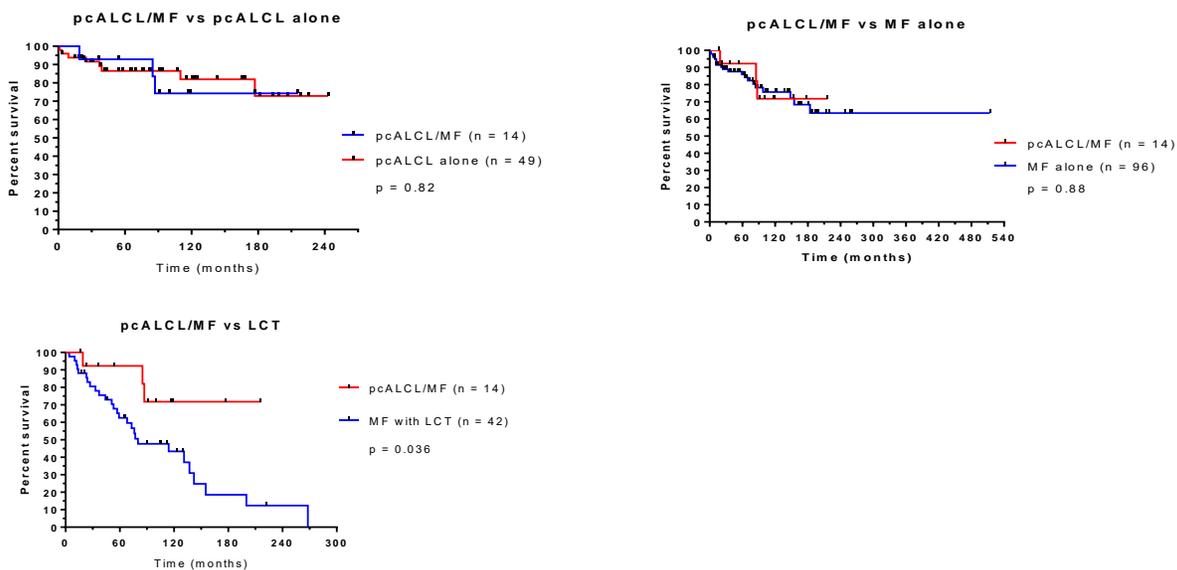
A total cohort of 85 patients with a diagnosis of pcALCL was analysed, of which 14/85 had co-existent MF (the largest cohort studied to date). Study endpoints included OS and time to next treatment. The outcomes of these patients were examined against those with:

- MF CD30+ (n = 40)
- MF CD30- (n = 56)
- MF with LCT CD30+ (n = 17)
- MF with LCT CD30- (n = 25)

Note: the total number of patients on our database with MF (excluding Sezary Syndrome) = 659. In this analysis we chose only those patients where CD30+ status was known at the time of entry into the database.

Our analysis of the data showed no difference in survival outcomes of those with co-existent pcALCL/MF compared to those with pcALCL alone (p = 0.82). Similarly, the outcomes were no different between those with pcALCL/MF and MF alone, regardless of CD30 status (p = 0.88). However, patients with pcALCL/MF demonstrated a significantly better outcome when compared to those with transformed disease (p = 0.036), particularly those with CD30-negative MF/LCT (p = 0.028).

Overall, the results of our study indicate that in patients diagnosed with pcALCL, having a coexistent diagnosis of MF does not confer poorer prognosis, and has no significant impact on survival. Importantly, it has demonstrated a statistical difference in survival between those with coexistent pcALCL/MF versus those with MF/LCT, emphasising the need to carefully discriminate between these two distinct pathological processes which have very different disease behaviours and outcomes.



111. The Myeloma and Related Diseases Registry (MRDR): The first five years: The myeloma landscape in Australia and New Zealand (ANZ)

Bergin K^{1,2}, Wellard C², Moore E², McQuilten Z², Wood E², Quach H^{3,4}, Blacklock H⁵, Mollee P⁶, Ho J⁷, He S⁸, Hocking J⁹, Walker T¹⁰, Prince M¹¹, King T⁷, Augustson B¹², Dickinson M¹³, Ramanathan S¹⁴, D'Rozario J¹⁵, Spearing R¹⁶, Horvath N¹⁷, Leung T¹⁸, Harrison S^{13,19,20}, Estell J²¹, Grigoriadis G²², Merriman L²³, Srivastava G²⁴, Sobieraj-Teague M²⁵, Johnston A²⁶, Wright T²⁷, Spencer A^{1,2}

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Background: "Real world" epidemiological and outcome data for MM are scarce with most data originating from clinical trials.

Methods: We reviewed all patients with diagnostic information registered from 01/06/2012-11/4/18 on the MRDR, a prospectively maintained database from Australia and New Zealand (30 sites). Baseline characteristics, therapy and outcome data were reviewed with comparisons made using chi-square tests for categorical variables and rank sum tests for continuous variables. Kaplan-Meier analysis was used to estimate survival (PFS/OS).

Results: Of 1808 patients enrolled, 1229 (68.0%) had MM. Median age was 67y (37% >70y). 68% met criteria for symptomatic MM, with bone lesions most common (56%). 15-25% had high-risk disease: (t(4;14), t(14;16) or del17p): 20%), ISS-3: 32%, R-ISS 3:15%), 15% had extra-medullary disease. IgG isotype was most common (59%), and 63% were kappa light chain (LC) restricted. LC-only disease accounted for 18.3%, 1.4% had non-secretory MM. Flow cytometry was performed in 47%. Cytogenetics/FISH were performed in 56% and 62% respectively (abnormal karyotype: 30%). 81% had diagnostic imaging: skeletal survey (SS): 47.9%, CT: 24.3%, MRI: 24.1%. In patients without lytic disease on SS (40.3%), 60 had imaging by another modality confirming MM bone disease in 45 (75%). Of patients with available treatment data (n=1128), 85% received bortezomib-based induction with 42% achieving ≥VGPR. Patients receiving non-bortezomib-based induction were older (median age 75yrs (67-82) versus 65yrs (57-72), p<0.001), had a higher ECOG (ECOG ≥2 46% versus 19% p<0.001) and only 25% achieved ≥VGPR. Median PFS (whole cohort) was 29.7 months with those receiving bortezomib-based therapy demonstrating improved PFS (30.6m versus 24.4m, p=0.014). Median OS (total cohort) was 58.8 months. Patients with higher risk disease had worse OS (R-ISS1: NR versus R-ISS2: 58.8m versus R-ISS3: 34.6m (p=0.001)).

Conclusion: Clinical registries provide a powerful tool to confirm the validity of extrapolating clinical trial data to everyday clinical practice.

Table 1: Plasma Cell Dyscrasia Frequencies on the MRDR

Diagnosis	N=1808
Multiple myeloma	1229/1808 (68.0%)
MGUS	393/1808 (21.7%)
Plasma cell leukemia	9/1808 (0.5%)
Solitary Bone Plasmacytoma	8/1808 (0.4%)
Solitary Extramedullary Plasmacytoma	2/1808 (0.1%)
Smouldering Myeloma	167/1808 (9.2%)

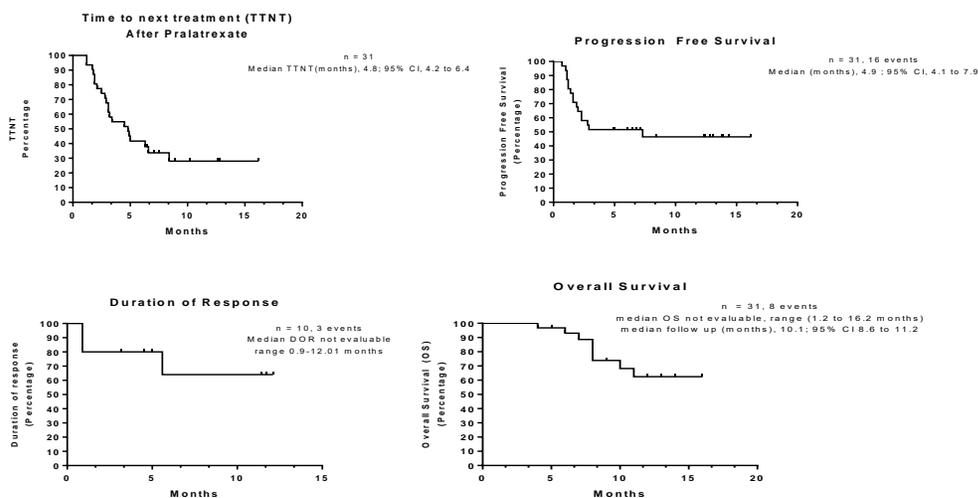
112. A retrospective analysis of Pralatrexate efficacy and tolerability in Australia

Admojo L^{1,2}, Van Der Weyden C², Gao C^{2,3}, Twigger R², Bazargan A⁴, Quach H^{1,4}, Zimet A⁵, Coyle L⁶, Lindsay J⁶, Radeski D⁷, Hawkes E⁸, Kennedy G⁹, Irving I¹⁰, Gutta N¹⁰, Trotman J¹¹, Yeung J^{11,17}, Dunlop L¹², Hua M¹², Giri P¹³, Yuen S¹⁴, Panicker S¹⁵, Moreton S¹⁶, Khoo L¹⁷, Scott A^{18,21}, Kipp D¹⁹, McQuillan A²⁰, Prince M^{1,2,3}

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Background: Pralatrexate has recently been approved for reimbursement in Australia for peripheral T-cell lymphoma (PTCL). Previous studies on the tolerability and efficacy of this agent have been performed in the USA (n=109)(1) and Japan (n=20) (2). Our study retrospectively evaluated patients with (relapsed/refractory) PTCL in Australia who received pralatrexate through a compassionate access program. **Methods:** Patient data was collected from treating physicians at multiple sites across Australia. The data was analysed for overall response rate (ORR), duration of response (DOR), time to next treatment (TTNT), progression free survival (PFS), overall survival (OS), and pralatrexate-induced toxicity rates. **Results:** A total of 31 patients (male=19 [61%], female=12 [39%], mean age 63.5 years) have been analysed to date. The median number of prior therapies are 3. Among 31 patients, PTCL-not otherwise specified (NOS) was the most common subtype (n=10;32%) followed by angioimmunoblastic T-cell lymphoma (AITL) (n=9;29%) and cutaneous T-cell lymphoma (n=8,26%). We demonstrated an ORR of 32.3% (n=10) including 2 complete responses (6.5%) and 8 partial responses (25.8%). After a median follow-up of 10.1 months for all alive patients, the median PFS was 4.9 months with a median DOR not reached. Median TTNT after pralatrexate was 4.8 months and median OS has not been reached. Mucositis (51.6%) was the most commonly observed toxicity, followed by thrombocytopenia (16%), skin rash (13%), and fatigue (13%).

This is the first pralatrexate study conducted in Australia and is the second largest cohort studied globally. We confirm similar results for efficacy and tolerability to previous studies. In conclusion, our study confirms that pralatrexate has an important role in the treatment armamentarium for patients with (relapsed/refractory) PTCL.



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113. Demographic analysis of cases referred for investigation of FIP1L1-PDGFR A positive chronic eosinophilic leukaemia (CEL) in Australia

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Aim

Since 2004, our laboratory has been testing referred specimens from patients with hypereosinophilia for FIP1L1-PDGFR A gene rearrangements. FIP1L1-PDGFR A positive CEL occurs almost exclusively in males with only few reported female cases. We sought to determine whether this male bias also exists in Australia and to analyse age and sex demographics in referred patients as a surrogate cohort of hypereosinophilia in the Australian population.

Methods

FIP1L1-PDGFR A fusion transcripts were detected by reverse transcription and polymerase chain reaction. De-identified data including presence of FIP1L1-PDGFR A, gender, age at first referral and geographic origin were collected from all referred specimens. Patient age distributions in 10-year bins were compared using the Kolmogorov-Smirnov test and using demographic data of the general Australian population. Incidence of FIP1L1-PDGFR A by gender was compared using Fisher's exact test.

Results

The patient cohort consisted of 895 males (55%) and 736 females (45%) with respective median ages of 62 (range 1-96) and 55 (range 5-93). The age distributions of the referred male and female cohorts were significantly different to the respective Australian male ($p < 0.0001$; median age 36 years) and female ($p < 0.0001$; median age 37 years) populations.

There were 39 male and 1 female FIP1L1-PDGFR A positive patients in the cohort with median ages of 53 (range 14-78) and 29 years, respectively. The incidence of FIP1L1-PDGFR A positive CEL was 2.4% of all patients tested and the male gender bias (97.5%) was significant ($p < 0.00001$).

Conclusions

When investigating patients with hypereosinophilia, causes other than CEL are likely to be important. In particular, females with FIP1L1-PDGFR A positive CEL are extremely rare. Differences in the age distributions of the patient cohort to the population suggest that increased age is a factor in the aetiology of hypereosinophilia. However, the extreme male gender bias in the incidence of FIP1L1-PDGFR A positive CEL observed in this cohort, and in cohorts reported other investigators, is suggestive of involvement of a recessive sex-linked predisposition or cooperative gene mutation in the aetiology of CEL.

114. Extended sequencing results from a cohort of triple-negative myeloproliferative neoplasm patients

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The myeloproliferative neoplasms (MPNs) have in common aberrant activation of JAK-STAT signalling. In around 90% of patients with primary myelofibrosis (PMF) or essential thrombocythaemia (ET) one of three common somatic 'driver' mutations affecting the JAK-STAT pathway can be identified. The remaining 'triple-negative' MPN patients pose a diagnostic challenge, since reactive conditions must be excluded if there is no marker of clonality. We identified a cohort of 31 triple-negative patients with PMF, ET, or an unclassifiable MPN (MPN-U). We used a next-generation sequencing panel including genes involved in myeloid neoplasia, DNA repair, or cell signalling with the aim of identifying additional mutations that might have diagnostic value. The most frequent diagnosis was ET (n=22), then MPN-U (n=5) and PMF (n=4). The mean sequencing depth was 430 reads. After applying a bioinformatic algorithm followed by manual curation we identified 2 patients with driver mutations (*JAK2* V617F, *MPL* W515L) at an allelic frequency below the limit of detection of our routine diagnostic methods. There were 12 likely somatic mutations in myeloid-associated non-driver genes, and 4 patients with previously unreported mutations in *MPL* or *JAK2*, that had a variant allele frequency close to 50% and were therefore likely germline (confirmation in progress). One patient with ET had biallelic *MPL* mutations. He and his identical twin were compound heterozygotes with isolated thrombocytosis, whereas simple heterozygotes in the same family were unaffected. Functional studies on JAK-STAT signalling in cell lines transfected with these mutations are in progress. The remaining patients had no diagnostically relevant mutation identified, and it is possible that these patients have reactive thrombocytosis or as yet unidentified determinants of thrombocytosis. Our data highlight the value of extended sequencing panels in the diagnosis of triple-negative MPN and add to the growing list of mutations that may cause germline thrombocytosis.

115. Reactive or proliferative? A novel scoring system to predict JAK2 status

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Aim

1. To design a decision aid to reduce unnecessary ordering of *JAK2* V617F mutation testing
2. To assess the clinical and laboratory parameters which would be useful in predicting *JAK2* V617F positivity

Method

All consecutive patients who had *JAK2* sequencing performed in the Liverpool Hospital molecular laboratory in 2014 and 2015 were included. Clinical and laboratory variables closest to the date of *JAK2* sequencing were collated from the patient medical record. *JAK2* sequencing was performed using a molecular based test, where genomic DNA was extracted from blood or bone marrow, and DNA was then amplified by real-time PCR. Association between *JAK2* V617F status and continuous variables were assessed using Spearman correlation and categorical variables using Mann-Whitney test. Significantly associated variables were combined in a scoring system to predict *JAK2* V617F status. The study was approved by the institutional review board of SWSLHD.

Result

In the 2014 training cohort *JAK2* V617F status was associated with white blood cell count (WBC) ($R=0.267$, $p=0.001$), platelet count ($R=0.267$, $p<0.001$) and inverse of the erythrocyte sedimentation rate (ESR) ($R= -0.299$, $p=0.006$). There was no association with C-reactive protein, gender, splenomegaly or haemoglobin. The 3 variables associated with *JAK2* status were combined into a scoring system where each variable was attributed 1 point for values separated by the median. Eighty seven were included in the model. A score of 0 was significantly associated with negative *JAK2* V617F status ($p=0.029$).

Conclusion

This preliminary analysis reveals that simple, routinely performed tests can be used as an effective screening tool to determine the pre-test probability of *JAK2* positivity. We hope to validate this tool with another cohort of patients, and in the future, implement screening in the inpatient setting, where reactive aetiologies are more likely to be the cause of blood dyscrasias than a myeloproliferative neoplasm.

116. Aetiology and differentiating characteristics of primary vs. secondary thrombocytosis – the clot thickens

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Aim

1. To determine the aetiology of thrombocytosis in patients measured at an Australian pathology provider, and
2. To determine what parameters are correlated with primary vs. secondary thrombocytosis, and whether these parameters could be used in a predictive model.

Method

We conducted a retrospective survey of all adult patients who had a platelet count $>450 \times 10^9/L$ collected between June 2015 and June 2016 at Mater Pathology, South Brisbane. The aetiology was classified according to clinical information from the electronic medical record, and concurrent full blood count and other relevant pathology data were collected. We used a binomial logistic regression using the diagnosis (primary vs. secondary) as the independent variable to determine which statistically significant and biologically plausible pathology parameters accurately modelled our data.

Results

994 patients met inclusion criteria – 904 (91%) secondary cases, 55 (5.5%) primary cases, and the cause was unable to be determined from the available record in 35 (3.5%) cases. The most common secondary causes were infection (34%), post-operative (21%) and non-haematological malignancy (20%). Our final logistic regression incorporated gender, age, platelet count, platelet distribution width, haematocrit and mean corpuscular volume, and modelled our data with 95% accuracy (positive predictive value 84.1%, negative predictive value 96.2%).

Conclusion

Primary thrombocytosis is an uncommon but important cause of an elevated platelet count in Australian inpatients. In our cohort, a model which incorporated only age, gender and a full blood count could predict primary vs. secondary thrombocytosis with a high degree of accuracy, especially in its negative predictive value. If supported by external and prospective validation, this model could exclude cases of primary thrombocytosis without the need for requesting and following up more sophisticated and expensive molecular tests.

117. Characteristics and outcomes of Therapy-Related Myeloid Neoplasms after ¹⁷⁷Lu-DOTATATE Peptide Receptor Radionuclide Therapy in patients with Neuroendocrine Tumours

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Peptide receptor radionuclide therapy (PRRT) is well established therapy in patients with metastatic neuroendocrine tumours (NET), however, development of therapy-related myeloid neoplasms (t-MN) remains a feared complication. Aim: To review the clinical features, genetic abnormalities and outcomes in patients who develop t-MN after PRRT with ¹⁷⁷Lu-DOTATATE. Methods: Retrospective analysis identifying patients diagnosed with t-MN from our cohort of 565 patients who received ¹⁷⁷Lu-DOTATATE PRRT. Results: 25 of 565 (4.4%) patients were diagnosed with t-MN, of these, 9 had Acute Myeloid Leukaemia (AML) and 16 had Myelodysplastic syndrome (MDS). The median latency period from cycle 1 of PRRT to diagnosis of t-MN was 26 (range 4 – 91) months. 22 of 25 (88%) patients had low-grade pancreatic or small bowel NET with moderate metastatic liver burden and only 6 (24%) had prior chemotherapy. PRRT response-assessment showed that 24 (96%) patients had disease stabilisation or a partial response. At the time of t-MN diagnosis, all patients presented with persisting \geq Grade 2 thrombocytopenia (median nadir $33 \times 10^9/L$) and 17 (68%) were NET progression free. The bone marrow of most patients demonstrated prominent dysmegakaryopoiesis and cytogenetic aberrations with unfavourable prognosis. 12 patients with MDS received supportive therapy only. Azacitadine was the most common utilised treatment for eligible patients, while 4 patients were treated with induction chemotherapy for AML. The median overall survival of patients was 13 months, cause of death was mainly due to haematological disease progression. Conclusion: The diagnosis of t-MN after ¹⁷⁷Lu-DOTATATE PRRT is a serious long-term complication; most patients are NET progression-free, present with thrombocytopenia, have unfavourable cytogenetics and poor overall survival.

118. Myelodysplastic syndrome (MDS) patients treated with azacitidine are at an increased risk of hospitalisation with fungal infection

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Aim

While infection causes significant morbidity in MDS, no consensus exists for use of antimicrobial prophylaxis in azacitidine (Aza) treated patients. This study characterises the burden of fungal infection in Aza-treated MDS patients.

Method

CT scan, microbiology results and hospital admission ICD codes from 1999 to 27 March 2017 were analysed for 657 MDS patients enrolled in the South Australian MDS (SA-MDS) registry. Risk factors for fungal infection were identified using cox regression analysis.

Results

There were 531 primary and 126 therapy-related MDS patients with median age of 69.2 (18-97) years. 44.7% of patients were classified as Intermediate, High and Very High IPSS-R risk group. 367 patients received best supportive care (BSC) and 241 had disease modifying therapy including azacitidine (n=132), chemotherapy (n=74) and stem cell transplantation (SCT) (n=25).

There were 2450 hospital admissions for 580/657 (88.3%) patients and 1312 (53.5%) were infection-related. 120 of 132 (90.9%) Aza-treated patients required 570 admissions, 349 (61.2%) involving infection.

Chest infections (29.1%) and febrile neutropenia (28.6%) were the most common infections, followed by skin and soft tissue (15.8%), urinary tract (8.1%), gastrointestinal (7.3%) and viral illness (6.8%). Causative organisms were largely unspecified (58.4%), but most commonly isolated were bacteria (24.2%), followed by viruses (12.2%) and fungi (5.2%).

Importantly, 16/120 (13.3%) Aza-treated patients had hospitalisations with invasive fungal disease (IFD), 69.2% during the first five cycles. 12 (68.7%) of patients met criteria for probable IFD and 3 (18.7%) for possible IFD. Rates of IFD were significantly higher with Aza than BSC (13.3% vs. 4.8%; $p < 0.002$). Charlson Comorbidity Index (CCI) was a significant predictor of development of fungal infection ($p = 0.029$).

Conclusion

Fungal infections are a significant cause of hospital admission in MDS patients. AZA-treated patients are at higher risk than BSC, particularly in the first 5 cycles, and warrant consideration of antifungal prophylaxis.

120. Haemolytic disease of the fetus and newborn - a personal perspective

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Background

As a red cell serologist I have become accustomed to dealing with immunised patients from the laboratory perspective. In my second pregnancy, at 5 weeks gestation, I was informed that I had Anti-D with a quantitation of 0.1 IU/mL.

At 20 weeks, the quantitation was 1.0 IU/mL. However, at 25 weeks the quantitation rose to 15.8 IU/mL and I was referred to a feto-maternal specialist. I learnt firsthand from a patient's perspective about Doppler scans, the risks of intra uterine transfusion (IUT), phototherapy and exchange transfusion guidelines. I had to understand the extent of intense phototherapy and support my baby whilst he received neonatal transfusions.

Case Report

From 25 weeks until delivery, I underwent weekly or biweekly Doppler scans and Fetal Assessment Ultrasounds. An IUT was considered at 27 weeks due to a raised Doppler. However, this did not proceed as there were no other signs of fetal anaemia and the follow up scan was normal. At 32 and 33 weeks, the Doppler scans were raised, though no IUT was considered necessary. The Anti-D quantitation continued to decline throughout the pregnancy and was 3.6 IU/mL at 35+ weeks.

Induction of labour occurred at 37 weeks. The cord results were O Rh(D) Positive, DAT Positive and Anti-D was eluted from the red cells. Based on a cord Hb of 125g/L, at 4 hours old, my son commenced phototherapy. His serum bilirubin (SBR) at 7 hours old was 116 µmol/L. He progressed well with intense phototherapy but at 9 days, his Hb dropped to 79g/L and he received a blood transfusion. Phototherapy continued until he was discharged on day 16 with a SBR of 208 µmol/L and a Hb of 119g/L. We continued outpatient monitoring and a second transfusion was required at 5 weeks when the Hb was 74g/L.

121. Non-invasive fetal RhD genotyping to target antenatal RhD-Ig prophylaxis and in sensitised pregnancies

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Haemolytic disease of the fetus and newborn is due to maternal red blood cell (RBC) alloantibodies, transferred to the fetus during pregnancy. Fetomaternal haemorrhage (FMH) or incompatible RBC transfusion may have induced the RBC alloantibody formation in the mother. The maternal RBC alloantibodies are pathogenic if the child is carrying the involved RBC antigen.

Anti-D immunoglobulin (RhIg) prevents RhD immunization due to FMH and dramatically reduced the prevalence of RhD immunized pregnancies. If RhIg is given during pregnancy and after delivery the risk to develop anti-D is less than 0.5%. In 2016, we calculated in the group of RhD-negative women in the Netherlands a prevalence of 0.6% of RhD-immunized women and incidence of 0.4%. Also HDFN due to anti-c, anti-E or anti-K is very rare, but in all cases it can result in severe disease necessitating intra uterine transfusions or preterm delivery with postnatally intensive phototherapy to treat hyperbilirubinemia and transfusion to treat (late) anemia.

Since more than 15 years, placenta-derived cell-free fetal DNA present in maternal plasma is used for prediction of fetal blood group antigen genotypes. Reliable assays with real-time quantitative PCR for so called non-invasive fetal typing for RhD, RhC, Rhc, RhE, K have been designed and used in daily practice. Since recently, also assays with digital droplet PCR are being validated. The latter platform has the advantage of high specificity, sensitivity and to run fetal DNA identifiers along with the test. Reliable fetal blood group antigen typing is nowadays used to select the high-risk pregnancies for monitoring of fetal anemia, which adds to patient-centered care approaches. Similarly, in the Netherlands, Denmark, Finland, Sweden and as a pilot in the UK, fetal RhD typing in pregnancy is used to target the administration of RhIg in pregnancy. In the Netherlands and Denmark, the fetal RhD typing result is also used to directly target postnatal RhIg, without a serological cord blood test result. In the Dutch program, a sensitivity for detection of fetal RhD of 99.94% (95% CI 99.89% to 99.97%) and specificity of 97.74% (97.43% to 98.02%) is reached. False negative results for fetal RhD testing are about 0.03%, (95% CI 0.01% to 0.06%). We continuously try to improve the technical performance of fetal RhD testing, but also the nowadays obtained screening test performance and the advantages of targeted antenatal and postnatal RhIg administration improved the logistics, prevented clerical mistakes and contributed maximally to a high performance of the RhIg program in the Netherlands with over 99% adherence.

122. Droplet digital PCR for non-invasive fetal genotyping

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There is clinical need for non-invasive prenatal tests (NIPTs) that accurately assess fetal blood group antigen status in women who are alloimmunised against atypical (non RhD) blood group antigens. NIPT to predict blood group antigens arising from single nucleotide variations (SNVs) is challenging because cell-free (cf)DNA in maternal plasma is dominated by the mother's genotype. Droplet digital PCR (ddPCR) permits detection of rare events in complex samples by partitioning the reaction into thousands of sub-reactions, minimising competition effects.

This presentation will discuss development, features and clinical validation of probe-based ddPCR assays to detect fetal SNVs that give rise to red cell antigens K/k, RhE, Rhc, Fy^a/Fy^b and platelet antigens HPA-1a/HPA-1b.

Optimisation work has demonstrated that all ddPCR assays can be performed using the same reaction conditions. Detection of a universal cffDNA marker, hypermethylated *RASSF1A*, can be accomplished by an in-tube restriction digest for 1 hour prior to amplification (contrasting with 16 hours using real-time PCR).

Blood samples were collected from 45 consenting pregnant women who tested positive to anti-Kell (n=28), anti-RhE (n=11), anti-Rhc (n=4), anti-Fya (n=3), anti-Fyb (n=1) and anti-HPA-1a antibodies (n=1). 13 participants provided 2 samples during pregnancy. Cord blood phenotyping or amniocyte genotyping is being used to evaluate test accuracy.

Fetal *KEL*01* (K) has been detected at 11⁺⁶ GA for one case in which the use of Streck BCT collection tubes permitted a fetal fraction estimate of 8.36%. For *RHCE*E* (RhE) and *RHCE*c* (Rhc) assays, fetal signals have been detected at 10 and 13 weeks respectively. Second sample results have matched initial findings. Correlations with cord blood phenotype or amniocyte genotyping are currently available for 12 cases – 8 for *KEL*01*, 3 for *RHCE*E*, and 1 for *RHCE*c* with all matching assay predictions.

Droplet digital PCR reliably detects cffDNA signals, and at earlier gestation compared to real-time PCR technologies. Capacity to run assays using the same conditions, and with reduced run time for a universal cffDNA control marker assay highlights the potential scalability, practicality and cost-effectiveness for this niche area of reference laboratory testing.

123. Appropriate platelet transfusions

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The majority of platelet transfusions are given to prevent bleeding in haematological malignancies. Other common uses are in surgery and intensive care. This talk will cover the evidence for platelet transfusion use to prevent bleeding (prophylaxis), to reduce the risk of bleeding prior to a procedure, and to treat bleeding. This will cover the latest evidence from clinical trials and systematic reviews.

124. Cold stored and cryopreserved platelets

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Platelets have a short shelf life (5 days) and are often discarded due to expiry. Smaller Australian hospitals often cannot justify keeping many (or even any) platelet units on-site. This could be addressed through alternative modes of platelet storage such as cold storage (2-6 °C), which could extend the shelf-life of platelets for up to 14 days, and cryopreservation (-80°C with DMSO), which could extend the shelf-life up to 4 years. Before cryopreserved or cold stored platelets can be approved for civilian use, more information regarding their efficacy, cost-effectiveness, and safety is required.

In vitro pre-clinical studies have been used to evaluate the impact of cold storage and cryopreservation on platelet quality and function, with comparisons to room temperature storage of platelets. Both cold storage and cryopreservation increase the procoagulant activity of platelets, with increased phosphatidylserine externalisation, generation of more procoagulant microparticles and increased thrombin generation, suggesting that they may be more haemostatically effective than conventional room temperature stored platelets, and therefore particularly useful for the treatment of haemorrhage.

The CLIP trial (ACTRN12612001261808), a pilot randomised, controlled, clinical trial of cryopreserved platelets versus conventional liquid-stored platelets for the management of post-surgical bleeding, has recently been completed. In total, 121 cardiac surgery patients at high risk of perioperative bleeding were randomised to receive either cryopreserved or conventional platelets. Of these, 42 (35%) received a platelet transfusion. There were no significant differences in any effectiveness outcomes, but there were trends for the cryopreserved group to require fewer red blood cell units, with less blood in their chest drains at 24hr. Cryopreserved platelets were associated with no evidence of harm.

These results warrant a larger, definitive non-inferiority study of cryopreserved platelets, with volume of postoperative bleeding as the primary outcome and sufficient power to exclude any meaningful difference in adverse effects. For cold stored platelets, only a single randomised controlled trial has been registered to date, which is designed to test their efficacy in treating postoperative cardiac surgical bleeding. Planning for other trials of cold-stored platelets is currently underway.

125. Antifibrinolytics in thrombocytopenia

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Despite the use of prophylactic platelet transfusions, a significant proportion of patients with thrombocytopenia due to disease or treatment develop bleeding. Except at very low platelet counts, the degree of thrombocytopenia does not strongly predict the risk of bleeding. Therefore, other interventions are required to prevent bleeding in this patient population. Two international, multicenter, randomized placebo-controlled trials (TREATT in UK/Australia and A-TREAT in North America), are currently underway to test whether prophylactic use of anti-fibrinolytics will decrease bleeding and demand for platelet transfusions in patients with thrombocytopenia. This presentation will review the rationale for use of anti-fibrinolytics in patients with thrombocytopenia, summarise the existing clinical evidence and present the key features and progress of TREATT and A-TREAT.

127. Red cell storage - of dogs and men

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The red blood cell (RBC) storage lesion refers to a series of biochemical, metabolic, and structural changes that occur when RBCs are stored *ex vivo* at refrigerated temperatures. The consideration that transfusion of longer-stored RBCs could potentially be associated with poorer patient outcomes was brought to the forefront by several observational studies which reported increased in-hospital mortality and morbidity in patients who had undergone cardiovascular surgery and were transfused with RBC units that had been stored for >14 days. These results raised major concerns in light of early studies documenting changes in pH, cationic changes, decreases in adenosine triphosphate (ATP) and 2,3-diphosphoglycerate (2,3-DPG), and the more recent application of “omics” technologies that reveal complex changes in metabolites, proteins, and lipids during RBC storage as well as dysregulation of several metabolic pathways. Such changes vary with unit processing techniques, additive solutions, storage period, and blood donor characteristics. Whereas randomized clinical trials in both adults and children have failed to confirm any adverse effect of RBCs stored for approximately 22 days vs. RBCs stored for a week in a variety of clinical circumstances, randomized clinical studies cannot address transfusion of the oldest cells for ethical reasons. Furthermore, a variety of clinical circumstances such as sepsis have not been adequately investigated. We have performed studies in a canine sepsis model that provide evidence of toxicity when red cells are stored for prolonged periods. As compared to transfusion of 7-day RBCs, transfusion of 42-day RBCs resulted in increased *in vivo* hemolysis, cell free hemoglobin (CFH), NTBI, and plasma labile iron and was associated with more severe lung injury and higher mortality rates. The lower survival rates observed in canines transfused with 42-day RBCs only occurred in the presence of infection and varied with its severity. We have further elucidated several potential mechanisms of this toxicity.

128. Pathogen reduction technologies

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Pathogen reduction technologies (PRT) for labile blood components continue to hold great potential for reducing risk of transfusion-transmitted infections and some non-infectious complications of transfusion. The range and characteristics of PRT technologies available for treating different components will be reviewed. For platelets, two photochemical inactivation technologies are available and approved in many settings: amotosalen with ultraviolet (UV) light treatment (Intercept™, Cerus) and riboflavin with UV light treatment (Mirasol®, TerumoBCT). In addition, an UV-only treatment (Theraflex, Macopharma) is in pre-approval clinical studies. PRT for plasma includes Intercept™, Mirasol®, solvent detergent treatment (Octaplas®, Octapharma), methylene blue with visible light (Macopharma and Springe). Each method has different means of inactivation and performance characteristics with respect to pathogen reduction and biochemical impact on labile components. The current status of development of PRT to treat red cells or whole blood briefly will be discussed. Two technologies are in pre-approval clinical studies: amustaline (S303) with glutathione quencher (Intercept™) for red cells and Mirasol® for whole blood. While there is widespread use of PRT for platelets and plasma in many high income countries, adoption is not universal. The available health economics data for many of the technologies is not robust, but the relative cost-effectiveness of these technologies may have contributed to decisions regarding implementation in several settings.

129. Infectious diseases and Australian blood transfusion safety: Emerging risks and current research

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Transfusion safety can be impacted by emerging risks, including those with an infectious origin. Emerging infectious diseases are those diseases that have rapidly increased in incidence or geographic range in the last 10–20 years or threaten to increase in the near future. Emergence is unpredictable and recent examples include Zika virus (ZIKV), and hepatitis E virus (HEV). These diseases have the potential to pose a risk to transfusion safety either directly, if they can be transmitted to a recipient in donated blood or indirectly, where outbreaks reduce the pool of available donors and therefore impact on the sufficiency of the blood supply. Many transfusion risks have become global; however, unique region-specific concerns exist. Research undertaken at the Australian Red Cross Blood Service investigates possible risks to the Australian blood supply to ensure continual safety.

Our research on HEV suggests that Australian blood donors, including those who have not travelled overseas, have been exposed to this virus. We have also provided evidence to suggest that the rate of HEV viremia is rare in Australia and lower than the published RNA prevalence estimates of other developed countries. We demonstrate that the risk of transfusion-transmitted HEV adverse outcomes is negligible and HEV RNA donor screening is not currently indicated.

We have also modelled the epidemic potential for ZIKV virus in Australia, assuming viraemic introduction, favourable weather conditions and presence of the vector (*Ae. Aegypti*). Modelled epidemic potential existed in a number of locations in northern Australia during the warmer months of the year. Interestingly, Australian locations that provide the greatest number of blood donors did not have epidemic potential for ZIKV. We are in the process of incorporating donor/donation parameters to assess possible impact to blood safety.

Collectively this research provides an evidence-based evaluation of emerging infectious threats to Australian blood transfusion safety. It will contribute the development of appropriate management strategies for future proofing our blood supply with respect to these emerging threats.

130. Pretransfusion tests in chronically transfused patients

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ABO/D typing and RBC antibody screening are the pretransfusion tests considered to ensure essential transfusion safety. Depending on the national/local rules and clinical background, other tests may be required: Rh(C/E/c/e)/K typing; extended phenotype; serological crossmatch; direct antiglobulin test; elution; adsorption; genotyping. Finding suitable blood for chronically transfused patients is challenging, especially for those with sickle cell disease (SCD). Indeed, people of African ancestry demonstrate specific features when compared to Caucasian donors: difference of prevalence for some common antigens; significant occurrence of rare types; high incidence of partial phenotypes; difference of prevalence for some low-frequency antigens. For example, VS+ and Js(a+) phenotypes, exceptional in Caucasians, are found in up to 40% of Africans. As those antigens are exceptionally present on reagent RBCs, the corresponding antibodies are usually undetectable. Intra-ethnic transfusion, often favored to match the patient's global phenotype, may lead to hemolytic reactions that are possible to mitigate by performing a systematic serological crossmatch. SCD patients often demonstrate potent autoantibodies and adsorption tests are required to rule out underlying alloantibodies. SCD patients are also subject to many variant phenotypes/genotypes of clinical significance, such as partial Rh antigens. Besides, an anti-e found in a e+ patient, that cannot be adsorbed onto autologous RBCs or identified after allogeneic adsorptions, is a probable surrogate marker for an antibody to a high-prevalence Rh antigen, e.g. anti-Hr^S or anti-Hr^B. The significant prevalence of clinically relevant variants in the Rh and MNS systems in SCD patients supports a systematic extended RBC genotyping, including *RHD/RHCE*. The growing complexity of pretransfusion tests in such patients needs to be considered by the health authorities in terms of budget allowance. It is all the more important because "allele matching", using DNA-chips and more recently exome sequencing, is expected to likely become a routine policy for SCD patients in the close future.

131. Pretransfusion testing in AIHA

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Transfusion can be life-saving in severely anemic patients suffering from autoimmune haemolytic anemia. Pretransfusion laboratory provides clues for the cause of the autoantibody-mediated blood cell destruction. The direct antiglobulin test shows if warm-reactive IgG autoantibodies, or complement-activating warm or cold reactive IgM class autoantibodies are present. Dependent on the urgency to provide donor blood, different approaches can be taken to select compatible blood. Adsorption of autoantibodies to exclude the presence of red blood cell alloantibodies has the advantage that also the specificity of autoantibodies can be determined to improve compatible blood selection. If transfusion can not be delayed, donor blood compatible for Rh CcDEe, K, Fy, Jk, Ss antigens and negative for Wr(a), Kp(a), Cw is selected in the Netherlands. This will prevent the formation of red blood cell alloantibodies, which may occur at a high rate in AIHA patients. However, this type of extended matching is not feasible for all transfusion episodes in AIHA patients, moreover, it may also not be necessary. To obtain improvements in the diagnosis of AIHA and prediction of its clinical course, including whether or not an inflammatory response is initiated upon transfusion, studies on the pathophysiology of AIHA are mandatory. This lecture will present the laboratory work-up in AIHA in the Netherlands, discuss the clues for the clinical advice serology can provide and the different approaches to select compatible donor units.

132. Transfusion support for patients with rare phenotypes

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What is a rare phenotype? The definition of a rare blood group is someone who is negative for a high prevalence antigen where the frequency of this antigen negative phenotype is less than 1 in 1000. People with a combination of antigen negative phenotypes may be considered “rare” where the prevalence of that combination is less than 1 in 1000 in the population. The lack of these common antigens is associated with a risk of alloimmunisation following exposure to red blood cells through pregnancy or following transfusion.

When a patient with a rare blood group is identified, particularly when they have antibodies, a sample should be referred to the Blood Service Reference laboratory to enable the confirmation of availability and suitability of potential donors to support the patient’s transfusion needs.

To minimise the need for transfusion, the Blood Service encourages treating clinicians to adhere to the National Blood Authority’s Patient Blood Management (PBM) practices. PBM practices describe a range of measures for conserving a patient’s own blood and minimising or avoiding the need for transfusion. Where transfusion is unavoidable, we begin the search for suitable components.

Rare red cells may be sourced from:

- The Blood Service national fresh inventory or frozen inventory
- Allocated donations from the Australian Rare Donor Panel called in specifically for the patient, autologous donations, or directed donations (including family testing)
- Donations from overseas which are accessed through the International Rare Donor Register

Despite our best efforts, sometimes we are unable to find antigen negative blood for transfusion. How we plan to support these patients will depend on the clinical setting, the antibody status of the patient, future transfusion needs and the clinical significance of the associated antibody.

Ensuring we have a sufficient supply of rare blood is a constant challenge. The keys to improving the availability of rare blood are continued international collaboration, selective mass testing of donors and recruitment of patients once they return to good health or family members that may have inherited the same rare blood group.

136. Investigation and management of FNAIT

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Fetal/neonatal alloimmune thrombocytopenia (FNAIT) is a rare condition that occurs in approximately 1 in 1000 new-borns, and results from incompatibility in human platelet antigens (HPAs) between mother and fetus. FNAIT is the leading cause of severe thrombocytopenia in term born infants and can cause severe intracranial haemorrhage (ICH). Antenatal management, based on the weekly maternal administration of intravenous immunoglobulin (IVIG), strongly reduces the risk of fetal haemorrhages. Optimal postnatal management is not well known and primarily based on expert opinion and small case series. Currently, various treatment strategies are used, including platelet transfusions (PTx) with a wide variation of thresholds (platelet count <20, 30 or 50 x10⁹/L) with either HPA-compatible or random-donor platelets, and/or IVIG. Despite the lack of evidence, transfusion with, HPA-compatible platelets is generally considered the treatment of choice. However, in case of emergency when HPA-compatible platelets are not directly available, transfusion with random-donor platelets has been suggested as a safe alternative, although these may have shorter survival time, due to the presence of HPA-alloantibodies in the new-borns' blood. Most cases of FNAIT are caused by HPA-1a antibodies. Already since the late 90's research is aimed to find the evidence whether an HPA-1a screening program would be of benefit to prevent ICH or other severe bleeding in newborns. In the Netherlands and in other European countries, prospective large scale studies are running to find the pieces of missing knowledge. Recent findings that HPA-1a antibodies specifically reactive with the endothelium via binding to the vitronectin receptor may point to a possibility to select high-risk bleeding pregnancies. The laboratory work-up if FNAIT is suspected, the ante- and postnatal treatment and the missing knowledge to decide on screening for immunization during pregnancy will be discussed in this lecture.

137. The role of Human Leucocyte Antigen (HLA) antibodies in Feto-Neonatal Alloimmune Thrombocytopenia (FNAIT)

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FNAIT is an uncommon, but not rare, complication of pregnancy. It occurs when IgG specific maternal anti-platelet antibodies, produced in response to maternal-paternal platelet antigen incompatibility, cross the placenta and bind to foetal platelets which have inherited paternal antigens. Varying degrees of thrombocytopenia occur which can cause bleeding in the foetus/neonate. In its most severe form FNAIT can result in intra-cranial haemorrhage and death.

As well as expressing specific human platelet antigens (HPA), platelets also express HLA Class I antigens on their cell surface. The role of HPA specific antibodies in causing FNAIT is well known and well documented in the literature. The role of HLA antibodies in FNAIT remains unresolved almost two decades into the 21st century. Although HLA antibodies are a common consequence of pregnancy, reports indicate 50% of maternal samples have HLA antibodies detected by Luminex technology. Yet 50% of all pregnancies do not result in thrombocytopenic babies.

The Platelet and Neutrophil Reference Laboratory of the Australian Red Cross Blood Service has been testing referred suspected FNAIT samples for four decades in Queensland. In the experience of this laboratory, less than 20% of investigations have identified HPA specific IgG antibodies in maternal serum. The remaining cases have either had no HPA or HLA antibodies detected, or only HLA IgG antibodies identified in maternal serum.

Improvements in testing technologies have allowed more detailed examination of HLA antibodies. Laboratory data from 2016 onwards, approximately 250 cases, will be presented and examined in an effort to shed some light on whether HLA Class I IgG antibodies can be grouped with HPA antibodies as being causative agents in FNAIT.

138. NAIT - it's uncommon, but potentially devastating: an update from the Australian NAIT Registry

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Introduction

Neonatal (fetomaternal) alloimmune thrombocytopenia (NAIT) is uncommon but can cause profound thrombocytopenia leading to severe haemorrhage in the fetus/neonate with devastating long-term sequelae. The Australian NAIT registry identifies and characterises cases of NAIT, providing local data on diagnosis, management and outcomes to inform practice.

Methods

All cases registered from 2009 to 2018 were included. NAIT cases were defined as:

- Pregnant women treated antenatally for NAIT, regardless of laboratory results
- Fetus/newborn with thrombocytopenia, bleeding and maternal HPA antibodies

Results

103 cases were identified from 31 hospitals across Australia.

The most common antibody specificities reported were anti-HPA1a (62%) and anti-HPA5b (6%), with anti-HPA3a, HPA5a and others also reported.

Thirty-four (40%) cases were antenatally anticipated or diagnosed, and 30% of these mothers received intravenous immunoglobulin (IVIg), for a total of 33,752 grams (\$1,974,492 based on current price of \$58.50/g). Complications of IVIg therapy were recorded in a small minority of women.

No intrauterine platelet transfusions were recorded. In 42 cases (41%) neonatal platelet transfusions were documented, with 28 neonates receiving IVIg in addition to platelets, and 5 receiving IVIg alone.

Short-term outcomes for babies with NAIT were generally favourable. The most common clinical features in affected babies were petechiae and purpura (29%). However, 9 (9%) cases had antenatal or postnatal intracerebral haemorrhage, and 4 (4%) deaths were recorded.

Conclusion

Short-term clinical outcomes reported to the NAIT Registry are generally positive; however, serious outcomes do occur. Costs of diagnosis (including HPA/HLA genotyping, antibody screening, and imaging to document bleeding) and initial management are considerable, but not well characterised overall, and no long-term costs of care or clinical outcomes data are available. Long-term follow-up of NAIT-affected pregnancies would be helpful.

Acknowledgement: We thank participating patients, institutions and staff for supporting the NAIT Registry.

139. Hints for successful systematic reviews

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Find out how to conduct a systematic review successfully from the Co-ordinating Editor of Cochrane Haematological Malignancies. Tips and tricks for conducting systematic reviews, as well as a brief introduction to GRADE for evidence synthesis.

140. Pitfalls in genotyping

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Blood types are routinely investigated by hemagglutination testing, with some limitations that may be overcome by molecular testing. Genotyping is claimed only to predict a phenotype, as several discrepancies with phenotyping may occur. However, false-positive reactions also exist for phenotyping methods. Many reasons explain those discrepancies, with four possible combinations:

False positive phenotype/True negative genotype

- Positive DAT (IgG) when IAT is required for serotyping (e.g. some reagents for extended phenotyping)
- Antigen-negative patient recently transfused with antigen-positive RBCs
- Polyclonal antisera including an antibody to a low-prevalence antigen
- Cross-reactivity (e.g. some widely-used anti-M clones cross-react with the Henshaw antigen)
- RBC polyagglutination
- Expression of epitopes by a variant homologous gene (e.g. D epitopes by *RHCE*, RhCE epitopes by *RHD*)
- Pseudoreactivity due to hybrid genes (e.g. gene conversion between *RHD/RHCE*)

2. False negative phenotype/True positive genotype

- Antigen-positive patient recently transfused with antigen-negative RBCs
- Partial antigen nonreactive with some clones
- Weak antigen expression
- Poor quality of antisera
- RBC alteration with antigen destruction

3. True negative phenotype/False positive genotype

- Silent alleles: mutation in the coding sequence of the gene, mutation in the gene promoter, alteration of a transcription factor
- Protein-protein interaction at the RBC surface
- Natural microchimerism
- Mistaken allele

4. True positive phenotype/False negative genotype

- Allelic dropout (heterozygote individual erroneously concluded as homozygous)
- Preferential amplification of one allele when its denaturation is favored
- No/weak amplification due to DNA inhibitors

Although there is a systematic use of appropriate positive/negative controls and implementation of proficiency testing programs in molecular testing, the occurrence of some genotyping errors are difficult to predict (e.g. allelic dropout). However, despite those limitations that we all need to be aware of, genomics is now considered an essential and reliable tool in immunohematology reference laboratories.

143. Haematological features, transfusion management and outcomes of Massive Obstetric Haemorrhage: Findings from the Australian/New Zealand Massive Transfusion Registry

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Introduction

Massive obstetric haemorrhage (MOH) is defined as blood loss of ≥ 1000 ml during pregnancy and the puerperium with rising incidence and severity in the developed world.

Methods

We performed a bi-national, multi-centred, cohort study of women who received massive transfusion for MOH using the Australian and New Zealand Massive Transfusion Registry (ANZ-MTR). MOH was defined as ≥ 24 weeks gestation requiring ≥ 5 red blood cells (RBC) units within 4h.

Results

249 patients from 18 Australian and 5 New Zealand hospitals met the inclusion criteria. Bleeding causes included obstetric trauma (n=48, 19%), uterine atony/abnormal forces of labour (n=56, 22%), placenta praevia (n=51, 20%), other types of morbidly adherent placenta (n=24, 9%) and other causes (n=22, 8%).

Ninety-five and 87% of women with prolonged nadir APTT/INR and nadir platelet count $< 50 \times 10^9/L$, respectively, received fresh frozen plasma (FFP) and platelets, while only 74% of women with nadir fibrinogen $< 2g/L$ received cryoprecipitate, with only 24% receiving > 5 units. The median FFP: RBC ratio (IQR) at 4h and 24h was 0.60 (0.33-0.80) and 0.57 (0.33-0.75) respectively.

Intensive care unit (ICU) admission and/or hysterectomy occurred in 44% and 29% of cases respectively. On multi-variable analysis, emergency caesarean section (OR 4.9, 95%CI: 2.0-11.7), placenta praevia (OR 7.2, 95%CI: 2.0 – 26.4) and cases with > 5 RBC units transfused before the first cryoprecipitate unit (OR 9.4, 95%CI: 3.1-28.1) were found to be independently associated with an increased risk of hysterectomy.

There were three deaths, including one due to amniotic fluid embolism.

Conclusion

This bi-national study is one of the largest cohorts of MOH described to date. FFP and platelets were more likely to be transfused than cryoprecipitate in patients with abnormal haemostasis parameters. MOH resulted in mortality and significant morbidity, including hysterectomy which was associated with emergency caesarean section, placenta praevia and later administration of cryoprecipitate.

144. Intra-uterine transfusions with adult RBC may exacerbate physiological anaemia of the newborn

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Aim: Retrospective audit of intra-uterine RBC transfusions (IUT) and related neonatal parameters in New Zealand (NZ), 2005 – 2017 to test the hypothesis: IUT with low oxygen affinity HbA-RBC exacerbates physiological anaemia of the newborn.

Methods: Maternal antibody, IUT and neonatal data from NZBS and DHB records. Statistical analyses: descriptive statistics, comparisons between individual babies, and in babies collectively, with data on healthy neonates¹, Pearson's correlation r and R^2 .

Results: Data on 77 pregnancies associated with IUT. 53/77(68%) involved anti-D, 12/77(15%) anti-K, 16/77(21%), other antibodies (some involved multiple antibodies).

Maternal antibody(n)	IUT median (range)	IUT – gestational age in weeks median(range)		Hb(g/L) median(range)		Post-natal RBC transfused median(range)
		1 st	last	birth	Lowest, 0 – 3 m	
Anti-D(53)	2(1-10)	28(19-35)	33(23-36)	133(54-183)	80(42-145)	2(0-12)
Anti-K(12)	1.5(1-5)	25(22-34)	31.5(23-34)	131(100-179)	81(70-102)	1(0-6)
other(16)	2(1-3)	33(24-36)	33(26-36)	132(34-165)	83(57-151)	2(0-8)
Median	2	28	33	132	81	2

Neonatal Hb, regardless of antibody or age, were lower than mean – 2SD for age. Though R^2 values were low for all comparisons, there were positive correlations between IUT numbers and age at last post-natal transfusion, birth Hb, and number of post-natal transfusions (r , 0.4). There were negative correlations between age at first IUT and age at last post-natal transfusion (r , -0.3), and number of post-natal RBC transfusions. r values comparing IUT numbers and highest/lowest Hb post-birth were near 0 as were those between age at first IUT and birth Hb, and highest/lowest Hb post-birth. With anti-K, there is stronger positive correlation between IUT numbers and number of post-natal transfusions (r , 0.5), and between age at first IUT and number of post-natal RBC transfusions than with anti-D. Likewise, with anti-K there is stronger negative correlation between age at first IUT and the highest Hb post-birth (r , -0.6).

Conclusion:

The hypothesis is supported but further studies are necessary.

Reference:

Palis, Segel. Blood Reviews 1998; 12: 106-114

145. Fibrinogen concentrates versus blood products in critical bleeding: systematic review and experience of massive transfusion in a tertiary referral hospital

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Background

Critical bleeding necessitating high volume blood transfusion occurs in settings such as major surgery, obstetric haemorrhage or extensive trauma. Massive Transfusion Protocols (MTPs) are often used to avoid dilutional coagulopathy. Hypofibrinogenaemia in this setting is associated with defective haemostasis however the ideal source of fibrinogen replacement in these situations is unclear. Options available include fibrinogen concentrates (FC), fresh frozen plasma (FFP) and cryoprecipitate (cryo). Evidence of which product is the most efficacious and cost effective is lacking.

Aim

To assess the evidence for fibrinogen concentrate versus standard blood products in critical bleeding and determine the economic feasibility of introducing fibrinogen concentrate to MTPs.

Methods

We performed a literature search using Medline, SCOPUS, EMBASE and CENTRAL databases as well as searching of references and trial protocol registries. Studies were included if they compared fibrinogen concentrate with allogeneic blood products. The primary outcome was all-cause mortality with secondary outcomes of blood loss, blood product usage, hospital stay, transfusion reactions and haemostatic parameters. An audit of MTP activations in our institution over a six-month period was conducted to assess for current product use and wastage.

Results

2167 papers were identified on initial searching. 11 relevant trials were identified, two randomised controlled trials and 9 non-randomised studies. 3 trials examined FC versus cryo whereas the remainder compared to FFP. No significant differences in mortality were observed in any trials. Product use was decreased with FC compared to FFP but not cryo. There were conflicting results for hospital stay, transfusion and minimal reporting of adverse outcomes. Viscoelastic parameters were improved in those receiving FC. Replacing cryo with FC would cost ~AUD\$100,000 a year at our institution.

Conclusions

There is weak evidence to support the use of FC over FFP however none over cryoprecipitate. Economic analysis did not support the transition to fibrinogen concentrate over cryoprecipitate for our hospital MTP protocol.

146. The use of an electronic tablet to enhance and improve the consent process for a blood transfusion

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Background/Aims

The consent process is essential step in the administration of a blood transfusion to patients. The quality of the process of consent is variable and can be influenced by the experience of the doctor and the time they have available to obtain informed consent. On occasion a patient has reported that they were not provided all of the essential information and were not well informed before giving consent. Our centre aimed to produce a short video outlining all of the essential information for the informed consent for a blood transfusion to ensure consistency of information and ensure all of the relevant information was delivered and to assess patient satisfaction with this method of information delivery.

Method

We developed a short video covering all essential aspects of the consent process for a blood transfusion for the population of patients who attended our haematology day treatment unit and delivered it to 20 patients. We developed a short questionnaire which was delivered to the patients after watching the video to assess their satisfaction with the use of an electronic device to deliver medical information as well as their satisfaction with the information delivered. We completed this study on both a population of patients who were having their first transfusion as well as those having subsequent transfusions. A secondary end-point was to assess those patient having subsequent transfusions and to compare their assessment of the e-consent material compared to that provided by a doctor. All patients who required consent were also attended by a doctor afterwards for a standard consent procedure.

Conclusion

We concluded that the use of an educational video as an enhancement to the consent process was satisfactory to patients, may reduce junior medical officer workload and ensured that all essential information was conveyed in a consistent manner.

147. Functional assessment of the impact of anaemia and transfusion

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Background

Transfusion in chronic anaemia primarily aims to improve quality of life, but this is difficult to measure and impacted by concurrent illness and life events. The haemoglobin concentration is often used as a trigger for transfusion in the absence of better indicators.

Aim

To determine the effect of anaemia and transfusion on exercise capacity and fatigue.

Method

Participants with and without anaemia performed the six minute walk tests (6MWT) as part of an ongoing observational study. A subgroup of participants had repeated assessments following transfusion. Participants were asked to rate their current symptoms of dyspnoea or fatigue before and after the 6MWT using the Borg scale. Interim analysis included Pearson correlations to determine factors associated with anaemia. Paired T tests were performed to evaluate the impact of changes in haemoglobin concentration or transfusion. The study was approved by the ACT Health Human Research Ethics Committee.

Result

There were 45 participants completing 58 6MWTs as part of this interim analysis. While there was a significant correlation between the haemoglobin concentration and 6MWT distance, there was considerable heterogeneity in distance unrelated to haemoglobin ($R^2 = 0.22$, $P < 0.01$). There was no difference in the reporting of dyspnoea or fatigue levels at rest, but there was a correlation with fatigue levels after exercise and haemoglobin levels ($p < 0.05$).

Pre and post transfusion testing was conducted in 11 patients, with a mean haemoglobin difference of 20.5g/L (Range 5-47g/L). Higher haemoglobin levels were associated with a lower pre-test fatigue score (mean difference of 1 on the Borg scale, $p < 0.02$), but a greater change in post exercise fatigue (mean difference of 1.4, $p < 0.01$). There was no change in dyspnoea scores with change in haemoglobin concentration or transfusion.

Conclusion

Functional assessment with exercise improves the ability to detect the impact of changes in haemoglobin and transfusion.

148. Optimising Group and Screen ordering in Elective Joint Replacements: Results of an Audit

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Aim: Pre-operative Group and Screen (G&S) testing is commonly performed in elective joint replacement surgery, with only a small proportion receiving a transfusion. We examined the incidence of G&S ordering, and the factors which influenced transfusion in this population. Our aim was to create an institution-specific recommendation to rationalise G&S orders.

Method: All patients undergoing elective hip and knee replacement surgery, from Jan 2017 to Feb 2018, were audited retrospectively. Electronic medical records and transfusion records were used to determine the pre-operative G&S ordering and transfusion rates. Surgical and patient factors influencing transfusion e.g. preoperative blood results, demographics and type of surgery were also recorded.

Results

100 of the 110 elective joint replacements had a pre-operative G&S. Unexpectedly, 17% of these had expired prior to the day of surgery. 14 (13%) patients were transfused during their admission, though only 3 patients transfused on the day of surgery. All 3 were female, with pre-operative anaemia and abnormal coagulation studies.

In terms of relative risk, revision/complex joints were five times more likely than primary joints to be transfused. Likewise, those anaemic pre-operatively were 8 times more likely than non-anaemic patients, and those with an eGFR of <60mls/min were 12 times more likely than those with eGFR > 60mls/min.

Factor	No Pts	No Transfused* (%)
Primary	95	8 (8%)
Revision/Complex	15	6 (40%)
Hips	45	7 (16%)
Knees	65	7 (11%)
Female	53	10 (19%)
Male	57	4 (7%)
Anaemia	20	9 (45%)
No Anaemia	90	5 (6%)
Ferritin <100	27	7 (26%)
Ferritin >100	49	5 (10%)
eGFR < 60mLs/min	19	10 (53%)
eGFR > 60mLs/min	91	4 (4%)

*during the acute surgical admission

Conclusion

The strongest predictors of transfusion during the admission were revision/complex surgery, pre-operative anaemia and renal impairment. All patients transfused within 48 hours of surgery had at least one of these risk factors. On the day of surgery, less than 3% of patients who had a G&S, went onto be transfused, giving a very low transfusion index of 0.03. It is therefore arguable that patients without the above risk factors do not need a pre-operative G&S, and further research is warranted.

149. Using the Toolkit for Maternity Blood Management to improve a woman's haemoglobin at childbirth

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Introduction

Routine ferritin screening is not recommended in obstetrics guidelines. If haemoglobin alone is measured, antenatal iron deficiency (ID) can go unnoticed. Increased iron demands during pregnancy may result in progression to iron deficiency anaemia (IDA). First trimester ID correlates with lower haemoglobin at delivery,¹ which increases risk for red cell transfusion in women with PPH.²

Methods

Using clinical practice improvement (CPI) methodology, four organisations collaborated towards sustained systemic changes to optimise a woman's iron and haemoglobin at childbirth. Haemoglobin assessment and optimisation action plan and flowcharts, audits, and patient handouts to identify and improve management of ID/IDA were developed and piloted. The toolkit created from these successful collaborations includes implementation considerations for change management and allows local customisation.

Results

High rates of ID (ferritin ≤ 30 $\mu\text{g/L}$) in pregnancy were identified: mean 67%, range 42-79%.³ In one hospital, there was a decrease in the rate of anaemia at delivery from 12.2% to 3.6% and red cell transfusions from 26 to 17 units/month (mean).⁴ Staff embraced the tools that provided a 'long needed guidance and consistent approach' and empowered them to assist women with the best possible management advice.

Discussion

The toolkit provides proven strategies for routine ferritin screening, which reliably detects antenatal ID and allows early provision of iron therapy, resulting in improved haemoglobin levels prior to delivery.

150. Transfusion associated circulatory overload: promoting awareness and reporting

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Background

The Serious Transfusion Incident Reporting (STIR) program has included transfusion associated circulatory overload (TACO) since its inception. There is ongoing concern regarding underrecognition and underreporting of TACO.

STIR identified 3 areas for practice improvement: staff awareness, risk assessment tools and single unit transfusion policies.

Aim

To describe activities to increase awareness of TACO among clinical staff.

Methods

An education campaign was developed to implement during September 2017 at 79 Victorian health services. This included posters, swing tags attached to blood bags and information sheets for blood fridges. The information was based on the TACO pre-transfusion checklist, SHOT Annual report 2016.

7000 tags were sent to pathology providers, with supporting material. The Transfusion Nurse or equivalents were informed.

Results

TACO notifications to STIR are low (average 8/year, range 1-14); however, severity is high (28% have a severity rating 2 - events that result in a temporary loss of function, unrelated to the natural course of the patient's illness and differs from the expected outcome of care), although no deaths reported. In the 6-months (Jan-Aug) prior to the campaign there were 7 notifications; in the 6-months (Sept-February) following the campaign there were 12 notifications.

Feedback was positive with several health services requesting additional tags and non-Victorian health services requesting tags. A survey of Transfusion Nurses demonstrated that the majority had participated and would again.

Conclusion

There has been an increase in reporting, however, it is difficult to determine if this is due to the campaign or normal fluctuations. In addition, any change in reporting may reflect increased recognition of TACO (increased reports) or improved clinical care for those at risk (decreased reports). Awareness campaigns, such as that described, help to educate clinical staff and will assist improving the care of those who require transfusion but are at risk of volume overload.

151. A practical and patient centred approach to the identification and management of iron deficiency and iron deficiency anaemia

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Background

Murrumbidgee Local Health District (MLHD) identified a significant increase in the number of patients admitted to acute facilities for management of diagnosed iron deficiency with or without anaemia. Current clinical management is lengthy iron infusions, which are costly, reduce acute bed access, with significant impacts on patients and carers. Patients were also requesting more information allowing greater involvement in treatment planning.

Methodology

A redesign methodology, consisting of a mixed-method approach was utilised to review gaps in best practice care. Diagnostics included: review of activity data; surveys; interviews; and value stream mapping. A collaborative cross-sector approach inclusive of the patient, primary, community and hospital care settings, was trialled by a pilot site. MLHD partnered with patients enabling provision of tailored health information and engagement in treatment planning with their GP. Patients were offered appropriate treatment options for iron repletion, including access to rapid iron infusion through primary care.

Outcomes/Results

This pilot indicated significant benefits through implementation of a cost effective, patient-centred approach to iron deficiency management that is evidence-based, and available locally reducing the imposts of travel and hospital admission. Initial results revealed a 74% reduction in iron infusions in the acute hospital setting, and a decrease from 90% to 25% of patients indicating they would like additional information on replacement therapy.

Following pilot site success, MLHD has extended changes to a district level, supported by the introduction of local policy promoting the safest, most cost-effective and evidence-based approach to management of ID (Iron Deficiency). Further primary care engagement continues through education sessions, newsletters and incorporating local policy into GP Health Pathways.

Conclusion

Iron deficiency management can be effectively managed utilising a comprehensive integrated approach in the community, primary and hospital settings to ensure the best outcomes for the patient, carers and health care services.

152. Health and quality of life impacts of switching from IVIG to SCIG treatment in patients with primary immunodeficiency disease

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Aim

To assess the quality of life (QoL) and health impacts in primary immunodeficiency disease (PID) patients who switched from hospital-based intravenous immunoglobulin (IVIG) to home-based subcutaneous immunoglobulin (SCIG).

Method

A project specific questionnaire regarding immunoglobulin treatment was developed and used. Ten adults PID patients treated at the Sunshine Coast Hospital and Health Services who were on IVIG and then switched to SCIG treatment were recruited. These patients completed the questionnaire when they completed three years of SCIG treatment.

Result

Side effects with SCIG were no different in year three compared to results from year one data (unpublished data). All patients experienced swelling at infusion site and 9/10 redness and 8/10 pain at infusion site. One patient suffered all 11 side effects listed on questionnaire and used paracetamol, antihistamine and anti-nausea medication to manage them. Another patient experienced 10 side effects and used paracetamol. Both of these patients rated the side effects as “somewhat manageable”, while all other patients deemed them as “always manageable”.

Some patients considered the SCIG infusion diaries provided as not important and stopped completing them. One patient suggested to replace the diaries with an app.

Patients commented that they:

- prefer SCIG due to less hospital visits, less antibiotic use
- less side effects with SCIG compared to IVIG
- support for self-injectors was limited to SCIG program sites

Two patients were retired, three on disability pension and five were employed. Employed patients commented that SCIG treatment resulted in less time off work for treatment. Overall, 7/9 patients stated their health was best on SCIG, and 8/9 patients scored their QoL best while on SCIG compared to IVIg.

Conclusion

While side effects with SCIG remained the same over the three-year period, patients reported that SCIG provided more benefits compared to IVIG.

153. National comparative audit

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The National Comparative Audit in the UK has been supporting quality improvement in transfusion since 2003. The NCA perform audits in all aspects of transfusion and its work will be highlighted with reference to the PBM surgery audits, audits in haematology patients, and the audit of patients at increased risk of TACO.

These have highlighted areas that require quality improvement and also areas where we achieved improvement in practice.

154. REDS-III

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This presentation will review the Recipient Epidemiology and Donor Evaluation Study (REDS-III). REDS-III is the largest transfusion medicine observational epidemiology study funded by the US National Institutes of Health, National Heart, Lung, and Blood Institute. The REDS-III program has conducted specific protocols on topics of high relevance in transfusion medicine, including risk factors for transfusion-associated circulatory overload, short-term outcomes of outpatient red cell transfusion in the elderly, and an assessment of donor demographic, genetic and metabolomics factors associated with spontaneous and stress haemolysis in stored leukoreduced red blood cell concentrates. In addition, a major focus of the program was the development of the linked donor-component-recipient database. The REDS-III linked database contains detailed information on donors, component modifications, and the electronic health records of both transfused and non-transfused patients. The database allows for the investigation of a range of research questions such as the general epidemiology of red cell, platelet, and plasma transfusion in the USA, and specific questions assessing the impact of donor characteristics on patient outcomes; for example analyses are in progress on the effects of donor age, sex and parity on recipient survival, as well as other specific questions including rates and correlates of alloimmunisation in recipients. The international component of the REDS-III program has conducted studies in Brazil, China, and South Africa focused on topics of high relevance in each of those countries. In Brazil, studies have centred on the risk and consequences of transfusion-transmitted dengue and Zika viruses, and a large cohort of sickle disease patients was enrolled in long-term follow-up to understand clinical outcomes in this frequently transfused population. In South Africa, a study of recently HIV-infected donors placed on treatment after being identified through donation testing may provide insights into the benefit of very early therapy on reducing the HIV reservoir relevant to disease cure. Through the overview of the scope and available findings from REDS-III, this presentation will contribute to the central objective of this session, a discussion on whether data can improve practice.

155. Red cell transfusion - precision vs imprecision medicine

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The discovery of blood groups led to the first example of “precision medicine.” By matching blood donors with recipients, personalized therapy improved transfusion safety. The US National Institutes of Health established an early partitioned data set on a mainframe computer with 2700 donors phenotyped by serology for 20 red cell antigens. Combining mid-20th century typing with emerging informatics enhanced donor-recipient compatibility and red blood cell inventory management. The current re-emergence of precision medicine employs inexpensive molecular typing paired with powerful bioinformatics for mass-scale blood cell genotyping. Rapid screening for nucleotide polymorphisms with automated DNA analyzers will supplement or replace serology for selecting the most suitable units for patients with multiple alloantibodies. In a US pilot program, a web-based interface allowed community hospitals to search local inventories for the most suitable red cell units via an antigen query portal, an example of precision medicine, largely invisible to the practicing physician, that could transform the way compatible blood is supplied and provide better, more efficient care.

In contrast, the decision to transfuse blood has become less precise. Current transfusion guidelines rely primarily upon a single hemoglobin / platelet concentration as a “transfusion trigger.” However no single measure is likely appropriate for all patients. Whereas these guidelines are based on randomized trials, the gold standard for evidence-based medicine, not all trials are created equal; appropriate controls are crucial. “Precision” medicine endorses adjusting therapies based on the individual patient’s genetic data, personal characteristics, comorbidities and severity of disease. More definitive controlled trials integrating personalized physiological and clinical factors that provide objective bases for initiating, continuing, or discontinuing transfusion should be undertaken. Protocol-driven therapy designed for the average patient may benefit the majority, yet still prove suboptimal or hazardous for a substantial minority. Indiscriminate reliance on fixed targets and rigid protocols should be defined as “imprecision medicine.”

156. Hemovigilance in the US

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The idea of national surveillance for detection, assessment, monitoring, and prevention of adverse effects associated with pharmaceutical products (“pharmacovigilance”) arose following a 1960’s public health catastrophe, phocomelia in infants born to women who had ingested the drug thalidomide during pregnancy. From the concept of pharmacovigilance arose the notion of “hemovigilance,” surveillance of the transfusion process from the collection of blood through follow-up of recipients to detect undesirable effects and prevent their recurrence. In the US, the discovery that blood transfusion could result in infectious hepatitis ushered in an era of hemovigilance focused on transfusion-transmitted infection. The roots of early US hemovigilance were cultivated by federal agencies, the NIH, CDCP, and FDA. A longitudinal study of linked donors and recipients at the NIH Clinical Center established that over a 40-year period, a variety of interventions resulted in a decline of transfusion-transmitted hepatitis following cardiac surgery from about 30% to near zero. NIH funded a similar multicenter study based in four cities across the US. The latter study, originally designed to monitor hepatitis risk, was broadened beyond hepatitis with a prescient designation as the “Transfusion-transmitted Virus (TTV) Study. There followed an alphabet of NIH studies: The Transfusion Safety Study (TSS), the Frequency of Agents Communicable by Transfusions Study (FACTS), the Retrovirus Epidemiology in Donors Study (REDS), and the Viral Activation Transfusion Study (VATS). Each had a slightly different focus, geographic distribution, and target population and importantly each supported a biorepository for future studies. REDS, after an extremely productive 20 years of studies, retained the acronym but evolved into the Recipient and Donor Study (REDS III) which contains an international element as well as large linked databases between blood providers and 7 participating hospitals. In addition, REDS III was designed to capture non-infections transfusion reactions.

The CDCP and FDA likewise supported hemovigilance initiatives. CDCP introduced a hepatitis surveillance system in 1975 and AIDS surveillance in 1985. Surveillance data were published in the CDCP’s Morbidity and Mortality Weekly report (MMWR). In 1975 the FDA introduced regulations requiring all registered blood establishments to report deaths associated with blood collection, transfusion and plasmapheresis. However no analysis of these events was publicly available until raw data were published in the peer reviewed literature. A decade later, a similar publication reviewed the FDA’s 10-year mortality data. The FDA also supported the MedWatch program for voluntary reporting of severe adverse or sentinel events. Although reports of transfusion reactions from physicians and hospitals were encouraged, MedWatch was used primarily for pharmaceuticals and by manufacturers; the raw data for blood reports were available in a public database but transfusion data were not presented for public information. The AIDS epidemic had a dramatic impact on hemovigilance in the US. Blood collectors such as the American National Red Cross were analyzing and reporting donor surveillance data as early as 1985. The Secretary of the US Department of Health, Education, and Welfare commissioned the Institute of Medicine (IOM) to analyze the response to AIDS. The IOM report of 1995 emphasized the “critical importance of a national system for proactive surveillance of new and emerging infectious agents that could pose a risk to the blood supply.” This report resulted in establishment of the Secretary’s Blood Safety and Availability Committee, the most influential US policy organ regarding transfusion, and the one that inspired the current U.S. hemovigilance efforts. In 2007, the CDCP, in collaboration with the AABB, designed a surveillance system to monitor transfusion-related adverse events nationally. This Hemovigilance Module was launched in 2010 as part of the National Healthcare Safety Network, CDCP’s existing voluntary, internet-accessible surveillance system used by more than 12,000 US health care facilities for describing health care-associated infections. DonorHart™ a partnership led by AABB to track and trend adverse events associated with blood donation is a voluntary web-based system designed to analyze facilities’ donor data, identify trends, and benchmark like organizations. These initiatives aim to rationalize what began in the US as a network of research studies and epidemiologic surveillance programs into a centralized, standardized reporting system capable of providing early warnings, analysis, and evaluation of risks to improve the safety of the blood collection and transfusion process.

157. The value of a structured haemovigilance program - experiences from Blood Matters serious transfusion incident reporting (STIR) system

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Haemovigilance reporting can identify priority areas for action and monitor the implementation of solutions. The importance of reporting has long been recognised, and in Victoria, the Blood Matters program established the serious transfusion incident reporting (STIR) system in 2005-6. It began as a pilot, and has expanded over the years to include 93 registered health services across four Australian jurisdictions (Victoria, Australian Capital Territory, Tasmania, and the Northern Territory). STIR plays an important role by tracking, trending and reporting events and providing recommendations to improve practice. Contributing to STIR also assists health services meet their reporting requirement outlined in the National Standards.

Haemovigilance reporting in Australia is voluntary, with the exception of sentinel events.

STIR receives both clinical and procedural events for fresh blood components, and in 2015 expanded to include cell salvage and RhD immunoglobulin events. To date a total of 1,942 cases have been reported.

Procedural events contribute a significant proportion of these events, highlighting that one of the biggest risks in the transfusion chain is related to human error, rather than product safety. Wrong blood in tube, near miss, incorrect blood component transfusion and RhD events account for 45% of reports. Patient identification issues feature commonly in these reports, and this has prompted Blood Matters to develop resources and provide targeted education.

Potential under-reporting of TACO events was raised as a concern. To promote staff knowledge and increase awareness, a TACO campaign was conducted in 2017. Positive feedback was received from health services, with requests for more of the campaign collateral, and a slight increase in TACO reports has been noted.

STIR is recognised as a robust haemovigilance system where data is validated through review by a multidisciplinary expert group. Contributing health services receive individual reports twice a year, with one coinciding with the annual report. The introduction of bulletins, highlight issues of interest or trends in a timely manner to health services, so they can make any changes necessary. An important feature of haemovigilance is the sharing of experiences and results nationally and internationally to improve patient outcomes.

158. International overview of haemovigilance

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The International Haemovigilance Network (IHN) defines haemovigilance as “A set of surveillance procedures covering the whole transfusion chain (from the collection of blood and its components to the follow-up of recipients), intended to collect and assess information on unexpected or undesirable effects resulting from the therapeutic use of labile blood products, and to prevent their occurrence or recurrence.”

Many countries have, or are developing, haemovigilance systems. Some countries or regions use modifications of the IHN definition, as their systems extend to include plasma-derived (fractionated) products, or are part of a broader biovigilance framework. Haemovigilance systems vary in scope and content: for example, voluntary or mandatory reporting? Donor, product and recipient events [true ‘vein to vein’], or only recipient adverse reactions? All events or just serious ones? All reports, or only confirmed cases? Cases accepted as submitted, or reviewed by expert group? Importantly, there is no ‘right’ or ‘wrong’ way to ‘do’ haemovigilance – what is important is that the system works within the health system in that country. All established systems have evolved over time, for example by moving from paper-based to computerised systems, or expanding to capture of additional events (such as ‘near miss’ events, cell salvage or incidents related to RhD immunoglobulin).

Definitions of most major donor and patient adverse reactions have been published collaboratively by the International Society of Blood Transfusion (ISBT), AABB and IHN. Additional work is underway, including on paediatric definitions, and in validation exercises. The definitions will require updating over time, reflecting experience with their applicability in practice, and as understanding evolves of the pathophysiology of some adverse reactions.

Most established haemovigilance systems publish reports, and are happy to share their processes, tools, and results. Guidance on establishing and sustaining haemovigilance systems is available from the World Health Organization and other sources. Individuals interested in haemovigilance are welcome to join ISBT’s working party on haemovigilance, and both established and developing haemovigilance systems are welcome to join IHN. Through these collaborations we can share experiences and participate in education, data sharing and analysis, and benchmarking at national and international levels.

159. Health economic analyses in blood safety

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Health economic analyses are important in many jurisdictions as contributing evidence to adoption or reimbursement decisions at the Ministry of Health or healthcare funder level. Health economic analyses measure the cost of illness, the cost of interventions to prevent, halt or cure disease, and the health benefits which result from use of interventions. In blood safety, health economics is controversial because many adopted interventions for blood screening do not conform to traditional normative values like cost-effectiveness thresholds used for pharmaceuticals and other health care interventions. Greater familiarity with the methods used in health economics may help blood services and clinical staff to be more informed consumers of the findings from these studies. Two types of analyses are important; budget impact analyses, an assessment of cost to implement as well as any potential savings achieved in averted health care expenditures, and cost-effectiveness analyses which directly assess the health benefits achieved for the transfused population relative to costs. As instructive examples, results from health economic studies of blood safety screens for Zika virus, HIV, HBV, and HCV will be discussed. Available health economic data for pathogen inactivation/reduction technologies will also be reviewed, where both budget impact and cost-effectiveness may be impediments to broader adoption in many jurisdictions. Overall, interventions in blood safety are less cost-effective (have higher cost per effectiveness achieved) than many other areas of health care. Demonstrated through the concept of revealed preferences, the expectation for a high level of safety, low tolerance for risk, and societal expectations for the prevention of transfusion-transmitted infections, in combination provide the justification for the adoption of interventions which would be considered cost-*ineffective* in other health care disciplines.

161. Platelet procoagulant potential is reduced in platelet concentrates ex vivo but appears to be restored in vivo following transfusion

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Aim: Platelet concentrates have reduced activation responses following ex vivo storage. However, little is known about their procoagulant responses pre- and post-transfusion. This study aimed to characterise the procoagulant potential of buffy-coat and apheresis platelets ex vivo and following transfusion, and to establish the procoagulant profiles of alternately stored platelets (cold storage and cryopreservation).

Method: Procoagulant platelets were assessed by flow cytometry (GSAO uptake with P-selectin exposure)¹ at rest and after agonist exposure (2U/mL thrombin ±10µg/mL collagen). Three ABO/RhD-matched, buffy coat-derived platelets were pooled (n=6) and compared to apheresis platelets (n=3), fresh citrated whole blood from healthy human volunteers (n=34) and fresh whole blood collected one hour after platelet transfusion from haematology patients with severe thrombocytopenia (n=3). Each pool was also immediately split to compare conventional (room temperature, RT) storage, cold-storage (2-6°C) or cryopreservation (-80°C with DMSO). Procoagulant platelets were measured at baseline, day 2, 5, 9, 14 for RT and cold-storage and immediately post-thaw for cryopreservation (n=6).

Results: Conventionally stored apheresis platelets had similar ex vivo procoagulant profiles to pooled platelets, however both had significantly fewer procoagulant platelets in response to agonist stimulation than fresh venepuncture blood from healthy volunteers (thrombin+collagen: Day 5 pooled 4.2±1.3% vs 12.5±5.8%, p<0.0001). After transfusion, procoagulant response to agonists was increased (thrombin+collagen: pooled 4.2±1.3 vs post-transfusion 20.1±4.3%; p<0.0001). Marked increase in procoagulant platelets was observed following cryopreservation (resting: conventional 0.3%; cryopreserved 25.6%; p<0.001). Cold stored platelets had significant increase in the resting procoagulant subpopulation on days 9 and 14 compared with RT (p<0.01 and p<0.001, respectively).

Conclusion: Conventionally stored platelets have reduced procoagulant potential when tested ex vivo, but significantly increase their procoagulant potential following transfusion. Cryopreserved platelets have high levels of procoagulant platelets pre-transfusion. Future studies are needed to determine the procoagulant potential of cold stored and cryopreserved platelets after transfusion

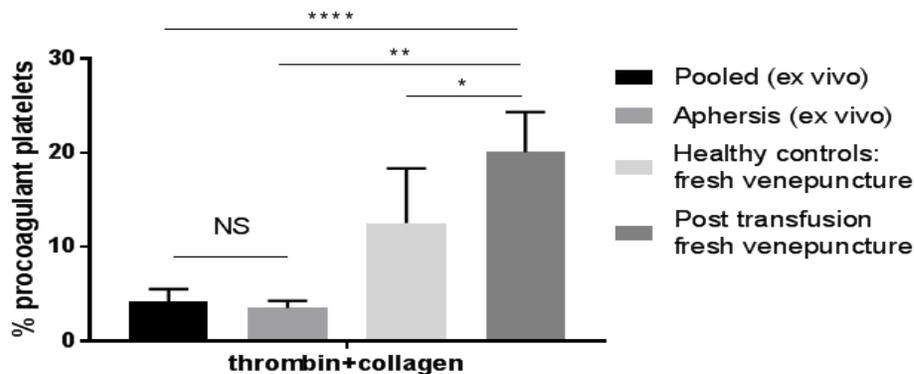


Figure 1: Comparison of thrombin and collagen stimulated buffy coat-derived pooled platelets (n=6), apheresis-derived platelets (n=3), fresh venepuncture from healthy controls (n=34) and fresh venepuncture from severely thrombocytopenic patients post-transfusion (n=3)

Reference:

Pasalic L et al, Novel assay demonstrates that coronary artery disease patients have heightened procoagulant platelet response, *J Thromb Haemost* 2018, 16:1-13

162. Predicting the number of Jk(a-b-) individuals in New Zealand using published datasets

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Aim

The need to provision Jk(a-b-) blood occurs commonly in New Zealand. This is due to large Polynesian, Māori and Southeast Asian populations and the high frequency of the *JK*02N.01* null allele in these groups. Previously, we presented genotyping results of 44 known Jk(a-b-) donors, identifying *JK*02N.01* and other null variants.¹ Here we aim to calculate the number of Jk(a-b-) individuals in New Zealand.

Method

Population Jk(a-b-) phenotype frequencies were constructed using gnomAD allele frequency data for the *JK* null variants rs78937798 (*JK*02N.01*, *JK*01N.06*), rs78242949 (*JK*02N.06*), rs565898944 (*JK*01N.04*, *JK*02N.08*), rs538368217 (*JK*02N.07*) and rs114362217 (*JK*02N.09*). Previous publications were used when relevant populations were not represented in gnomAD. Census data was used to predict the predict numbers of Jk(a-b-) individuals in these groups. Goodness of fit with observed donor data was measured by Fisher's Exact test.

Result

We predict 2,417 Jk(a-b-) individuals in New Zealand, at the time this data was collected. Individuals identifying as Pacific Islander, Māori and Filipino groups contributed 1,829, 230 and 327 individuals to this prediction, respectively, and compare well to the donor cohort (p-value = 0.74; Fisher's exact test). Inclusion of other groups no longer produces a good model (p-value = 1.81×10^{-10}). The exact binomial test indicated that the Caucasian donors were over-represented (adj. p-value = 4.54×10^{-5} ; Bonferroni correction).

Conclusion

The predicted number of Jk(a-b-) individuals in New Zealand is quite substantial. Caucasians were overrepresented in our donor cohort, if compared to allele frequency data reported on gnomAD. Our observed phenotype frequency in Caucasians is 3.88×10^{-5} . Likely, this differs from reported European frequencies due Polynesian or Māori ancestry among New Zealand Europeans.

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- 3) Henry S, Woodfield G. Frequencies of the Jk(a-b-) phenotype in Polynesian ethnic groups (letter). *Transfusion* 1995;35:277.
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163. Reversal of the anti-aggregant effect of ticagrelor using untreated platelets

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Aim

Ticagrelor is an antiplatelet agent that is indicated for prevention of thrombosis after acute coronary syndrome or after intra-coronary stent implantation. Ticagrelor increases the risk of bleeding, including major bleeding and fatal bleeding, which is difficult to manage because there is no antidote. Platelet transfusion has the potential to reverse ticagrelor by providing functional platelets. Our aim was to examine the dose and time dependent effects of donor platelets on reversing ticagrelor.

Method

Healthy subjects took ticagrelor and aspirin for five days. In vitro platelet mixing studies were performed where donor platelets were added to platelets from subjects who were treated with ticagrelor and aspirin. Platelet aggregation was measured using light transmission aggregometry induced by 10 μ M adenosine diphosphate. Reversal of the effect of ticagrelor was studied using nine different quantities of donor platelets, immediately prior to the last dose, and at 2, 10, 24, 48, 72, and 96 hours after ticagrelor.

Results

Consistent results were obtained for 10 subjects. Spontaneous offset of the effect of ticagrelor was complete at 72 hours after the last dose. Addition of donor platelets enhanced the recovery in a time- and quantity-dependent fashion. Donor platelets achieved partial ticagrelor reversal between 2 and 24 hours after the last dose, major reversal between 24 and 48 hours, and were unnecessary after 72 hours. The addition of the equivalent of six apheresis platelet units produced a 50% reversal at 10 hours, and major reversal (>90%) at 24 hours.

Conclusion

Donor platelets enhance reversal of the effect of ticagrelor in vitro. Our study is the most comprehensive in vitro study of ticagrelor reversal because we have evaluated more time-points and mixing quantities than previous studies. The results provide clinicians with information on the appropriateness of platelet transfusion to reverse ticagrelor in patients who develop bleeding or require emergency surgery.

164. Visualising interaction of monocytes with RBC sensitised with clinically significant antibodies

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Background

The presence of clinically significant antibodies in patient plasma can lead to the sensitisation of transfused antigen-incompatible red blood cells (RBC) resulting in the subsequent removal of those RBCs by monocytes/macrophages. To date, processes involved in the attachment or phagocytosis of sensitised RBC by monocytes have largely been observed using light or fluorescent microscopes. Scanning electron microscopy (SEM) allows closer examine of cell-to-cell interactions and cellular responses that occur during attachment and removal of sensitised RBC by monocytes.

Aims

To visualise interaction between monocytes and RBCs sensitised with clinically significant antibodies.

Methods

2.5×10^5 peripheral blood mononuclear cells (PBMC) were seeded onto 22x22mm glass coverslips (1hr, 37°C, 5% CO₂). Non-adhered cells were removed and RBCs sensitised with clinically significant antibodies (e.g. anti-D) were added onto the cell layer and incubated (1hr, 37°C, 5% CO₂). Coverslips were then washed with PBS and prepared for SEM: Glutaraldehyde fixation, post-fixation with osmium tetroxide, ethanol dehydration and hexamethyldisilazane dried before coating with gold nanoparticles. Zeiss Sigma Scanning Electron Microscope was used for visualisation.

Results

The interaction between monocytes and sensitised RBCs was analysed using SEM. Evidence of monocytes activation, including increased adherence with extended membrane ruffles was observed following exposure to sensitised RBCs. In addition extension of monocytes pseudopodia to capture sensitised RBCs was observed.

Summary/Conclusions

We used SEM to visualise monocyte interaction with RBCs sensitised with clinically significant antibodies. Understanding these interactions provides a basis for modelling associated with the removal of incompatible RBCs post-transfusion.

165. Soluble factors in packed red blood cells augment inflammasome activation

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Background

Packed red blood cell (PRBC) transfusion has been associated with modulation of recipient immune responses. Interleukin (IL)-1 β is an important mediator of the inflammatory response involved in proliferation, differentiation and apoptosis. The canonical pathway of IL-1 β maturation and release is dependent on inflammasome activation. While there are many biologically active proteins, lipids and enzymes in PRBC that could modulate the inflammasome, there has been no specific assessment of these processes.

Aim

To investigate inflammasome activation by soluble mediators in PRBC.

Methods

Supernatant (SN) was collected from fresh (D2) and stored (D42) PRBC via centrifugation. In a model of transfusion and concurrent infection, monocytes (from healthy volunteers) were cultured (4 hours, 37°C, 5% CO₂) without stimulation, or stimulated with lipopolysaccharide (LPS, 1 μ g/mL), LPS+D2-PRBC-SN, LPS+D42-PRBC-SN or LPS+ATP (positive control). IL-1 β , caspase-1 and macrophage migration inhibitory factor (MIF) were quantified in the D2- and D42-PRBC-SN and the culture supernatants of the transfusion model. LPS alone was used as the comparator (Paired T-test, n=18, P<0.05).

Results

IL-1 β and caspase-1 were not detectable in the fresh or stored PRBC-SNs. Both fresh and stored PRBC-SN augmented LPS driven IL-1 β (P<0.001) and caspase-1 (P<0.001) production in monocytes indicating canonical inflammasome activation. MIF, a known modulator of inflammasome activation was detected in both fresh and stored PRBC-SN (19 ng/mL, 247 ng/mL respectively). Using a spike in approach based on a 2-3 unit transfusion, we found recombinant MIF did not augment LPS driven IL-1 β or caspase-1 production from monocytes.

Conclusions

Inflammasomes play a critical role in regulating inflammation, auto-immune diseases and cancer. Soluble mediators present in PRBC augmented inflammation through activation of the inflammasome. We found MIF wasn't responsible for modulating inflammasome activation and suggest further investigation into the specific biological mediators and mechanisms associated with activation of the inflammasome by PRBC is warranted.

167. Diagnosis and management of HIT

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Heparin-induced thrombocytopenia (HIT) is a prothrombotic adverse drug reaction mediated by IgG antibodies that target multimolecular complexes of platelet factor 4 and heparin. HIT is a high-stakes diagnosis. Delays in diagnosis and initiation of therapy are associated with a 6.1% daily risk of thrombosis, amputation, and death. On the other hand, misdiagnosis may lead to unnecessary exposure of thrombocytopenic patients without HIT to alternative anticoagulants and their attendant bleeding risk. The therapeutic landscape in HIT is changing. There is a shift away from “niche” anticoagulants (e.g. argatroban, bivalirudin, danaparoid) to “non-niche” anticoagulants (e.g. fondaparinux, direct oral anticoagulants). The next shift may involve treatment with novel non-anticoagulant therapies that target pathways proximal to activation of coagulation. In this lecture, an evidence-based approach to the clinical and laboratory diagnosis of HIT will be proposed and the evolving landscape of HIT therapy will be reviewed.

168. Basic research approaches assessing heparin-induced thrombocytopenia (HIT)

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To mediate platelet activation, platelets carry rapid response receptors such as glycoprotein (GP) VI which binds collagen, and Fc γ R11a (also known as CD32a), the low affinity receptor for immunoglobulins (Ig). These are the main signalling receptors on platelets that initiate prothrombotic events. Fc γ R11a is the pathological receptor mediating platelet dysfunction and platelet loss (thrombocytopenia) induced by anti-platelet autoantibodies in heparin-induced thrombocytopenia (HIT) and in immune thrombocytopenia (ITP). Antibody Fc domains within an immune complex are able to bind to Fc γ R11a and activate platelets, leading to spontaneous platelet aggregation (thrombosis) and platelet clearance. We showed that platelet activation induced by anti-platelet autoantibodies isolated from patients with HIT or ITP cause a rapid and irreversible proteolytic shedding of the platelet GPVI ectodomain, soluble GPVI (sGPVI). Neither GPVI, nor Fc γ R11a, nor their molecular pathways that initiate and drive the prothrombotic, prothrombocytopenic response in platelet autoimmune disease, are targeted by current antiplatelet therapeutics. To achieve this, significantly more information is required about these receptors and how they function. We will discuss a molecular pathway triggered by pathological antiplatelet autoantibodies that cause human disease and we will evaluate the utility of measuring some of these molecular events as a means to assess pathogenicity of anti-platelet autoantibodies in HIT. We will also explore Fc γ R11a genetic signatures that may predispose an individual to HIT propensity and thrombotic risk.

169. Laboratory investigation of heparin induced thrombocytopenia

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Heparin induced thrombocytopenia (HIT) is a rare but potentially fatal complication of heparin therapy, which in a proportion of patients causes platelet activation and thrombosis [1]. Initial clinical assessment of the likelihood of HIT, typically by use of the 4T score, is facilitated by laboratory testing to confirm or exclude HIT. We present some recent data related to contemporary laboratory testing for HIT, including some findings from a recent published study [2]. This study involved a prospective investigation, performed over an 18-month period, that involved testing of over 300 test samples from over 100 consecutive patients, and which was performed as part of a collaboration with other NSW based laboratories. Clinical assessment by 4T score was undertaken where available, as supplemented by laboratory tests that comprised both immunological (lateral flow ('STiC'), chemiluminescence (AcuStar; HIT-IgG(PF4-H)), ELISA (Asserachrom HPIA IgG)) and functional assays (SRA, platelet aggregation using whole blood ('Multiplate') and platelet rich plasma ('LTA')). The study identified both false positive and false negative test findings with most assays. Overall, the whole blood aggregation method provided a reasonable alternative to SRA for identifying functional HIT. STiC, AcuStar and ELISA procedures were fairly comparable in terms of screening for HIT, although STiC and AcuStar both yielded false negatives, albeit also resulting in fewer false positives than ELISA. The 4T score had less utility in our patient cohort than we were expecting, although there was an association with the likelihood of HIT. Nevertheless, we accept that our observations are based on limited test numbers. In conclusion, for the published study, no single approach (clinical or laboratory) was associated with optimal sensitivity or specificity of HIT exclusion or identification, and thus, a combination of clinical evaluation and laboratory testing best ensures the accuracy of diagnosis. We are continuing our studies with another planned multi-center study, currently in progress.

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171. Why won't my VAD patient stop bleeding, my surgery is perfect?!

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Durable mechanical circulatory support is used as a Bridge to Transplant (BTT) in Australia. Most commonly used are implantable ventricular assist devices. The perioperative bleeding surrounding the procedure is disproportionate to the surgical insult. This talk examines the rheological effect of the devices and their effects on the blood or "haemocompatibility". Treatment options will also be discussed.

172. Extra-corporeal life support from the haematologist's perspective

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Extra-Corporeal Life Support (ECLS) has been a major contributor to improved survival outcomes in intensive care units over the past four decades, particularly in the paediatric & neonatal setting. Where conventional therapies are inadequate, ECLS provides cardiac and respiratory support through mechanical circulation and oxygenation of blood via large bore cannulae placed in central vessels. While Extra-Corporeal Membrane Oxidation evolved from cardio-pulmonary bypass, and is most often used in the post-cardiac surgery setting, ECMO is rapidly being established in emergency situations, such as ECMO-CPR. The highly invasive nature of such an intervention leads to many complications, of which haematological issues remain the most important; including bleeding, thrombosis, anti-coagulation, haemolysis, cytopenias & altered leukocyte/platelet function, and transfusion. It also raises many issues in the intersection of point-of-care and laboratory testing. This talk will provide a brief outline of ECLS modalities, in order to highlight how and where haematological complications arise, before focussing on the main issues of anticoagulation, bleeding and thrombosis.

174. An Integrated Approach to Inherited Platelet Disorders: Results from a Research Collaborative, the Sydney Platelet Group

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Aims

To improve the diagnosis of inherited platelet functional (IPFD) and number (IPND) disorders through an integrated approach combining platelet phenotypic and genetic diagnostic platforms available at three Sydney tertiary hospitals.

Methods

Patients referred to the Sydney Platelet Group with suspected inherited IPFD/IPNDs were evaluated by clinical assessment and comprehensive platelet phenotyping using full blood count, light transmission and lumiaggregometry, whole blood impedance aggregometry, flow cytometry (glycoprotein analysis, activation and aggregation assessment and mepacrine staining), whole mount electron microscopy, transmission electron microscopy, immunofluorescence staining and next generation sequencing.

Results

41 patients have been evaluated, 16 with suspected IPFD and 25 with thrombocytopenia. Bleeding scores were higher in individuals with IPFD (mean 6.5, range 1-17) than those with IPNDs (mean 2.3, range 0-12). In cases with suspected IPFD, 4 individuals were found not to have a definitive platelet function defect; diagnosis to the level of the defective pathway was achieved in 11/12 (92%) patients, whilst an undefined defect was noted in 1 case. Our analysis exceeded a 2014 international survey by the ISTH that reported respondent laboratories failed to achieve a diagnosis to this level in 35% of cases. In our cohort, disorders of signal transduction/primary secretion defects were the most common abnormality detected (n=6). These individuals had mean bleeding scores that were not significantly different to those of the second most common defect identified, namely dense granule deficiencies (n=4) (mean score 5.7 vs 6.3, P=0.84 respectively). Genetic testing has been performed in 22 patients to date. Likely pathogenic and pathogenic variants were detected in 7/22 (32%) patients; 6 were in individuals with thrombocytopenia and included variants associated with extra-haematological complications (*DIAPH1*, *MYH9*) and potential for malignancy (*RUNX1*).

Conclusion

The level of platelet investigation undertaken by this initiative is currently not available elsewhere in Australia and initial results confirm the utility of this integrated phenotypic-genetic approach

175. Lessons learnt from local real-life experience with idarucizumab for the reversal of dabigatran

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Background: Idarucizumab is a specific antidote to the direct thrombin inhibitor oral anticoagulant, dabigatran etexilate. It has been used with increasing frequency in Australia since it was granted Therapeutic Goods Administration approval in October 2016.

Aim: To assess idarucizumab usage, effect on coagulation parameters and clinical outcomes in patients who received idarucizumab in Western Sydney Local Health District (WSLHD).

Method: A retrospective audit was conducted of all patients who received idarucizumab in WSLHD between September 2015 and December 2017.

Result: Of the 23 patients who received idarucizumab, 17 (74%) had bleeding and 6 (26%) required urgent surgery/procedure. Thrombin time (TT) or activated partial thromboplastin time (APTT, when TT not available) remained prolonged at 24 hours post idarucizumab infusion in 10/20 (50%) patients. Renal impairment at admission was associated with prolonged TT/APTT at 24 hours ($P = 0.02$) (Figure 1). In addition, there was a trend towards increased weight being associated with prolonged TT/APTT at 24 hours ($P = 0.05$). Of the 6 (26%) patients who died during hospital admission, 5 had raised TT/APTT at 24 hours ($P = 0.05$). Two deaths were due to continued bleeding despite idarucizumab. Only 17% of patients received prohaemostatic treatments and none received plasma derivatives. Despite assay availability, dabigatran drug level was only measured in 8 patients.

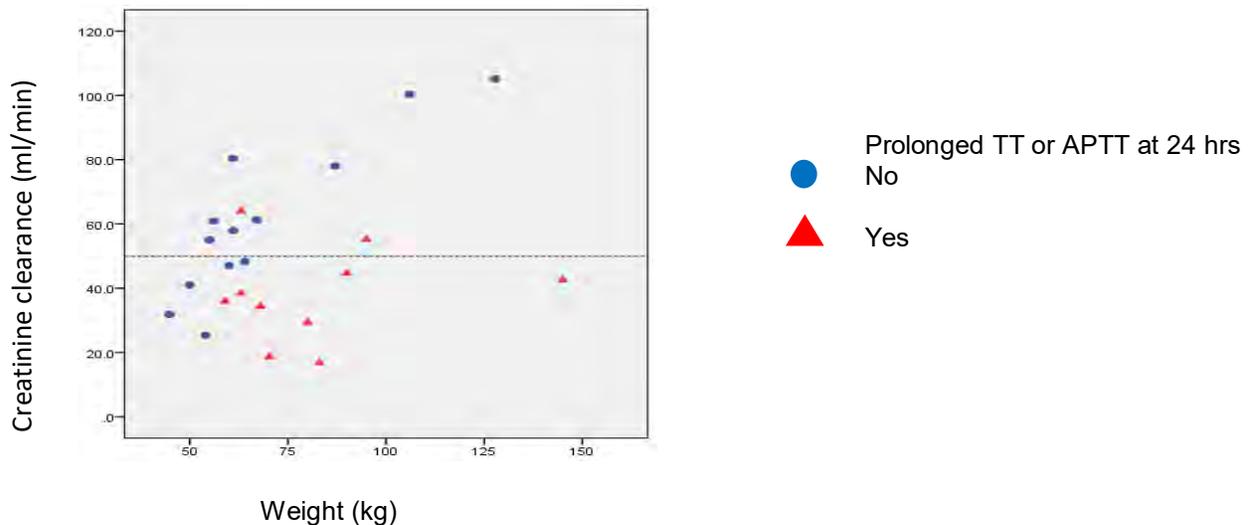


Figure 1. Association between prolonged TT/APTT at 24 hrs post idarucizumab with renal function and weight.

Conclusion: Idarucizumab helped achieve haemostasis in 15 bleeding patients and allowed 6 patients to undergo urgent surgery. Half the patients had prolonged TT/APTT at 24 hours post idarucizumab, which was more likely to occur in patients with impaired renal function.

176. Pharmacokinetics of pre-operative DOAC levels in traumatic hip fractures

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Aim: Current guidelines on the pre-operative management of direct acting oral anticoagulants (DOACs), rely on delay of surgery up to 72-96hrs post last dose(1). For acute hip fracture patients in whom early surgical intervention (<48hrs) reduces mortality(2), this can be problematic. The measurement of DOAC levels was implemented at our site to guide surgical eligibility. We aim to characterise these DOAC levels.

Methods: Patients admitted between 2015 and 2017 were identified from the Australia and New Zealand Hip Fracture Registry (ANZHFR). Time of last DOAC dose (TLD) was documented from the electronic medical records. DOAC levels were assayed via automated chromogenic analysis of direct factor Xa activity (STA-R Stago®), for apixaban and rivaroxaban or Dilute Thrombin Time (Haemoclot, Hyphen-Biomed®) for dabigatran(3). A pre-operative DOAC level of <50ng/mL allowed surgery to proceed. For patients with >1 measurable level, half-lives (T_{1/2}) were calculated assuming first-order kinetics.

Results: A total of 61 patients (84±7yrs) had DOAC levels taken, 58 patients underwent surgery. Results are presented in Tables 1 and 2.

Table 1: Characterisation of DOAC levels

	Apixaban (n=36)	Rivaroxaban (n=19)	Dabigatran (n=6)
Drug level range (ng/mL)	<20-221.5	<25-501	<10-132.1
Mean admission serum creatinine (umol/L)	90±31	83±23	89±22
Mean TLD to level <50ng/mL (hrs)	36.8±12.6	34.1±11.8	39.4±17.8
TLD to level <50ng/mL is <48hrs (%patients)	89%	94%	83%
Time level <50ng/mL to surgery (hrs)	16.5±12.3	14.6±9.1	13.4±10.6

Table 2: Patient specific half-lives

	Apixaban (n=15)	Rivaroxaban (n=2)	Dabigatran (n=2)
Mean T _{1/2} (hrs)	15.8	21.1	13.7
Range T _{1/2} (hrs)	5.8-32.6	5.8-36	12.2-15.2

Conclusion: More than 83% of DOAC patients had a level <50ng/mL 48 hours post last dose. This suggests the timeframes recommended in current Australian perioperative guidelines are adequate(1, 5) and possibly too conservative. Our results suggest the vast majority of acute hip fracture patients can have surgery within 48hrs, to thus minimise their mortality.

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177. Post-anticoagulation cessation D-dimer testing reduces VTE recurrence in real-world Australian audit

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Aim: Abnormal D-dimer after cessation of anticoagulation is a well-recognised risk factor for recurrent venous thromboembolic events (VTE). In Australia however, D-dimer has not been widely used to risk stratify VTE recurrence. This study aims to retrospectively analyse the effect of routine D-dimer testing on VTE recurrence.

Methods: Patients attending a tertiary hospital with a diagnosis of VTE between January 2013 and December 2016 were retrospectively evaluated.

Results: 1024 patients were reviewed with median follow-up of 12 months (range 0-59 months). D-dimer was tested in 189 patients (18.5%) within 90 days of anticoagulation cessation. Abnormal D-dimer (>500) was found in 72 patients (38.1%) – of these, 25 patients were restarted on anticoagulation because of elevated post-cessation D-dimer. Of the 164 patients with post cessation D-dimer testing who remained off anticoagulation, there were a total of 24 (14.6%) episodes of recurrent VTE. One patient developed VTE recurrence whilst on low dose apixaban 2.5mg BD. Patients with elevated D-dimer had a higher rate of recurrence with the highest risk in patients with D-dimer >1000 RR7.38 (p<0.01) [table 1].

Table 1. Rates of VTE recurrence stratified by D-dimer in patients off anticoagulation

D-Dimer	Pts with recurrent VTE	Recurrence rate	Average months to recurrence	Relative risk (compared to patients with D-dimer <500)
>1000	4	50%	2.67	RR 7.38 (95%CI 2.6-20.9) p<0.01
500-1000	11	26.8%	8.7	RR 3.96 (95%CI 1.7-9.15) p<0.01
<500	8	6.8%	18	

In patients with no residual thrombus, elevated D-dimer was a significant risk factor for VTE recurrence RR 6.4 (p<0.01). Patients with normal D-dimer and no residual thrombus had the lowest rate of recurrence 5.4% (n=4).

Table 2. Stratification by combination of D-dimer and residual thrombus

D-dimer = DD	No. patients	Patients with recurrent VTE	Recurrence rate
Normal DD & residual thrombus	30	3	10.0%
Normal DD & NO residual thrombus	74	4	5.4%
High DD & residual thrombus	24	3	12.5%
High DD & NO residual thrombus	42	10	23.8%

*20 patients did not have repeat imaging

For patients with unprovoked above knee deep venous thrombosis (AKDVT) or pulmonary embolism (PE), having D-dimer tested post anticoagulation cessation, regardless of result, was associated with lower rates of VTE recurrence RR0.30 (p=0.02) compared to those who had no D-dimer testing.

Conclusion: Post-treatment D-dimer can stratify the risk of VTE recurrence, with the highest in those with levels >1000. Patients with no residual thrombus and a negative D-dimer conferred the lowest rate of recurrence. Patients with unprovoked AKDVT or PE who had post cessation D-dimer testing had a significantly lower rate of VTE recurrence compared with patients without D-dimer testing, which may relate to specialist review and recommencement of anticoagulation in high risk patients.

178. Arterial thrombosis, how far are we?

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ACS is one of the common causes of mortality and morbidity both in Australia and worldwide. Acute myocardial infarction with ST-segment elevation is typically caused by the rupture or erosion of an atherosclerotic plaque. This results in exposure of the endothelial layer and subendothelial matrix, that provides a strong platform for activation of blood cells and the coagulation system that ultimately culminates in the formation of an arterial thrombus that may fully occlude the coronary artery.

Traditionally the arterial thrombus is considered to consist of mainly platelets and fibrin, known as “white clot”. Most of the current understanding of the mechanism of arterial thrombosis comes from in vivo models. However, there is still a gap of knowledge in the present concept of arterial thrombosis model and its composition.

The aim to characterise the composition of arterial thrombus aspired from patients with ACS.

Method

We have conducted immunohistological analysis of 30 thrombi from the patients undergoing emergency PCI for an ACS.

Result

We identified two distinct groups of thrombi based on their composition. We have identified two distinct groups of thrombus samples that have different cellular ratio of RBC, neutrophils and platelets: thrombus samples from RBC-rich-group contain higher number of neutrophils, the netotic burden was greater compare to the platelet-rich thrombi. Interestingly, we noticed that in the platelet-rich thrombus have exacerbated netotic areas in the vicinity of RBCs infiltrates. Component of coagulation cascade have also been identified in the surroundings of neutrophils.

Conclusion

In this current work we-show that arterial thrombus is more diverse in its cellular composition than the ‘white clot’. We have identified RBC-rich and platelet-rich arterial thrombi. That number of neutrophils, is positively corelated with the RBC content. Additionally, the number of netotic events was positively corelated with the RBC-content.

179. Enhanced fibrinolysis and reduced microvesicles after remote ischaemic preconditioning in non-diabetic coronary artery disease patients

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Aim: Brief non-harmful ischaemia, remote ischaemic preconditioning (RIPC) has been shown to confer benefit to patients with coronary artery disease (CAD). Some studies indicate lesser benefit in patients with diabetes¹. Previous studies have suggested RIPC enhances fibrinolysis^{2,3} [ENREF 2](#). **Hypothesis:** RIPC causes an immediate increase in fibrinolytic potential through release of fibrinolytic factors from the endothelium or fibrinolysis-supporting microvesicles and this effect is less evident in patients with diabetes.

Method: Consecutive patients at Concord Hospital's Cardiac Catheterisation Laboratory with suspected CAD were randomised to RIPC (sphygmomanometer on the arm, 3x5 min cycles, n=31) or sham (same protocol, 10 mmHg only, n=29) treatment carried out prior to angiography. Blood was collected pre- and immediately post-treatment. In platelet-free plasma, global coagulation/fibrinolytic potential (overall haemostatic potential assay)⁴, tissue plasminogen activator (tPA), urokinase plasminogen activator (uPA), plasminogen activator inhibitor (PAI-1) (ELISAs), and plasminogen (chromogenic activity assay) were assessed. Microvesicles were assessed by flow cytometry⁵ using surface markers for phosphatidylserine (PS, lactadherin-binding), platelets (CD41a, CD61, CD62P), leukocytes (CD45), monocytes (CD14), MAC-1 (CD11b), endothelial cells (CD144) and erythrocytes (CD235a). Changes pre-post RIPC were assessed by paired t-test.

Result: In the whole population there was no effect of RIPC on fibrinolytic factors or concentrations of microvesicles. However, in non-diabetic patients, RIPC increased overall fibrinolytic potential (pre 86.3±5.1% vs post 88.2±4.1%, p=0.004, n=17) and decreased platelet-derived microvesicles (pre 1.5×10³±1.0×10³, post 1.2×10³±0.9×10³ PS+/CD61+ events/μL plasma, p=0.04, n=8), but RIPC did not affect levels of circulating fibrinolytic factors tPA, uPA, PAI-1, and plasminogen. These effects were not seen after sham treatment. None of the effects of RIPC were seen in patients with diabetes mellitus.

Conclusion: There is a global increase in fibrinolytic potential after RIPC treatment in patients without diabetes mellitus, which is not explained by altered circulating tPA, uPA, PAI-1 or plasminogen but may be contributed to by decreased platelet-derived microvesicles.

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180. Acquired haemophilia A: The Queensland Haemophilia Centre experience

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Acquired haemophilia A (AHA) is a rare, but potentially life-threatening bleeding disorder. Development of an inhibitor (antibody) against factor VIII can occur secondary to pregnancy, autoimmune disorders, malignancy, drugs, or can be idiopathic in up to 50% of cases. Prompt diagnosis and initiation of treatment is imperative as there is high risk of morbidity and mortality related to untreated acute bleeding. The two primary goals of treatment focus on control of bleeding and eradication of the underlying factor VIII inhibitor.

Treatment challenges include delayed diagnosis, difficulty achieving haemostasis and durable remissions, and complications associated with the use of haemostatic and immunosuppressive therapy in a primarily elderly and comorbid patient group. No randomized clinical trials have been completed to direct optimal treatment approaches.

This presentation will address both established (bypassing agents) and newer (recombinant porcine factor VIII) haemostatic approaches to managing severe bleeding in AHA. Laboratory challenges in diagnosis and monitoring will be explored. Recent QLD experience with an inhibitor eradication protocol including upfront low dose Rituximab in combination with prednisone will also be reviewed.

Keywords: Acquired haemophilia, immunosuppression, Rituximab

181. Laboratory monitoring of extended half-life factor VIII and factor IX replacement products

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Current therapy for haemophilia A and haemophilia B consists largely of the use of replacement FVIII or FIX products, with dosing assisted by the use of one-stage clotting factor assays that measure the level of infused product in plasma. The recent introduction of extended half-life (EHL) recombinant replacement products has potentially altered the laboratory testing process due to differences in molecular structure of the new products, and the effect this has on post-infusion recovery levels when measured by the laboratory's usual APTT reagent with calibration against human plasma standards. The current status in Australia is the roll out of a limited number of EHL products for prophylactic use outside the setting of clinical trial cases. The modifications present in EHL products include pegylation, albumin-fusion, or Fc fusion, which have resulted in post-infusion half-life extensions for FVIII of approximately 1.5 times and FIX of around 4-5 times, thus reducing the required infusion frequency for patients on prophylaxis. A number of product manufacturer sponsored field studies have been performed where spiked samples are issued to multiple clinical laboratories who are asked to perform recovery estimates by their standard methods. Local field studies of these products can assist in determining suitability of different factor assays to the extent that local test methodologies were not covered in the overseas studies. Due to the many available APTT reagent/analyser combinations in use these studies are essential for determining test system suitability for EHL product measurements. In many cases, the existing test systems have been shown to be mostly satisfactory in providing results close to target, namely the product manufacturer's assigned potency value, such as for the Fc- fusion proteins for FVIII and FIX. Some studies reveal quite marked over-recovery or under-recovery of the spiked samples between different reagents, to the extent that the same factor assay methodology cannot be applied in to patient sample testing. There are a number of potential strategies available to the haemostasis laboratory to overcome this limitation. These are: the use of product-specific calibrators instead of human plasma calibrators; use of an alternative APTT reagent known to give acceptable results; application of correction factors to existing results; or use of chromogenic FVIII or FIX assays. In all cases where an alternate assay methodology is required the laboratory must have a way of knowing which product any given patient is receiving, to prevent the risk of over- or under-dosing from application of unsuitable methods. In summary, it is important to recognise that differences exist between treatment products, and to employ appropriate testing methods.

182. The new kids on the block: Extended half-life replacement factor products in haemophilia management

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Haemophilia is an inherited bleeding disorder that is caused by a quantitative deficiency in either clotting factor VIII (8) or factor IX (9); Haemophilia A and Haemophilia B respectively. Treatment today is very effective and is achieved by intravenous injections of recombinant factor concentrate to replace the missing factor. For those with severe haemophilia the standard of care is prophylaxis which involves the regular injections of clotting factor concentrate to prevent bleeding into joints, muscles and organs.

Treatment adherence is challenging for both the paediatric and adult haemophilia community with difficulties including frequency of dosing, venous access issues, bleed management and burden of treatment. In the last few years there are several new long-acting drugs that have become available for use overseas and these have now been introduced in a limited supply arrangement to the Australian market for haemophilia management.

This presentation will provide an overview of the extended half-life recombinant factors including mechanism of action and recommended dosing regimens. Case studies will demonstrate our recent experience with these new drugs and the reduced burden of prophylactic treatment for both the paediatric and adult cohort.

Keywords: Haemophilia, extended half-life, recombinant factor

183. Haemostasis and innate immunity

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Initiation of the tissue factor (TF) coagulation pathway is directly coupled to innate immune sensing and inflammation. Innate immune cell responses to cell injury signals, i.e. ATP activating the P2X7 receptor, directly couples pro-inflammatory interleukin 1 β and the generation of prothrombotic, TF bearing extracellular vesicles by a common upstream inflammasome pathway activating caspase 1. Furthermore, the hemostatic system and complement cascades are reciprocally amplified not only in sepsis, but also in venous thrombosis and acquired thrombophilia, specifically the antiphospholipid syndrome. In this context, complement activation supports the activation of monocyte-expressed TF by thiol-disulfide exchange mechanisms to a procoagulant form that mediates intravascular fibrin formation and thrombosis. TF's procoagulant and signalling functions are controlled at the cellular level by integrin trafficking pathways and contribute to acute and chronic inflammatory processes. A growing list of intracellular ligands for the TF cytoplasmic domain control signalling specificity and participate in the regulation of TF expression in vascular and immune cells. On the extracellular side, co-receptors, including integrins and the endothelial protein C receptor, determine signalling specificity of TF-associated proteases through protease activated receptors (PAR). Coagulation protease signalling regulates acute inflammation as well as chronic inflammatory processes in cardiometabolic diseases. New animal models help define the relevant proteases that activate PARs in the initiation and regulation of inflammatory diseases.

184. Targeting the platelet thrombin receptor, PAR4, for thrombosis prevention

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Thrombin is the body's most potent activator of platelets and is a major contributor to platelet-dependent arterial thrombosis. Thrombin activates platelets via two protease-activated receptors (PARs), PAR1 and PAR4. Both of these platelet thrombin receptors are targets for novel anti-platelet therapy – a PAR1 antagonist (vorapaxar) was recently approved for clinical use and PAR4 antagonists are in Phase 2 trials. However, a commonly expressed SNP in PAR4 that results in a PAR4 sequence variant has recently been described that may impact the efficacy of current PAR4 antagonists. The frequency of this SNP in PAR4 (rs773902) is remarkably high (19–82% of people, depending on the population). Critically, this SNP renders the receptor hyper-responsive to agonists and hypo-responsive to current antagonists, such as those in clinical development. Heterozygosity results in an intermediate phenotype. These findings suggest that current PAR4 inhibitors may have limited applicability across all patients. To overcome this, we have pioneered the development of PAR4-specific antibodies as inhibitors. Our recently-developed PAR4 antibodies target a distinct domain on the receptor to that blocked by existing small molecules and overcome the major limitation of small molecule inhibitors by blocking the PAR4 sequence variants equally effectively. Our findings suggest our antibody-based approach will provide superior anti-thrombotic therapy across the population than other approaches currently in clinical development.

185. How to diagnose, treat and prevent VTE in pregnancy

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Pregnancy and the postpartum period put women at risk for venous thromboembolism (VTE), which is the leading cause of maternal mortality in the Western world. Furthermore, up to half of women with pregnancy-related VTE experience lifelong consequences, in particular post-thrombotic syndrome after iliac vein thrombosis.

Interestingly, many clinical issues of pregnancy-related VTE have not been well studied. In this case-based, interactive masterclass, the specific challenges of diagnosis, treatment and prevention of VTE in pregnancy will be discussed.

Pregnant women have generally been excluded from diagnostic management studies. Various diagnostic scenarios, including issues such as maternal and fetal radiation will be reviewed. With regard to treatment of VTE in pregnancy, the use of anticoagulants that are safe for the fetus will be discussed, as well as how to deal with bleeding risk around delivery and neuraxial anesthesia. Finally, identifying women at risk of VTE, and secondary prevention of recurrent VTE during pregnancy and in the postpartum period in women with a history of VTE, will be discussed.

186. Direct Oral Anticoagulants in Cancer-Associated Thrombosis

Engelbrecht S

Malignancy increases thrombosis risk and cancer-associated thrombosis (CAT) is the number one cause of non-malignancy related deaths in these patients. Breakthrough thrombosis in this patient group is not unusual and the underlying disease process makes bleeding with anticoagulation more common. Previous studies have demonstrated the superiority of low molecular weight heparin over warfarin in the treatment of CAT. However, parenteral administration is tedious and often needed long term, leading to variable compliance. Recently data have become available on the use of direct oral anticoagulants (DOAC) in CAT, making them a feasible option for management. Despite this there are still areas where caution with their use should be exercised and others where the data remain lacking. This presentation will use case studies to give an overview on the available data for DOAC, underline where they can be safely used, illustrate some of the difficulties encountered in this patient group and to highlight ongoing uncertainties with possible management options in these scenarios.

187. Targeting the platelet internal membrane reveals a novel approach for improved anti-platelet therapies

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Background

The class II PI3K, PI3KC2 α , is a broadly expressed lipid kinase with emerging biological roles. We have recently shown that PI3KC2 α is important in platelet structure and function using a mouse genetic approach - PI3KC2 α -deficient mice have impaired thrombotic function that appears due to a dysregulated open canalicular system (OCS) structure (Mountford, Nat Comm 2015). However, without pharmacological inhibitors of PI3KC2 α , it remains unknown if a similar mechanism occurs in human platelets and whether targeting this is a viable anti-thrombotic approach.

Aim

To determine the role of PI3KC2 α in regulating human platelet membrane structure and function, and assess the viability of targeting PI3KC2 α as an anti-thrombotic strategy.

Methods

A rational drug design approach was used to develop an inhibitor of PI3KC2 α , MIPS-19416. MIPS-19416 was used to examine the impact of PI3KC2 α inhibition on the structure of the platelet OCS using both TEM and FIB-SEM. Platelet function was examined in a series of standard in vitro assays, alongside ex vivo thrombosis in human blood, and in vivo thrombosis in mice.

Results

PI3KC2 α inhibition with MIPS-19416 in human platelets fully recapitulated the structural and functional effects of PI3KC2 α -deficiency in mouse platelets. Here, MIPS-19416 increased the volume of the OCS in human platelets. These membrane changes did not impact in vitro platelet activation or aggregation. However, thrombus formation was significantly reduced with MIPS-19416 in two distinct in vivo mouse models, and two ex vivo human whole blood flow models, including one where thrombosis occurs largely independently of canonical platelet activation.

Conclusion

PI3KC2 α is involved in regulating platelet membrane structure and function in both mouse and human. Inhibition of PI3KC2 α has an anti-thrombotic effect that occurs specifically under shear stress and largely independently of platelet activation, suggesting that targeting the platelet membrane via PI3KC2 α may provide potential as a novel anti-thrombotic drug target.

188. Compression force sensing regulates integrin $\alpha_{IIb}\beta_3$ adhesive function on diabetic platelets

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Background

Diabetes mellitus is one the major healthcare problems of the 21st century with over 80% of diabetes-related deaths due to atherothrombosis. Platelets play a central role in the development of coronary artery disease by initiating and propagating plaque development, as well as promoting thrombus formation on the surface of disrupted plaques. Whilst it has long been recognised that platelets from individuals with diabetes exhibit a prothrombotic phenotype, the mechanisms regulating this remain incompletely understood.

Results

Utilising mouse and human diabetic platelets in conjunction with distinct in vivo thrombosis models and a unique biomembrane force probe (BFP) assay, we demonstrate, for the first time, the existence of a compression force sensing mechanism linked to $\alpha_{IIb}\beta_3$ adhesive function that leads to a distinct prothrombotic phenotype in diabetes. Whilst chronic hyperglycaemia did not result in increased platelet sensitivity to soluble agonist stimulation in vitro and in vivo, in contrast, chronic hyperglycaemia resulted in an enhancement in biomechanical $\alpha_{IIb}\beta_3$ activation, leading to a shear and red blood cell (RBC)-dependent increase in discoid platelet adhesion and aggregation in vitro and in vivo. Biomembrane force probe analysis of platelet adhesion receptor–ligand kinetics at a single-platelet level indicates that in diabetics, increased sensitivity of platelets to shear forces is due in part to dysregulated integrin $\alpha_{IIb}\beta_3$ compression force sensing. This compressive force-induced integrin activation is calcium and PI 3-kinase dependent, resulting in enhanced integrin affinity maturation. Strikingly, this process was not inhibited by therapeutic doses of aspirin and clopidogrel, but is eliminated by PI 3-kinase inhibition.

Conclusion

These findings define a distinct diabetic prothrombotic mechanism linked to dysregulated biomechanical integrin $\alpha_{IIb}\beta_3$ activation that may partly explain resistance to oral antiplatelet therapies and suggest therapeutic targeting of integrin $\alpha_{IIb}\beta_3$ signaling pathways may represent an innovative approach to reduce the prothrombotic effects of diabetes.

189. Plasma inhibitors of platelet sheddase activity – Rocks to the scissors on the paper

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Aim

Platelet collagen/fibrin receptor glycoprotein (GP)VI initiates thrombus formation/growth. GPVI is stable on circulating platelets but the ligand-binding domain is rapidly metalloproteolytically shed from activated platelets by A-Disintegrin-And-Metalloproteinase (ADAM)10. How ADAM10-mediated GPVI shedding is controlled remains unclear. Tissue-inhibitor-of-metalloproteinases (TIMPs) regulate vascular metalloproteinase activity and possibly integrin function. We assessed TIMP/platelet interactions and evaluated roles for regulating ADAM10 activity, and platelet function.

Methods

TIMPs levels were assessed on resting and activated human platelets by flow cytometry using anti-TIMP antibodies. Effects of recombinant human (rh)TIMPs on platelet ADAM10 activity and aggregation were explored using a fluorescence resonance energy transfer assay and light transmission aggregometry, respectively. We also provided quantitative measures of thrombus formation under fluid shear using collagen-coated microfluidic chambers and optical micro-holography.

Results

TIMP1-4 were detectable on resting washed platelets with significant levels of TIMP2 detected above background ($p=0.0313$, $n=6$ donors). TIMP1-4 levels increased on treatment with calcium ionophore ($p<0.001$, $n=6$) and collagen treatment increased TIMP3 ($p=0.044$), suggesting platelet activation enhanced TIMP binding. rhTIMP1 or rhTIMP3 reduced platelet ADAM10 rate of substrate cleavage (43% and 39%, respectively) and reduced overall ADAM10 activity (33% and 37%, respectively, $n=3$). Platelet aggregation triggered via engagement of protease-activated receptor-1, was inhibited by rhTIMP2 and rhTIMP4 by 75% and 46%, respectively ($n=2$), but not by rhTIMP1 and rhTIMP3. Inclusion of rhTIMP1-4 reduced aggregate volume when platelet-rich plasma was perfused over collagen-coated surfaces, suggesting TIMPs can modulate thrombus formation.

Conclusions

We describe a functional role for TIMPs on platelets. TIMPs were detected on circulating platelets and levels increased upon activation. TIMP1 and TIMP3 reduced platelet ADAM10 activity. TIMP2 and TIMP4 partially inhibited platelet aggregation. Our findings suggest new mechanisms for regulation of metalloproteolytic shedding of platelet receptors and aggregate formation. Dynamic TIMP levels may explain variability in platelet responses to standard agonists in healthy populations.

190. Patients with coronary artery disease have increased circulating procoagulant platelets and appear primed to undergo loss of platelet mitochondrial integrity

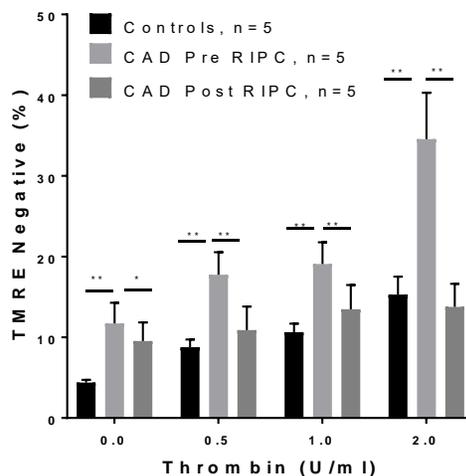
Liang H^{1,2,3}, Campbell H^{1,2,3}, Lau J^{1,2,3}, Kritharides L^{1,2,3}, Chen V^{1,2,3}

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Background and Aim: It is traditionally believed that procoagulant platelet formation requires exposure to strong agonists such as thrombin and collagen. However, we recently demonstrated that platelets from coronary artery disease (CAD) patients have increased **circulating** procoagulant platelets as well as an increased response to thrombin. We **hypothesised** that this is related to altered platelet mitochondrial membrane potential (MMP) and that CAD patients may benefit from a strategy aimed at mitochondrial membrane stabilisation.

Method: Circulating procoagulant platelets were measured by flow cytometry (combination of GSAO uptake and P-selectin exposure) in patients with angiogram-proven CAD and healthy controls (n=80). MMP in platelet-rich plasma was measured in parallel (n=10) by tetramethylrhodamine ethyl ester perchlorate (TMRE) uptake, a fluorescent potential-sensitive probe for mitochondria by flow cytometry with and without exposure to increasing doses of thrombin (0.5-2U/mL) with or without collagen 10ug/mL. Five patients were exposed to brief non-harmful ischaemia, remote ischaemic preconditioning (RIPC) using sphygmomanometer on the arm, 3x5 min cycles, 200mmHg. Blood was collected pre- and immediately post-treatment.

Results: Compared with healthy controls, CAD patients had increased circulating GSAO+/Pselectin+ platelets ($2.3\pm 1.2\%$ vs $1.1\pm 0.5\%$, $p<0.001$) independent of antiplatelet agent exposure and increased circulating platelets without detectable TMRE by flow cytometry ($9.2\pm 1.7\%$ vs $4.5\pm 0.4\%$, $p<0.01$). A significant correlation was demonstrated between loss of TMRE uptake and GSAO+ procoagulant platelet formation ($r=0.52$, $p<0.001$). CAD patients had increased loss of TMRE in response to agonist stimulation compared with healthy controls at all concentrations of agonist exposure ($p<0.01$). RIPC was associated with a reduction of TMRE loss ($p<0.01$).



Conclusion: CAD patients appear to have altered platelet MMP and are sensitised to loss of mitochondrial activity with agonist exposure. This sensitisation can be ameliorated by brief exposure to RIPC, and we speculate that this may be a mechanism of action by which RIPC confers protection in CAD.

191. Influence of ibrutinib and acalabrutinib on platelet function in healthy volunteers

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Aim

Bleeding is a common complication of ibrutinib therapy in patients with chronic lymphocytic leukaemia (CLL). Acalabrutinib, a second generation BTK inhibitor with higher selectivity, is thought to confer a lower bleeding risk. We compared the effects of ibrutinib and acalabrutinib on clinically utilised platelet function assays.

Method

After informed consent, blood samples from 15 healthy volunteers were spiked with comparable plasma concentrations of ibrutinib (0.3µM, 1.0µM) and acalabrutinib (1.8µM, 6.0µM) attainable during the treatment of CLL. Platelet function was evaluated using whole blood multiple electrode aggregometry (MEA - Multiplate®) and light transmission aggregometry (LTA - AggRAM®) in response to varying concentrations of aggregation-inducing reagents (collagen, CRP-XL, ADP, TRAP, ristocetin, arachidonic acid, and adrenaline), and PFA-100®. Inhibition of aggregation was deemed present if there was ≥20% reduction in mean aggregation response compared to vehicle controls.

Results

Both ibrutinib and acalabrutinib exhibited dose-dependent inhibition of platelet function, with inhibition of aggregation evident in response to collagen, CRP-XL, ristocetin and adrenaline. Neither drug impaired aggregation responses to ADP, arachidonic acid or TRAP. Ibrutinib more potently inhibited platelet aggregation, however overall similar degrees of inhibition were observed with acalabrutinib at higher, clinically-achievable, concentrations. MEA appears more sensitive and reproducible than LTA to describe the various inhibitory effects on platelet aggregation. Ibrutinib-treated samples also demonstrated significant prolongation of PFA-100® collagen/adrenaline closure times, an effect not observed with acalabrutinib.

Conclusion

Acalabrutinib induces a platelet function defect similar to that observed with ibrutinib, with the exception of shear-induced platelet adhesion (PFA-100®). Routine platelet function assays are capable of quantifying BTK inhibitor-induced platelet dysfunction, with the most sensitive and reproducible measure being collagen-induced aggregation by MEA. Such assays may have utility in managing patients presenting with bleeding or requiring urgent surgery during therapy with BTK inhibitors.

192. A Genotype-Phenotype Correlation of Haemophilia A in Victorian patients with a description of novel mutations

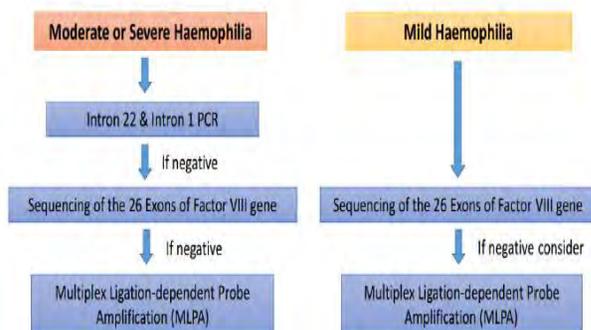
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Aim: Hemophilia A (HA) is caused by abnormalities in the Factor VIII gene. Certain abnormalities correlate with disease severity. Here, we report the genotype-phenotype correlation for all Victorian HA patients.

Methods: Using the Australian Bleeding Disorders Registry, Victorian HA patients were identified. All genetic testing was conducted at Southern Health. The testing algorithm is summarized in Figure 1.

Figure 1 – Testing algorithm at Southern Health



Mutations were compared with the list of known Factor 8 mutations on the Champ and EAHAD F8 Variant Databases. A PubMed search was undertaken for any mutations not on either database. If this too was unrevealing, the mutation was designated novel. In-silico analysis was conducted on all novel mutations using three open-access, online prediction tools: a) Mutation Taster; b) Poly-Phen 2; c) Human Splice Site Predictor.

Results: 318 patients with matched clinical and genetic records were identified. 275 had known FVIII mutations and 36 novel FVIII mutations were discovered. Eight patients (3%) had no mutations identified.

Table 1 – Frequency of different FVIII mutations

Phenotype	Number (patients)	Type of Mutation							
		Missense	Nonsense	Deletions/Insertions			Intron 22 Inversion	Others (spl site/duplications/etc)	Unidentified
				Large Deletions	Small Deletions	Insertions			
Mild	173	165	0	0	0	0	0	4	4
Moderate	23	19	0	0	0	0	3	1	0
Severe	122	17	28	5	10	8	47	3	4
Total	318	201	28	5	10	8	50	8	8

In severe HA the intron-22 inversion was the most common mutation (47/122, 38%). Missense mutations predominated in mild and moderate HA. Inhibitors were present in 44/318 patients, the majority of whom had 26/44 (59%) severe HA. 20/36 novel mutations (55%) were associated with severe HA, 12/36 (33%) with mild HA and 4/36 (11%) with a moderate HA. Novel mutations associated with non-severe phenotypes were mostly missense mutations (15/16); more diversity was seen in the novel mutations associated with severe HA. *In-silico* analysis predicted that all novel severe HA mutations were likely to be pathogenic. Inhibitors were seen in 7 patients with novel mutations.

Conclusion: This study adds 36 novel mutations to the currently known FVIII haemophilic mutations. It also confirms that the frequency and correlative clinical severity of known genetic mutations is similar to that described internationally.

193. Management of TTP

Cuker A¹

¹*Penn Comprehensive Hemophilia and Thrombosis Program*

Thrombotic thrombocytopenic purpura (TTP) is characterized by microangiopathic haemolytic anaemia, thrombocytopenia, and ischemic organ injury due to platelet-rich microvascular thrombi. TTP arises from severe deficiency of the von Willebrand cleaving protease, ADAMTS13, due either to biallelic mutations in the *ADAMTS13* gene (congenital TTP) or, more commonly, to autoantibodies that either neutralize or induce clearance of ADAMTS13 (immune TTP). Conventional therapy involves prompt initiation of plasma exchange in conjunction with corticosteroids. Rituximab has been shown to reduce days on plasma exchange as well as rates of exacerbation and relapse. Whereas it was previously used almost exclusively in the relapsed/refractory setting, rituximab is now being used with plasma exchange and corticosteroids as upfront therapy. Novel treatments in development include caplacizumab, a nanobody that blocks the interaction between von Willebrand factor and platelets, and recombinant ADAMTS13. These agents are poised to change the TTP treatment paradigm. In this lecture, the use and limitations of conventional therapy, the evolving use of rituximab, and the potential place for caplacizumab and recombinant ADAMTS13 in the management of TTP will be reviewed.

195. Tissue factor and malignancy

Ruf W¹

¹Johannes Gutenberg-University, Mainz, Australia

Cancer-associated thrombosis is a major complication of cancer and interactions of cancer cells with the hemostatic system remain of continuing interest for basic research. Tissue factor (TF) is upregulated on both, tumor and stromal cells, and orchestrates distinct tumor promoting activities mediated by TF-associated proteases. TF protease complexes influence the tumor microenvironment and metastasis through protease activated receptor (PAR) signalling. Our studies with PAR2 mutant mice selectively resistant to certain coagulation proteases have shed new light on the functions of PAR signalling in regulating tumor progression and the polarization of tumor-associated macrophages. Complementary studies with cell-type specific deletion of coagulation proteases further define the roles of macrophage-synthesized proteases and their signalling functions in immune evasion. These extravascular functions of coagulation proteases in the tumor microenvironment have significant implications not only for tumor development, but also for the selection of appropriate target-specific anticoagulants in the therapy of cancer patients.

197. Cancer associated VTE: Can we reduce the burden of treatment?

Middeldorp S¹

¹University of Amsterdam, Amsterdam, Netherlands

Patient with cancer have a strongly increased risk of VTE. Furthermore, they are at high risk of recurrence despite the use of therapeutic anticoagulants. LMWH has been shown to be more effective than VKAs in preventing recurrences in these patients and has been the recommended treatment for the first six months after the acute VTE. However, the burden of treatment by daily subcutaneous injections is considerable.

Direct oral anticoagulants (DOACs) are the current preferred treatment for patients with VTE, and have an oral route of administration. Whether DOACs are effective and safe in patients with active cancer has been addressed in two recently published trials. The Hosukai-Cancer VTE study showed that the factor Xa inhibitor edoxaban was non-inferior to LMWH in the treatment of cancer associated VTE, with a composite endpoint of recurrent VTE or major bleeding. An apparent greater efficacy was balanced against an increase in major bleeding, particularly from the gastrointestinal tract. The smaller Select-D study that compared rivaroxaban with LMWH and from which patients with upper gastrointestinal tract cancers were excluded showed similar results. A similar trial comparing apixaban with LMWH is currently ongoing.

It remains uncertain if patients with all types of cancers have the optimum risk benefit balance. The current evidence-based guidelines have not yet been updated after the two published trials, but it is to be expected that the use of DOACs in this populations will rapidly increase.

In this lecture, the current evidence and considerations that are applicable to patients with cancer associated VTE will be discussed in detail.

198. Laboratory measurement and reversal of DOACs

Cuker A¹

¹Penn Comprehensive Hemophilia and Thrombosis Program

The direct oral anticoagulants (DOACs) include the direct thrombin inhibitor, dabigatran, and the direct factor Xa inhibitors, apixaban, betrixaban, edoxaban, and rivaroxaban. These agents are approved for prevention of stroke and systemic embolism in patients with atrial fibrillation and for prevention and treatment of venous thromboembolic disease. Their usage and indications continue to expand. Although the DOACs do not require routine monitoring of anticoagulant effect, there are special situations in which laboratory assessment may be desirable.

Conventional coagulation assays are limited in this regard. Specialized assays for quantitation of drug levels are available. An important advantage of DOACs is that they cause less major bleeding than vitamin K antagonists. Nevertheless, emergency situations may call for reversal of anticoagulation, particularly in the case of serious bleeding or need for an emergent unplanned procedure. Both non-specific strategies (e.g. prothrombin complex concentrate, activated prothrombin complex concentrate) and targeted antidotes (e.g. idarucizumab, andexanet alfa) may be employed in these settings. In this Master Class, a case-based format will be used to review laboratory assessment of the DOACs, both when specialized assays are and are not available. Indications for reversal agents and management of DOAC-associated bleeding using non-specific strategies and targeted antidotes will also be discussed.

200. Australian and New Zealand Registry of Anticoagulation in the Obese

McCaughan G^{1,2}, Crowther H^{3,4}, Chen V^{2,5,6}, Merriman E⁷, Rebeiro P³, Pasalic L^{1,4}, Tahir F^{2,5}, Hall L^{2,5}, Curnow J^{1,4}

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Aim: To examine anticoagulant prescribing in the obese in Australia and New Zealand; determine an appropriate LMWH dosing strategy; evaluate whether obese patients achieve appropriate DOAC levels and evaluate the efficacy and safety of anticoagulation in the obese.

Method: We are prospectively registering patients with a BMI >35kg/m² or weight >120kg receiving anticoagulants at sites in Australia and New Zealand. Demographic data, weight, height, indication, anticoagulant, efficacy, adverse events and drug levels are being collected.

Results: Currently 58 patients have been recruited across 4 sites with 5 further sites awaiting approval. Baseline data was available for 53/58. Median BMI was 44.1kg/m² (range 35.3-87.5), median weight 123kg (R92-290), median age 53y (R27-87) and 30/53 were female. Indications for anticoagulation were PE (18), lower limb DVT (21) or other (4). Initial (or long-term) anticoagulant was rivaroxaban (20), apixaban (12), dabigatran (2), LMWH (10) or warfarin (with LMWH bridging) (9).

Table 1: DOAC levels

Anticoagulant	Dose	Median peak (ng/ml) (range)	Median trough (ng/ml) (range)
Rivaroxaban	20mg daily	281 (160-561) (n=7)	36 (28-122) (n=7)
	15mg BD		46 (<25-55) (n=3)
Apixaban	5mg BD	112 (66-158) (n=6)	40 (25-71) (n=7)

3 patients were changed from rivaroxaban to apixaban due to menorrhagia (n=2) and undetectable rivaroxaban trough (n=1). 2 patients on apixaban developed menorrhagia not requiring cessation. There have been no recurrent thrombotic events on either agent and all patients have had clinical/radiological improvement. Median enoxaparin dose to achieve therapeutic Anti-Xa (0.5-1.2U/ml) (n=12) was 0.83mg/kg (range 0.52-1.01). All patients (n=5) weighing <200kg achieved therapeutic Anti-Xa on 150mg BD (0.52-0.75mg/kg). 1 patient on enoxaparin developed a right arm haematoma and another had new PE.

Conclusion: Most (29/30) (of the measured DOAC levels within this cohort appear appropriate relative to published 'on therapy' ranges and reassuringly there have been no recurrent thrombotic events. Further data regarding appropriate dosing of enoxaparin is required, in particular in those weighing >150kg. More complete follow-up will be available in October.

201. Pregnancy, childbirth and neonatal outcomes in women with inherited bleeding disorders

Clarke L¹, Curnow J¹, Kidson-Gerber G²

¹*Westmead Hospital, Westmead, Australia,* ²*Prince of Wales Hospital, Randwick, Australia*

Aim

Pregnancy and childbirth pose unique haemostatic challenges, with severity of bleeding complications increased in women with inherited bleeding disorders. National guidelines exist to direct management of such women however there is limited published outcome data. This study aims to review the demographics, management, and bleeding complications of a local cohort of women with inherited bleeding disorders throughout pregnancy and childbirth.

Method

A retrospective analysis of records across two tertiary maternity services in NSW was performed between 2011-2018 to describe maternal characteristics, factor levels and requirements, pregnancy, birth and neonatal outcomes.

Results

Twenty seven women have currently been identified, accounting for 28 pregnancies and 29 live births. Diagnoses included Haemophilia A carrier (n=6), mild Haemophilia A (n=5), Haemophilia B carrier (n=2), Type I von Willebrand Disease (VWD) (n=8), Type 2B VWD (n=3), Type 2N VWD (n=1), Factor XI deficiency (n=2) and Hypofibrinogenaemia (n=1). At delivery median age was 32 years, gestation 39 weeks and birthweight 3486g. Prenatal gender assessment was performed in 40% of pregnancies. Factor replacement at delivery was required in 1/5 mild Haemophilia A women, 3/8 Type I VWD women, and all women with Type 2 VWD. Caesarean section accounted for 18% of deliveries. Neuroaxial analgesia was provided in 14/28 deliveries, including 3/6 Haemophilia A carriers, 5/5 Mild Haemophilia A women, 2/2 Haemophilia B carriers, 3/8 women with Type I VWD, and 1/2 women with Factor XI deficiency. Intervention was required in 4/28 deliveries. Postpartum haemorrhage (PPH) was reported in 7/28 deliveries (86% primary), with Haemophilia A carriers, mild Haemophilia A and Type 1 VWD accounting for the majority. All those with PPH had adequate factor levels at delivery or received factor replacement.

Conclusion

This study demonstrates that women with inherited bleeding disorders can safely deliver and be provided with neuroaxial analgesia when best practice is adhered to.

202. Alternative Splicing as a Future Treatment for Haemophilia A

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¹WACTH Murdoch University, Murdoch, Australia, ²CCG Murdoch University, Murdoch, Australia

Aim

Targeted skipping of F8 exon14 from pre-mRNA splicing using 2'-O-methyl and/or phosphorodiamidate antisense oligoribonucleotides (AOs) to induce a truncated but functional F8 protein.

Method

AOs specific to predicted F8 exon14 splice site elements on the pre-mRNA were introduced in HuH7 cells. Following 24h transfection, total RNA was extracted, converted into cDNA and PCR-assessed using primers spanning exon13&14 and 14&15 boundaries. Truncated PCR products were assessed for inframe F8 coding. Factor VIII protein was analysed by immunoblotting with anti-F8 antibodies.

Results

We have successfully induced exon skipping as determined by RT-PCR amplification of F8 fragments from AO treated cells. Different AOs induced different F8 pre-mRNA splicing in HuH7 cells. A wild-type product (3Kb) was present in all treatments, and excision events were observed in AO1-4, and 6 but not AO5. Of the excision products, 2 main F8 products were observed, 150bp and 800bp in size. Sanger sequencing confirmed 2 distinct truncated F8 gene transcripts with different disruptions to the reading frame. One had the intended B domain coding exon14 completely deleted. An alternative transcript partially excised exon14 sequences, but retains sequences towards the 3' end including the furin cleavage site.

Conclusion

Gene skipping of mutant regions of the F8 B domain at the pre-mRNA stage is a potential novel treatment strategy for Haemophilia A. This study successfully excised exon14 of the F8 gene to generate a B domain deleted, as well as a partially deleted B domain F8 protein.

204. Thrombin generation via calibrated automated thrombogram: an alternative measurement of Rivaroxaban anticoagulant effect?

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¹Northern Health, Epping, Australia, ²Northern Pathology Victoria, Epping, Australia, ³Australian Centre for Blood Diseases, Melbourne, Australia

Aim: Routine coagulation monitoring is not required for Rivaroxaban, a factor Xa inhibitor, due to its predictable pharmacokinetic and pharmacodynamic profile. However, there are certain circumstances in which quantification of rivaroxaban can be helpful and commercially available assays may not be widely available. Measurement of thrombin generation using calibrated automated thrombogram (CAT) may provide a readily available and convenient alternative. Hence, we aim to assess the anticoagulant effect of Rivaroxaban using CAT in correlation to plasma anti-Xa level and time to last dose.

Methods: Patients on Rivaroxaban for venous thromboembolism were recruited from the thrombosis clinic at Northern Hospital, Melbourne. Citrated whole blood was obtained and double spun to generate platelet-poor plasma for the evaluation of thrombin generation using CAT.

Results: Thirty-one patients (median age 57 years) on rivaroxaban were evaluated. The median duration from last dose of rivaroxaban was 7.25 hours (range 1.00-50.70). Lag time showed positive linear correlation to plasma anti-Xa level ($r_s = 0.91$; $p < 0.001$). Endogenous thrombin potential showed a weaker but significant correlation to time to last dose ($r_s = 0.43$; $p = 0.02$) while increasing levels of thrombin peak corresponded well to longer duration from the last dose ($r_s = 0.58$, $p < 0.001$) and decreasing rivaroxaban plasma anti-Xa level ($r_s = -0.74$; $p < 0.001$). Of note, variation in thrombin peak was observed even in low levels of anti-Xa. Velocity index also correlated to the timing of dose ($r_s = 0.60$, $p < 0.001$) and anti-Xa levels ($r_s = -0.74$, $p < 0.001$).

Conclusion: Thrombin generation parameters using CAT, particularly thrombin peak, show significant correlation to the anticoagulant effect of Rivaroxaban and appears to be useful in the assessment of an individual's in-vivo anticoagulated status. Variation in thrombin peak despite low anti-Xa levels may indicate clinically significant anticoagulant effect. Further studies is required to validate these findings and translate them into clinical use.

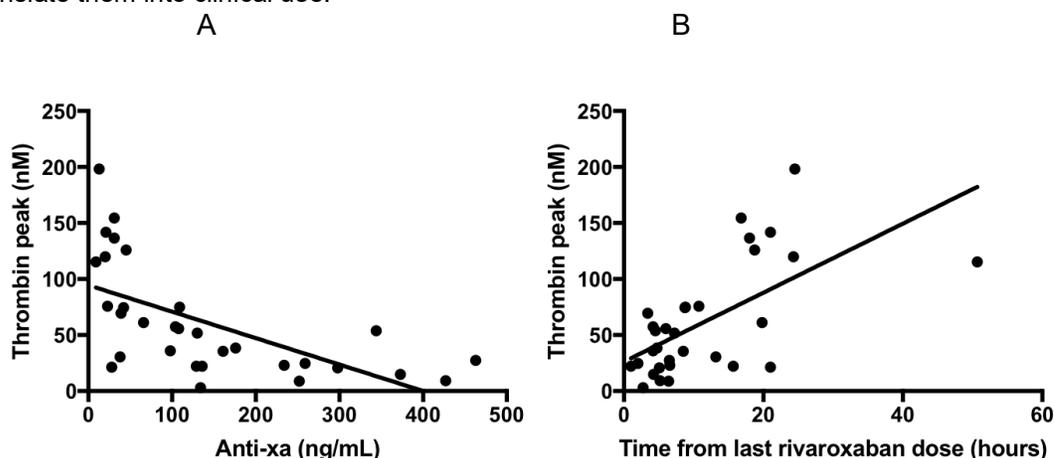


Fig 1. Correlation of thrombin peak with anti-Xa levels (A) and time from last rivaroxaban dose (B).

205. Predicting thrombosis in obese pregnant women - Maternal thrombin generation in obesity and pregnancy study (MaTOPs)

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Aim

To perform a pilot study assessing endogenous thrombin potential (ETP) using a thrombin generation assay in obese pregnant women (Group 1) and non-obese pregnant women (Group 2). To assess maternal and neonatal outcomes between groups.

Method

Participants were recruited from maternity units at Western Health and Royal Women's Hospital Melbourne, Australia and categorised into two groups according to BMI at first antenatal visit. Group 1 (BMI \geq 30kg/m²) and Group 2 (BMI 20-24.9kg/m²) had n = 81 and n = 69 participants recruited to date, respectively, with an aim that n=63 in each group will show a 5% statistically significant difference between groups. Blood samples were collected into sodium citrate tubes from participants at three time points, 26-28 weeks gestation, 36-40 weeks gestation and 6-12 weeks postpartum. Platelet poor plasma was analysed using a Calibrated Automated Thrombogram (CAT) assay and ETP was reported as mean \pm SEM. Maternal and neonatal outcomes were also recorded. CAT assays have been carried out on Group 1 n = 57/81 and Group 2 n = 33/69 participant samples to date. Data analysis will be completed by July 2018. Two sample t-tests and multiple linear regression analysis is performed using Stata14.

Result

Changes in ETP in the non-obese group showed increased thrombin during pregnancy (1805.27 \pm 66.35nM/min to 1968.72 \pm 133.33nM/min) which dropped during the puerperium (1425.92 \pm 95.82nM/min). Contrastingly, obese women maintained constantly higher ETP levels than their non-obese counterparts. Interim analysis only has been performed and has not shown statistical significance to date. Women in Group 1 had higher rates of gestational diabetes, pregnancy induced hypertension, premature delivery, C-section (47% vs 33%) and post-partum haemorrhage (41% vs 33%).

Conclusion

Thrombin generation may be higher in obese vs non-obese pregnant women. Definitive results will be available after completion of analysis in July 2018.

208. Immune therapy

Zitella L¹

¹University of California, San Francisco, Australia

How can the immune system be manipulated to eradicate cancer? This lecture will provide a comprehensive overview of the immune system, the history of immunotherapy, and current immunotherapeutic strategies such as monoclonal antibodies, checkpoint inhibitors and CAR T cell therapy. The discussion will include review of innate and adaptive immunity, how tumours avoid immune detection and destruction, and how immunotherapy can overcome tumour immune escape strategies.

209. Mucosal barrier injury laboratory - confirmed bloodstream infections

Gavin N¹

¹Royal Brisbane & Women's Hospital, Brisbane, Australia

Improvements in central venous access device (CVAD) management saw a 58% decrease in central line associated bloodstream infections (CLABSI) from 2001 to 2009 in the intensive care population. However, these reductions have not been realised in the cancer population where between 9 and 80% patients will be diagnosed with a CLABSI. The CVAD is often considered responsible for the infection and is subsequently removed, thus necessitating reinsertion which increases additional risk of infective and mechanical complications. Between 70 and 85% of CVADs unnecessarily after laboratory analysis. Cancer and its treatment decreases the ability to fight infection and damages the mucosal barrier, resulting in mucositis. This damage allows micro-organisms from the mouth and gut to translocate into the blood. Distinguishing bloodstream infections (BSI) related to CVADs from those that occur through other mechanisms will facilitate BSI prevention efforts and improve reliability of benchmarking comparisons of CLABSI. A new classification to differentiate mucosal barrier injury laboratory-confirmed bloodstream infection (MBI-LCBI) has therefore been developed by the National Healthcare Safety Network to address this clinical problem. The uptake of this classification in research and clinical practice has been limited however. The introduction of a more rigorous process for determining MBI-LCBI will increase awareness and understanding of the new classification and facilitate a change in clinical practice. This in turn will allow for more accurate BSI classification, treatment and management in this vulnerable cancer population to reduce unnecessary CVAD removal and replacement, improve antibiotic stewardship and consequently reduce healthcare costs.

210. It's not rocket science: Recognizing and responding to patient deterioration

Massey D¹

¹University of Sunshine Coast, Brisbane, Australia

Nurses' ability to recognize and respond to signs of patient deterioration in a timely manner plays a pivotal role in optimising patient outcomes. There is increasing awareness of the factors inhibiting nurses from escalating care for patients who deteriorate and the avoidance of preventable harm. These factors include, the level of knowledge and skill of the health professionals, the culture of the organisation and assessment frameworks.

This presentation argues that recognition and response to patient deterioration is a fundamental element of the nurse's role, and that by promoting and using a holistic patient assessment framework nurses can demonstrate their contribution to patient safety and ensure that recognition and response to patient deterioration is timely and appropriate.

211. When it is more complex than just the malignancy...

Marsh J¹

¹The Townsville Hospital, Douglas, Townsville, Queensland, Australia

This session will explore the complexities of treating transformed disease when coupled with a socially complex patient and family

Topics covered

CML – transformed disease / TKI inhibition / Mutational testing

Treatment options

Managing the patient with complex social issues, impacts on outcomes and nursing staff

212. Outside the box: Exploring aspects of holistic nursing assessments

Loft N¹

¹Central Adelaide Local Health Network, Adelaide, Australia

Nurses have a unique opportunity to build trust, rapport and respect with their clients, which can assist to identify what really matters and how their care can be optimised to meet their needs. This presentation will explore the role of the haematology nurse in patient assessments, focussing on the attributes that the nursing insight brings to the multidisciplinary team.

213. Patterns and outcomes of unplanned readmission post allogeneic stem cell transplant in the first 150 days of transplantation

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¹*Peter MacCallum Cancer Centre, Melbourne, Australia*, ²*The Royal Melbourne Hospital, Parkville, Australia*, ³*Wellington Hospital, Newtown, New Zealand*

Aim

Unplanned readmission post allogeneic haematopoietic stem cell transplant (allo-HSCT) has a significant burden on inpatient services and is often demoralising for patients. We sought to analyse the contribution to inpatient bed days from unplanned readmission with a view to aid post-transplant nurse coordinators prioritise their care and advice to patients.

Method

Retrospective file audit of 82 sequential patients between 2017 and 2018 from two metropolitan haematology units (1 Australia, 1 New Zealand). Donor source, conditioning intensity, durations and admitting diagnoses, and outcomes were collected up to day 150 post-transplant. Patients were excluded from data analysis if they died before ever being discharged or received a second transplant.

Result

Overall, 71% of patients were readmitted at least once. The combined readmissions resulted in an average of 21.5 extra inpatient bed days per patient. Intensity of conditioning did not appear to correlate with readmission rates or their duration. However, there were marked variations in readmission results based on donor source. The proportion of patients ever readmitted, by donor source were; haploidentical 100% (n=8), matched unrelated donor (MUD) 76% (n=45) and sibling 61% (n=28). The average number of extra inpatient bed days by donor source was: haploidentical 43 days, MUD 23 days, and sibling 11 days. The most common reason for readmission was infection (43%), followed by graft-versus-host disease (19%) and drug toxicity (13%).

Conclusion

Patients are likely to be admitted post discharge after allo-HSCT. Efforts to reduce the allo-HSCT inpatient bed burden should not only focus on outpatient chemotherapy and the early transplant period. Nursing care in the immediate post-transplant period should prioritise patient education, early identification and treatment of graft-versus-host disease and infection, and assessment of drug toxicities.

214. Is there balance? CD34 Cell Prediction versus Actual CD34 Cell yield

Milton C¹, Wills M¹

¹Calvary Mater Newcastle, Newcastle, Australia

Introduction

The purpose of this retrospective review was to evaluate the inbuilt CD34 collection yield prediction tool on our apheresis machine to assess the concordance of data provided to actual CD34 cell yield.

Aims

In this review we wanted to answer the following questions; is there a correlation between the predicted yield and the actual CD34 cell yield? And how can the tool data be incorporated into clinical practice?

Method

This was a retrospective review of predicted and actual CD34 cell yield data from 2010 to June 2017 for various haematological and oncological malignancies in our autologous apheresis unit.

Results

Between 2010 and June 2017 we collected CD34 cells from 300 patients in a total of 452 procedures. 21 patients were removed from data analysis: 4 had incomplete data, 15 failed to collect target CD34 cell dose (8 \geq 1 recollection to reach predetermined CD34 cell target and 7 failed to collect) and 2 removed for other reasons. This equated to 279 (n=279) total patient collections for the review and comparison.

In 210 patients yield (75%) the actual yield was better than the predicted CD34 cell count yield, 13 patients (5%) had the same yield as the predicted and 56 patients (20%) results were less than the predicted outcome.

Conclusion

Actual CD34 cell yield was equal to or more than the inbuilt machine prediction tool in 80% of cases, making this a useful clinical indicator. However there are other variables that need to be considered, and so our unit does not rely on this data alone in the clinical decision making for patient collection. Our unit utilises this tool for quality control and monitoring, communication to patients, as a predictor for decision making around need for other mobilising agents such as plerixafor and as a staff workload predictor.

215. Qualitative immersion of patients with Chronic Lymphocytic Leukaemia to identify patient lived experience and develop innovative strategies to address needs

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¹The Leukaemia Foundation, Fortitude Valley, Australia

Aim

The aim of this study was to discover the psychosocial needs and aspirations of Chronic Lymphocytic Leukaemia (CLL) patients, the complex factors influencing their quality of life and understand their information and support seeking behaviours from the point of diagnosis through to treatment to identify innovative strategies to address their unmet needs.

Method

Analysis of a six month internal structured intervention pilot program identified low Quality of Life (QOL) scores compared to broader populations in a group of self-recruiting CLL patients to the program. From this pilot a study utilising innovative patient immersion methodology was developed. In depth semi-structured face-to-face interviews with 25 CLL patients residing in various locations in Australia were held. Researchers, trained in immersion interview technique, followed a discussion guide to explore the patient's journey, the diagnosis experience, sources of support, networks, engagement with support providers, frustrations and compliance with treatment. Interview content, facilitated by an external innovation group, was analysed for clues and insights which was further categorised into themes upon which new innovative support services has been developed.

Result

1200 verbatim facts were examined and correlated into themes including, scan anxiety, fraudulent concerns relating to their CLL – “good cancer”, isolation, connection, living well and longer, wait and worry and an identified concern with this group, suicide. Alarming five out of the 25 patients interviewed, freely offered thoughts of suicide since diagnosis, three had had a plan and one patient required intervention at interview. Development of innovative services have been developed and consultation with CLL patients undertaken for impact.

Conclusions

CLL patients may be viewed as requiring lower supportive care compared to other acute haematological conditions. This study has exposed implications for health professional's supportive care approach to this group and current strategies in development should be further examined to ensure effectiveness in improving QOL outcomes.

216. Improving vascular access care for haematology patients

Gavin N^{1,2,3}, Lippiatt R¹, Northfield S¹, Somerville M¹, Larsen E^{1,2}, Marsh N^{1,2}, Rickard C^{1,2}

¹Royal Brisbane And Women's Hospital, Herston, Australia, ²Griffith University, Nathan, Australia, ³Queensland University of Technology, Kelvin Grove, Australia

Aim

Central venous access device (CVAD) registries provide clinicians with data about device-related complications and patient outcomes. Our registry collects information about the patients requiring CVADs within Cancer Care Services (CCS), type of CVADs being inserted, complications and reasons for removal. The CVAD Registry captures data to identify variances and trends in the quality of CVAD care provided.

Method

The CCS CVAD Registry has captured information on all adult cancer patients who received a CVAD from 1st April 2016 at the Royal Brisbane and Women's Hospital.

Results

Currently we have 729 patients (421 haematology and bone marrow transplant, 297 oncology, 7 surgical, 3 medical and 1 renal) in our CVAD Registry with 1,160 CVADs. These comprise of 734 peripherally inserted central catheters (PICC), 189 tunnelled cuffed CVADs, 168 totally implantable VADs, 28 non-tunnelled CVADs, 18 tunnelled PICCs, 17 haemodialysis CVADs and 6 tunnelled non-cuffed CVADs.

Less than half of our patients (44.5%) completed their treatment with one CVAD. A quarter of patients had their CVAD removed due to suspected infection (26.6%), local infection (2.2%), CVAD-related thrombosis (4.4%), occlusion (3.5%), accidental dislodgement (5.5%), CVAD migration (1.8%), CVAD rupture or fracture (0.8%) and infiltration or extravasation (0.2%).

Conclusion

Our CVAD Registry has provided the hospital with CVAD failure data, both mechanical and infective. This knowledge has empowered clinicians, researchers, educators, safety and quality officers to drive quality improvement initiatives. This data has led to the Improving Vascular Access Care in Cancer Care study which has conducted a point prevalence survey in February 2018 and four months of targeted education to improve hand hygiene, aseptic non-touch technique, site inspection, catheter maintenance/occlusion management and documentation from March to June 2018.

218. Subcutaneous Immunoglobulin (SCIg) Journey at Gold Coast Hospital and Health Service

Royal D¹

¹Gold Coast University Hospital, Gold Coast, Australia

On 1 March 2013, the Jurisdictional Blood Committee (JBC) approved the introduction of subcutaneous immunoglobulin (SCIg) under the national blood arrangements, subject to certain requirements. The SCIg program provided patients with the ability to deliver their treatment at home. Hospitals wanting to participate in the National SCIg program had to secure the approval and support of their Chief Executive. The Gold Coast Hospital and Health Service (GCHHS) implemented a SCIg program in September 2014.

This presentation will provide an overview and first-hand experience of the SCIg journey at GCHHS. It begins with the process of seeking approval for our SCIg program, dealing with governance and patient criteria, and it presents the lessons we learnt. We will discuss some of the key activities involved with supporting the transition of patients from hospital care to in the home, including the impact on nursing resources, consumables use and different hospital costs associated with SCIg program. Impacts on nursing practice involving documentation and different monitoring requirements of our SCIg patients will be highlighted. We will report on how we have been able to improve patient adherence and share solutions designed to manage the administration process of this therapy. And importantly share how SCIg has benefited our patients.

218. Subcutaneous Immunoglobulin (SCIg) Journey at Gold Coast Hospital and Health Service

Clark F¹

¹Gold Coast Hospital and Health Service

On 1 March 2013, the Jurisdictional Blood Committee (JBC) approved the introduction of subcutaneous immunoglobulin (SCIg) under the national blood arrangements, subject to certain requirements. The SCIg program provided patients with the ability to deliver their treatment at home. Hospitals wanting to participate in the National SCIg program had to secure the approval and support of their Chief Executive. The Gold Coast Hospital and Health Service (GCHHS) implemented a SCIg program in September 2014.

This presentation will provide an overview and first-hand experience of the SCIg journey at GCHHS. It begins with the process of seeking approval for our SCIg program, dealing with governance and patient criteria, and it presents the lessons we learnt. We will discuss some of the key activities involved with supporting the transition of patients from hospital care to in the home, including the impact on nursing resources, consumables use and different hospital costs associated with SCIg program. Impacts on nursing practice involving documentation and different monitoring requirements of our SCIg patients will be highlighted. We will report on how we have been able to improve patient adherence and share solutions designed to manage the administration process of this therapy. And importantly share how SCIg has benefited our patients.

219. Haploidentical transplantation

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¹*Royal Brisbane & Women's Hospital, Brisbane, Australia*

Traditional allogeneic stem cell transplantation is a treatment option for patients with blood related cancers and disorders. Traditionally it was necessary for recipients and donors to closely match Human Leukocyte Antigens (HLA) to minimize risks of Graft vs Host and other complications. Recent medical advances have enabled the possibility of transplants to be undertaken with partial HLA matching. This is known as haploidentical transplantation. Haploidentical donors are often first-degree relatives with partial HLA matching. Nursing consideration for care of patients undergoing haploidentical transplantations will be discussed including changes in conditioning protocols and graft v host prophylaxis as well as management of complex side effects and complications.

221. Subcutaneous immunoglobulin: a new choice for patients in Victoria

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Background

Subcutaneous immunoglobulin (SCIg) allows patients to self-administer immunoglobulin replacement therapy at home. In 2013, SCIg was approved for patients with primary and secondary immunodeficiency (PID & SID). To promote uptake, and provide patients with a choice of therapy, the Victorian Department of Health and Human Services offered seed funding in February 2017, for the development of home based SCIg programs. To support program development, Blood Matters employed a Project Nurse in November 2017.

Aim

Assist and support Victorian health services to develop and implement SCIg programs.

Method

The Project Nurse works with sites to identify eligible patients, educate and promote the benefits of SCIg, and improve program uptake. Train the trainer education is provided, supported by a suite of resources.

Extensive promotion to clinicians, nurses, and patients through SCIg introduction sheets, education sessions, journal clubs, and general meet and greets.

Results

The number of registered SCIg treatment providers has increased to 15. Approximately 1200 patients are eligible for SCIg by diagnosis; the number of patients receiving SCIg has increased from 51 in September 2017 to 106 in May 2018. Up to 30% of eligible patients are expected to transition to SCIg.

Important relationships have been established with patient advocacy/support groups, both to increase awareness of SCIg, and seek their input when developing resources. Initial patient feedback is positive.

A suite of implementation tools, and educational resources have been developed and are available on the Blood Matters website.

Formal feedback for patients and health services to evaluate the impact, including challenges and strategies to improve implementation and achieve sustainability, is under development.

Summary/Conclusion

The uptake of SCIg is increasing; however, further work is required to ensure sustainability of SCIg programs. With new process come challenges and ongoing work to overcome them. PID and SID patients now have a choice of therapy.

222. Blood and blood product transfusion in a community setting in South Australia

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¹RDNS SA, Adelaide, Australia, ²SA Health, Adelaide, Australia, ³Blood Move, Adelaide, Australia

Aim

To audit blood and blood product transfusion practices in a community setting in South Australia. The Royal District Nursing Service (RDNS) SA is part of the Silver Chain Group (and as an approved provider for SA Health) has been providing services based on sound clinical practice, efficient processes supported by Clinical Governance and strict adherence to cold-chain measures and protocols. The practice provides the client a timely and safe blood/blood product transfusion in the comfort of their home.

Method

All transfusion provided by RDNS from 2011 to May 2018 were included in the audit. Referral sources (hospital/GP), patient demographics including diagnoses, location, and product wastage and transfusion reaction were collected and analysed.

Result

A total of 1345 transfusion episodes (421 patients) were analysed. The patients had a median age of 83 (75-89) with an approximate 50/50 gender split. The service started in 2011 with 136 episodes and had a gradual increase to 301 episodes in 2017. More than half (51%) of the referrals were from public hospitals, 29% from GPs and 16% from residential care facility (RCF). Patient diagnoses were predominantly anaemia, haematological malignancies, blood disorders and other medical conditions. Over the study period, there was minimum blood wastage (1x discarded due to venous access, 2x due to incorrect storage at site), one (1) clinical transfusion reaction (non-haemolytic febrile) and five (5) operational incidents.

Conclusion

This audit has revealed there is an increasing trend in blood transfusion in the home setting. The source of referrals i.e.. public hospitals, GPs and RCFs suggests that this clinical partnership assists in reducing the overburden in the public healthcare system. Patients benefit at many levels as they avoid travel to the hospital and remain in the comfort of their normal living surrounds. With correct patient and blood supply processes, this form of blood therapy is ideally suited for certain patient groups.

223. HaemFit: A pilot implementation trial of a hospital exercise and wellness program for haematology in-patients

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¹Calvary Mater Newcastle, Waratah, Australia, ²Hunter Medical Research Institute, New Lambton, Australia, ³Hunter New England Local Health District, New Lambton, Australia

Aim

The aim of this study was to develop and implement a structured exercise program for haematology cancer in-patients. Main outcomes were rate of patient adherence and the difference in lean muscle mass between admission and discharge. Secondary outcomes included quality of life and patient satisfaction with the program.

Method

This single centre pilot study was conducted in a 12 bed haematology unit over a 12 week period (Feb- May, 2018). All patients admitted with a haematological malignancy, an expected length of stay ≥ 7 days and able to undergo impedance testing using InBody570 were eligible. On admission and discharge all consented participants completed Hospital and Anxiety Depression Scale (HADS), and a Quality of Life Questionnaire (QLQ-C30). On admission, each participant had consultation with physiotherapist to set daily exercise targets and a dietician to discuss nutritional goals. The exercise program was prescribed, prompting nursing staff to regularly enquire and encourage patients. Participants completed an exercise diary recording compliance and an evaluation of the program at discharge.

Result

There were 13/16 eligible patients who consented to the study (81% accrual rate). Two participants were lost to follow-up and only 8/11 participants handed in their exercise diaries. All patients were able to complete some of the exercises, but only 3 achieved 50% or over, giving an overall adherence rate of $54.37 \pm 26.6\%$. All but 1 participant lost significant muscle mass (average = $-4.62 \pm 3.12\%$, $p=0.003$, $n=10$), with 4 participants losing $>6\%$. Although there was no significant improvement in QLQ-C30 or HADS scores, feedback from patient satisfaction survey was overwhelmingly positive.

Conclusion

We were able to successfully implement an exercise program that could be performed by patients in the ward. Although patient adherence and satisfaction with the program was high, muscle loss was still significant. Exercise modifications may be required to improve patient outcomes.

224. Lymphoma Australia: Bridging the gap in care

Gairns D¹

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Introduction

Lymphoma and Chronic Lymphocytic Leukaemia (CLL) affects more than six thousand Australians every year. Patients affected are geographically dispersed across Australia and as a result are not always given the opportunity to be referred to a specialist lymphoma service, a clinical trial or access to a specialist lymphoma nurse. In 2016, Lymphoma Australia committed to fund three Lymphoma Care Nurses (LCN). This was achieved through a model that provides support for patients, carers and nurses at both the local and national level.

Aim

The aim was to address gaps in service provision, to ensure patients, carers and health professionals have access to specialist support from a LCN regardless of where they live within Australia.

Description

The Lymphoma Coalition invited patients and carers to participate in a survey to identify unmet needs during their cancer experience, with a response from over 6000 people globally, including 254 Australians. In response to the findings, Lymphoma Australia funded LCN's to develop and deliver initiatives to improve patient outcomes. This is underpinned by the need for all patients, carers and health professionals to have equitable access to the latest information, treatments, clinical trials and support within Australia.

Outcome

The LCN's achievements to date include, education and support via resources, newsletters, education events and webinars; Lymphoma Nurse Specialist Interest Group, including a closed nurse portal and Facebook group for information and peer support; Lymphoma Nurse Hotline, to access a LCN anywhere across Australia; patient advocacy and provide clinical input for Pharmaceutical Benefits Advisory Committee submissions for new treatments; collaboration with national and global lymphoma related committees, organisations, government and pharmaceutical companies, including attendance at key haematology and oncology events.

Conclusion

Lymphoma Australia is committed to funding more LCNs to ensure national equity for support, access to information and the best available treatments, that will ultimately improve patient outcomes.

225. Outcomes from a haematology survivorship clinic - a single centre experience

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¹*Austin Health, Heidelberg, Australia*

Aim

Patients who have completed treatment for a haematological malignancy experience a range of physical and psychosocial unmet needs. The purpose of this study was to describe the needs and follow-up care of patients attending a haematology survivorship clinic.

Method

Patients attended the multidisciplinary clinic for two indications. The first was for patients with any haematological malignancy, ≥ 3 months post treatment completion, who attended for nurse-led survivorship consultation. The key components of which were assessment, planning and referral for ongoing support. The second, was patients ≥ 5 years post treatment for lymphoma, with curative intent including radiotherapy or ≥ 2 years post allograft who attended for dedicated late effects monitoring. Patients completed the Distress Thermometer and Problem Checklist, the Cancer Survivors Unmet Needs survey and the Healthy Living Questionnaire prior to attending the clinic.

Result

One hundred and thirty-five patients (n=115 for group 1, n=20 for group 2) with a median age of 48 years (range 18-75) have attended. The majority were female (57%) and diseases included hodgkin lymphoma (30%), myeloma (15%) and DLBCL (13%). The median time from diagnosis to attending was 11 and 74 months respectively for the 2 groups (range 4-362). Patients attending nurse-led (group 1) reported a range of issues including fatigue (57%), worry (50%), memory/concentration problems (44%), fear (34%) and sadness (32%), and demonstrated poor compliance with healthy lifestyle behaviours including diet and physical activity. Referrals implemented included the ONJ Wellness Centre (100%), healthy living after cancer (CCV) (29%), psychology (25%), the ONJ Centre Survivorship LiveWell program (24%), and dietetics (11%).

Conclusion

These observations highlight that patients with haematological malignancies require complex, tailored survivorship and long-term follow-up interventions. Plans are underway to evaluate the outcomes of these interventions. Survivorship care is now routinely integrated into standard follow-up care post treatment completion.

226. The Development of the Nurse Practitioner in a Highly Specialised Area

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¹Westmead Hospital, Westmead, Australia

The Nurse Practitioner (NP) has been a member of the health care team in Australia since 2000 when the initial authorisation of the role began. In the first 18 years the numbers of nurses authorised to practice and the areas of practice have grown. Many positions were primarily based in the community or the emergency department, however, this is now not so, with many Nurse Practitioners practicing in specialist areas. This paper will outline the first 18 months of a NP role in Blood and Marrow Transplantation (BMT). Initially, the role's remit was to care for patients in the first 100 day of transplant, however, the position has developed a model of care that goes beyond the confines of the first 100 days and has become based on patient needs. The paper will discuss the collaborative model of care established to allow for a reduction in readmissions, faster access to specialised care and meet the needs of this patient group following discharge. The paper will debate the interaction of the NP role with medical and nursing staff and analyse these interactions over the past 18 months, comparing them with the experiences of Nurse Practitioners documented in the published literature. In conclusion, it will demonstrate how such a specialised role can save inpatient bed days and support patients to achieve intended health outcomes and minimise the need for further hospital admission

227. Assisted dying

Willmott L

Assisted dying is an issue that is being grappled with in many western countries. Assisted dying, in some form, is now lawful in Canada, eight jurisdictions in the United States, Belgium, the Netherlands, Luxembourg and Switzerland. In Australia, there has also been much agitation for reform. The Northern Territory in Australia was the first jurisdiction in the world to legalise euthanasia. However, the Rights of the Terminally Ill Act 1995 (Northern Territory) was short-lived as it was overturned by the Commonwealth of Australia through the enactment of the controversial Euthanasia Laws Act 1997 (Commonwealth). More than two decades and over 40 legislative attempts later, Australia's second most populated State, Victoria, enacted the Voluntary Assisted Dying Act 2017 (Victoria) on 29 November 2017. The Act permits assistance to die in limited circumstances, and will commence on 19 June 2019.

This presentation will look at the state of the law internationally, and the historical and current legal landscape in Australia. It will look in particular at the Voluntary Assisted Dying Act 2017 in Victoria, its pathway to enactment, and what it means for patients and their families.

228. Using patient reported outcome measures (PROMS) in routine patient care

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This presentation will include an overview of PROMs, including what they are, how they are developed and how they are used in healthcare.

Historically, PROMs were developed for research purposes to quantitatively capture quality of life, with the first developed in 1901. Moving forward to 2018, PROMs now have a wide range of applications from population data used in health economics, to the care of individual patients in routine clinical practice.

There are many PROMs available, each developed with a specific purpose. The different types of PROMs will be discussed, and the many applications of PROMs in healthcare. A summary of the key literature and trends in using PROMs in individual patient care will be presented.

229. Telehealth survivorship care

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In Australia, survivorship care is recognised as an important phase of the cancer trajectory. Nursing training, education and practice emphasises holistic patient assessment, symptom management and care planning, cancer nurses (as the largest cancer care workforce) are therefore ideally suited to deliver survivorship care. With the increase in the number of cancer survivors, there is a pressing need to develop strategies for enabling nurses to make the most of the available opportunities to support patients along their survivorship journey. The Clinical Oncology Society of Australia (COSA) Model of Survivorship Care describes the critical components of cancer survivorship care in Australia. These components include, but not limited to, risk stratification to inform pathways of care; development of a survivorship care plan incorporating a treatment summary; care coordination; and use of specialised strategies such as motivational interviewing and telehealth to promote well-being - all provided in a timely and accessible manner. Drawing on findings from multiple sources (i.e. government frameworks, systematic reviews and observational studies), implications for practice and research in relation to (i) nurse-led survivorship care provision, and (ii) the use of telehealth as an enabler will be discussed.

230. Achieving equity for regional haematology patients with nurse led initiatives

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Aim

The Victoria cancer plan 2016-2020¹ has as one of its key aims to achieve equitable outcomes for all Victorians. Regional patients requiring intensive haematology treatment represent a high needs group at risk of reduced access to optimal care. We describe a cross organisation, nurse led initiative to mind the gaps for this vulnerable group.

Method

In 2017 two new expert haematology nurse roles were created. At Latrobe Regional Hospital (LRH) a Haematology Clinical Nurse Consultant (CNC) provides expert haematology nursing support for patients across the Gippsland region including coordination of their care at a range of tertiary centres. At Alfred Health (AH) a Regional Nurse Coordinator (RNC) provides coordinated care for all outer metropolitan and regional malignant haematology patients attending AH.

The CNC and RNC collaboratively developed a nurse led shared care model to facilitate all aspects of care for haematology patients between AH and Gippsland. Patient satisfaction surveys are completed to monitor the service. The service is supported by Gippsland lymphoma and myeloma multidisciplinary meetings (MDMs) attended by clinical staff from all sites.

Result

From May 2017 to June 2018, 18 patients were enrolled in the shared care program between LRH and AH. 9 patients received pre and post autologous stem cell transplantation (ASCT) care, 5 patients received reduced intensity treatment and supportive care for acute myeloid leukaemia and 4 patients received a treatment for high grade lymphoma at both sites. The service has saved more than 10,000 KM of travel time.

Patients surveyed reported high satisfaction with the coordinated service. A recurrent theme is the confidence of collaboration between LRH and AH where patients experience a seamless service.

Conclusion

Improving the provision of cancer care for regional patients with high risk haematological conditions requires strong collaboration between regional and tertiary centres focused on patient centred outcomes.

1. Department of Health & Human Services Victoria Victorian cancer plan 2016–2020 <https://www2.health.vic.gov.au/about/health-strategies/cancer-care/victorian-cancer-plan> (accessed June 2018)

231. Refugee case study

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Aim

In the literature, refugees are identified as a particularly vulnerable population who often experience poorer health outcomes, more complications and greater distress compared with Anglo-Australians. The purpose of this case study is to critically reflect and evaluate the care received by a refugee during and after bone marrow transplantation for B-Acute Lymphoblastic Leukaemia.

Methods

A case study approach will be used to evaluate the care and identify the health care needs of this patient.

Case Study

Pt XM had a history of B-Acute Lymphoblastic Leukaemia for which he received an unrelated stem cell transplant. Pt XM was a refugee who had been living in Australia for 6 years prior to diagnosis. XM had no previous medical history or interaction with the Australian Health Care System prior to his diagnosis with B-Acute Lymphoblastic. XM was of Afghanistan cultural heritage and supported by his large family including brothers, sister, their partners, his wife and mother all residing under the same roof. The transplant process itself was relatively uneventful aside from mucositis and neutropenic fevers, both of which resolved quickly with count recovery. However, during the post-transplant period pt XM experienced extreme financial, physical, and psychological distress which impacted on his quality of life.

Results

This case study highlights that while XM received efficient and appropriate medical care, his psychosocial needs were not well looked after. During the 4 years pre/post-transplant, XM has only had an interpreter provided for one appointment despite being of non-English speaking background. XM experienced emotional distress related to financial hardship, functional impairment, depression and reduced quality of life post-transplant.

Conclusion

Refugees are a vulnerable population that require culturally appropriate care and assistance in navigating our complicated Australian Health Care System.

232. Caring for rural and remote haematology patients in far north Queensland – Aboriginal and Torres Strait Islanders

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¹Queensland Health, Brisbane, Australia

Cancer is the second most common cause of death for Australian Aboriginal and Torres Strait Islander people, with 60% more likely to die from their cancer than non-Aboriginal people (Newman et al., 2018). At Cairns Hospital, the Cancer Services department recognises that there are higher rates of mortality from cancer and it is markedly higher for Indigenous compared with non-Indigenous Australians². Together with Cancer care co-ordinators, Indigenous liaison officers, nurse navigators, allied health team, nursing staff and doctors we are able to assist with cultural differences and provide culturally safe care.

The Cairns Hospital and Hinterland Health Service delivers health services across the continuum of care and also provides services to the Torres and Cape Hospital and Health Service. The Cairns and Hinterland region has the largest absolute population number (n=31,172) of Aboriginal and Torres Strait Islander people of any Health Service in Queensland, with 12.6 percent of the resident population identifying as Aboriginal and Torres Strait Islander, compared to only four percent for Queensland as a whole (Health.qld.gov.au, 2018)

Treatment of rural and regional acute haematology Aboriginal and Torres Strait Islander patients involves travel from their home to the treatment centre in Cairns. From 2012 to 2017, 9.3% of the total haematology patients identified as Aboriginal or Torres Strait Islander. From the total identified, 201 patients lived outside of the Cairns area in regional and remote communities. This group was again smaller at a total of 52 for requiring admission for treatment and management of their haematological malignancy. When receiving treatment for an acute haematological issue, it requires them to stay as inpatients or in accommodation while receiving treatment then staying close by for follow up until being well enough to go home. Being away from their home can be up to 4-6 months. The patient needs to leave their family and community and is placed into foreign and clinical area. The challenge to treating this group of patients is over coming barriers, language, health literacy, customs, attitudes, compliance during treatment, beliefs and preferred ways of doing things to maintain some normality so the patient and the team are able to engage with each regarding their malignancy, treatment and future plans.

References:

Health.qld.gov.au. (2018). *About Us | Queensland Health*. [online] Available at: https://www.health.qld.gov.au/cairns_hinterland/about_us [Accessed 22 Aug. 2018].

Newman, C., Gray, R., Brener, L., Jackson, L., Johnson, P., Saunders, V., Harris, M., Butow, P. and Treloar, C. (2018). [online] *Cancercouncil.com.au*. Available at: <https://www.cancercouncil.com.au/wp-content/uploads/2015/03/One-size-fits-all-Cultural-Difference-paper.pdf> [Accessed 22 Aug. 2018].

233. Caring for LGBTIQ+ people

Farmer G¹

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Caring for LGBTIQ+ People

LGBTIQ+ people have many different health needs and issues that require some sensitive care and understanding.

Often these health care needs are overlooked or not considered which can lead to poorer physical and mental health outcomes for LGBTIQ+ people.

It is important for health care professionals to understand the diversity of people that exist under the umbrella term LGBTIQ+ and to understand sound care pathways that will provide meaningful and successful outcomes.

Diversity in sex, gender and sexuality are important aspects that may require very specific approaches and an understanding of lived experiences from LGBTIQ+ people and their families and partners.

The LGBTIQ+ community also experience higher rates of suicide due to discrimination, stigma and often abuse that has occurred. This has profound impacts on mental health and other health outcomes for people of diverse sexualities, genders and bodies.

Brisbane North PHN is one of the National Suicide Prevention Trial Sites and has identified the LGBTIQ+ Community as one of the priority groups as part of the Trial.

The presentation will examine terminology, sensitivities and ways to work more successfully with LGBTIQ+ people that can assist with care pathways.

234. Age friendly care for young adults

Broadbent A

Mater Young Adult Health Centre Brisbane provides excellence in transition from paediatric services, care during the adolescent and young adult period and subsequent transition to adult services. Mater Young Adult Health Centre Brisbane features new innovative service models for patients and their families that will focus on their primary condition as well as issues that impact on adolescents and young adult development.

235. Neuro atypical client groups

Bagshaw T¹

¹The Prince Charles Hospital, Brisbane, Australia

The neuro atypical client group present unique challenges to provide assessment and treatment to.

This session intends to discuss briefly neuro atypical client groups such as autism spectrum, intellectual impairment and significant mental illness in the context of establishing engagement, rapport and facilitating treatment.

The session will then focus on practical tips to apply including environmental, communication and interventions.

236. People living with blood cancer at the heart of our decision making

Huntley K¹

¹*Leukaemia Foundation, Brisbane, Australia*

Aim: The profile of people living with blood cancer is becoming varied with increasing demands on our support services to address the full suite of a people's physical, emotional, social and practical needs. Expectations are also changing. Access to online health information, growth of informed and assertive health consumers as active participants in their treatment decisions, are changing the dynamics and need for credible curated information. As the treatment landscape changes the "journey" of blood cancer and needs of support evolve.

To remain relevant to our stakeholder's, extensive discovery research will guide an organisational structure and strategy to ensure relevancy and value to our primary stakeholders, people living with blood cancer.

Method: In November 2016, five stakeholder discovery focus groups were undertaken, involving acute, chronic, metro and regional blood cancer patients in various locations around Australia, as well as a carer specific focus group. Structured in depth and open-ended dialogues were recorded, transcribed before analysis and categorising into meta-themes and primary and secondary stakeholder value opportunities. Each opportunity was then ranked to identify the problems, aspirations and experiences that when addressed by the Leukaemia Foundation would have the greatest impact and value.

Result: The discovery process identified seven themes related to the individual person with blood cancer including:

- inform me
- assist me
- accompany me
- represent me
- assure me
- nurture me
- actualise me

These themes have been incorporated into the newly developed support framework and strategy.

Conclusion: We have restructured the organisation that places our stakeholders at the centre of everything we do. The organisation has been realigned to enable greater opportunity to broaden and increase the impact on people living with blood cancer. Our purpose has and always will be to add value to the lives of people living with blood cancer.

237. Partnering with consumers

Kulperger S¹

¹Metro North Hospital & Health Service, Brisbane, Australia

Connecting for Health: strategy for inclusive engagement, involvement and partnerships 2015-18 is Metro North Hospital and Health Services' framework for partnering with consumers.

Partnering with consumers occurs at all levels of the organisation and is everyone's responsibility: from the way our clinicians daily engage and work collaboratively with patients and families in decisions about care through to a range of innovative projects in which consumers are involved as co-designers and instigators, and up to our Community Board which governs the performance of our operations and strategies and includes consumer advisors and representatives as equal members.

To realize our Strategy, every area of Metro North Hospital and Health Service develops an annual plan for consumer partnership with dedicated consumer engagement lead roles in each of our hospitals coordinating and supporting staff in working with consumers. Each hospital across our district has a consumer advisory group or network – some are formal committees chaired by consumers and some are more informal networks with a pool of active consumers that are engaged as partners in a range of activities.

Annually, we report to the community, to our Board and Community Board on our achievements, progress and the lessons we have learnt.

Beyond the achievement of our Strategy and ensuring accreditation standards are met, partnering with consumers is about building a culture. Our role is to facilitate the many voices and experiences of consumers – to understand, respect, respond and work with consumers – and ensure that partnering with consumers is done in a way that is respectful, ethical and meaningful. We also encourage an approach to partnering with consumers creatively and flexibly. Through this we have continued to build capacity, relationships and trust and have continued to innovate.

For this presentation, a slideshow of images of consumer engagement "Our annual Yearbook" will be run along with a short video clip of two consumers talking about why they have become involved.

238. In conversation: Memoirs of a professional patient

Barrie J

John-Michael was diagnosed in mid-2010 with extranodal (stage IV) non-Hodgkins t-cell lymphoma. At time of diagnosis, his was the eighth case recorded worldwide, and the first in the Southern Hemisphere. After eighteen months of chemotherapy, a failed autologous bone marrow transplant, and a successful against the odds allogeneic transplant, he was declared cancer free in early 2012. Despite a ten-out-of-ten unrelated bone marrow match, chronic GVHD replaced cancer as the primary threat to his health, and caused numerous issues with his recovery. He became a consumer representative with Metro North HHS in 2017.

John-Michael wrote *Indomitable Will* with two major aims. First, he believed it important to record this tumultuous period of his life, as cancer and GVHD tried to kill him four times in five years. Along the way, he explored the Five Steps of Grief from a first-hand experience, finally defining Acceptance from a survivor's perspective. *Indomitable Will* explores the impact his cancer diagnosis had himself personally, his wife, and the people close to him. The second reason was the hope that if *Indomitable Will* spares even a single future patient a tiny amount of the emotional, physical, or mental pain along their own journey.

There will be a Q&A discussion format, followed by short excerpt from *Indomitable Will*. If possible, we would like a table with two chairs. We would prefer lapel microphones if available. There will be a single image projected for the duration of the session. (*Memoirs of a Professional Patient*)

239. Interpreting pathology results

Zitella L¹

¹*University of California, San Francisco, USA*

Interpreting pathology results

The pathology report, cytogenetic analysis, and molecular diagnostics provide critical information to render a cancer diagnosis, understand prognosis, and help choose appropriate cancer therapy. Advances in genomic technology has led to increased recognition of genetic mutations associated with haematologic malignancies as well as identification of targeted therapies to inhibit these mutations and more effectively treat the cancer. This lecture will review interpretation of a pathology report, cytogenetics, FISH, and molecular diagnostics in haematologic malignancies

241. Adult related stem cell donor care – related donors' and transplant nurses' experiences and perceptions

Zomerdijk N¹

¹Royal Brisbane and Women's Hospital, Brisbane, Australia

Rationale

Advances in the stem cell transplantation field, notably haploidentical transplants, have led to an increased demand for related donors (RDs). However psychosocial issues for RDs have received little attention to date.

Aim

This study aimed to explore Transplant Nurses' (TNs) and RDs' experiences and perceptions of related donor care in a QLD and NSW cohort.

Method

Thirty RDs completed 3 semi-structured interviews - pre-donation, on the day of donation, and 30 days post-donation. Seven TNs completed 1 interview. Interviews were audio-recorded, transcribed, and subjected to thematic analyses.

Results

TNs described concerns about: responding to RDs who expressed uncertainty; communication challenges (international RDs, transplant time pressures); variations in practice; pre-existing psychosocial issues in RDs; and lack of protocols for RD follow-up. Suggested improvements included: improved provision of information before HLA testing; development of referral pathways to address RD psychosocial needs; psychological assessment before donation consent; follow-up support particularly in cases of severe recipient complications, relapse or death; and communication skills training for TNs. Psychosocial issues identified by RDs and barriers to improving RD care will also be discussed.

Conclusion

Despite technical excellence, this growing population must be seen in a broad context, requiring both physical and psychosocial care. The results of this study have informed the development of a psycho-educational resource that is tailored to the specific needs of RDs. A pilot study assessing the acceptability of the resource is currently ongoing. We anticipate progression to a website platform in the future.

242. Lessons learnt form child bearing age donors

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Related or unrelated, male or female stem cell donors are imperative to any Bone Marrow Transplant (BMT) unit. Generally, males are the first preference in donor selection, however females are sometimes the only option and have proven to be equally successful for patient related outcomes . All donors are assessed both physically and emotionally as per local guidelines, but critically, female donors and their child-bearing potential are stringently assessed to protect both the female donor and any potential pregnancy. This case study explores a timeline of events of a 26yo unrelated stem cell donor who despite undergoing a serum bHCG pregnancy test and education, was discovered to be pregnant on Day 3 of GCSF mobilisation (Day -3 of BMT recipient conditioning), causing urgent cessation of both GCSF for the donor, and conditioning of the recipient. This adverse event instigated urgent protocol reviews and practice change to prevent event reoccurring, whilst also allowing personal reflection of the surrounding sensitivities associated with female stem cell donors and their child bearing potential. As one of the largest BMT centres in Australia, with many different national and international accrediting bodies, alignment of efficient practice to satisfy all guidelines is an ongoing process and sometimes pose a challenge.

243. Children as haematopoietic stem cell donors: Complexities in ethics and law

Then S¹

¹Queensland University of Technology, Brisbane, Australia

Children have been used as tissue donors for sick family members for decades. The great good that can come about through their participation is at the cost of the donor child undergoing physically invasive and unnecessary medical procedures. While accepted medical practice, the non-therapeutic participation of donor children raises a number of ethical issues and regulatory challenges. While historically, child donors were not focussed upon and may have been 'forgotten', in the past decade, more attention and research has been given to those that take on the child donor role. This presentation explore these issues, identifying the complex legal regime in Australia, the ethical issues involved and the regulations that seek to guide practice with the aim of identifying whether we are doing enough to support child donors.

244. Collaboratively managing a patient with a body surface area of 3.3 through HSCT for MDS

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Introduction

A 39-year-old male patient was planned to receive a Haematopoietic Stem Cell Transplant (HSCT) for a haematological malignancy. The patient's background included Cerebral Gigantism with height and weight 213cm and 189kg respectively, (Body Surface Area of 3.3). His body size made him ineligible for TBI based conditioning, so the prescribed conditioning was fludarabine and melphalan. The patient lived in a care facility which provided customised equipment to accommodate his size and needs. The patient's discharge destination was his parent's home which was also customized to accommodate his needs.

Management and Outcome

The preparation and execution of this HSCT hospital admission required extensive planning and collaboration between the Multidisciplinary team, pharmacy and various hospital departments. Specialist bariatric equipment was sourced. Despite guidelines recommending actual body weight to be used to calculate chemotherapy doses, adjusted body weight of 150kg (BSA=3) was used due to lack of guiding evidence. The dose of other supportive medicines was individualised. The patient was discharged after 34 days. Discharge planning was precise, including equipment organised, at home physiotherapy and Webster packs organised for medications. The patient had no further hospital admissions or complications, and was weaned off immunosuppressants without evidence of graft-versus host disease. At twelve months' post-transplant, he is well, only requiring regular physiotherapy. He also underwent a total knee replacement.

Discussion

The ability to offer a HSCT to such a patient was made possible only by the collaboration of many disciplines. Despite a lack of evidence and experience in the management of such a clinical situation, through execution of diligent planning and communication, the HSCT was successful with minimal obstacles. This case demonstrates that a large BSA should not be a barrier to offering HSCT to such patients.

245. A single centre experience in managing hodgkin lymphoma in pregnancy – it takes a village...

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The diagnosis of Hodgkin Lymphoma (HL) in any patient is a life changing event, often associated with increased levels of stress and anxiety. For the rare group of women diagnosed during pregnancy, significant additional medical, ethical and emotional dilemmas await the patient, her family and the multidisciplinary team.

The presence of any cancer in pregnancy remains a relatively rare event, being observed in approximately 1 in 1000 pregnancies. The management of HL in pregnancy is extremely challenging and currently no cancer registries collect this data in Australia. The goal of treatment is to achieve curative long-term maternal outcomes whilst optimising delivery of a healthy baby.

We discuss our recent experience at University Hospital Geelong with two cases of HL in pregnancy to illustrate the complexity of these patients, including diagnostic and therapeutic management. One patient presented with rapidly enlarging cervical lymphadenopathy whilst the other patient was diagnosed incidentally following a routine pregnancy screening test. In both cases, there was a general consensus regarding the feasibility and requirement for treatment after the first trimester. The cases also demonstrate the different issues faced by each patient and the need to tailor their management accordingly. Issues regarding safe diagnostic imaging, timing and dosing of chemotherapy, supportive care and timing of delivery will be addressed and reviewed within these cases.

HL in pregnancy is rare and poses challenges for patients and health professionals. A multidisciplinary team approach combining expertise in haematology, high risk obstetrics, radiation oncology, paediatrics, nursing, midwifery, allied health, and a nurse coordinator who is able to augment the communication and delivery of care is essential. Considering the excellent outcomes for HL outside pregnancy, our management demonstrates the aim for curative intent while minimising foetal harm.

246. Yarning about Blood- Development of an Aboriginal and Torres Strait Island specific blood transfusion consent information brochure

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Aim: To develop a blood transfusion consent information brochure for Aboriginal and Torres Strait Island Australians that is culturally appropriate and easy to understand.

Method: As Standard & Blood and Blood Products 7.10.1 states, the patient should be provided with adequate and understandable information about their blood transfusion that is meaningful and easy to understand. Aboriginal and Torres Strait Island patients have different lifestyle and health challenges such as poor eyesight and hearing, literacy and language barrier. Therefore, the general hospital information brochure may not be appropriate for this population of patients.

After discussion at the local Transfusion Nurse Education Group, it was agreed that a working party would be developed between the Transfusion nurses from three major public hospitals.

An internet search was undertaken of National and State specific resources which identified that there was no existing Blood transfusion consent information brochure in a suitable format for Aboriginal and Torres Strait Island patients. Discussion with health workers from other states provided guidance and tools to help create the brochure. Other health related Aboriginal resources were reviewed to identify appropriate wording and layout. Ideas were workshopped with Aboriginal and Torres Strait Island nursing students, as well as the Aboriginal Health Liaison Officer (AHLO) to improve understanding of specific cultural needs regarding the providing of education and information to these patients.

Results: After consultation with key stakeholders, a draft brochure was created, and reviewed by the local Transfusion Nurse Education Group. Changes were made and sent to the AHLO and Consumer group for review.

Conclusion: Despite there being many health-related resources available for Aboriginal and Torres Strait island Australians, minimal information surrounding consent or blood products appears to exist. The development of this brochure will fill this gap, with the long-term goal being to introduce a state-wide resource.

247. Hands up for hand hygiene in cancer care

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Aim

Hand hygiene is the most effective measure to reduce hospital-acquired infections (HAIs). This project took a novel approach to engaging healthcare workers, patients and their carers to understand and describe their attitudes, perceptions, motivations and behaviours towards hand hygiene. We aimed to improve hand hygiene compliance and provide a successful model of engagement in Cancer Care Services (CCS).

Method

We held the first workshop to identify issues around hand hygiene and inform the development of the interactions for the *InstaBooth*, which is a methodology for stakeholder engagement. A final workshop analysed the data and designed a range of interventions to the issues raised. Effectiveness of educational interventions was assessed using the monthly Hand Hygiene audits.

Results

The first workshop provided a forum for consumers, carers and healthcare workers to share their experiences, ideas and suggestions for improving hand hygiene practices and/or reducing HAIs. The *InstaBooth* was deployed for 12 days in August/September 2017. It elicited 642 separate interactions over six activities. A second workshop developed interventions which were tested in the clinical environment (March-June 2018). Personal stories revealed themes such as vulnerability, trust, power and professionalism which have been used effectively to improve Moment 2 compliance through education interventions. In May 2018 Moment 2 compliance was 92% across CCS – the highest compliance in the past year.

Conclusion

The *InstaBooth* deployment and workshops revealed a high level of hand hygiene awareness and willingness to learn more and do better. Hand hygiene is integral to the prevention and control of HAIs. Immune suppressed cancer patients are particularly at risk of developing infections. Our education interventions improved Moment 2.

249. Out-patient BMTs

Crosbie T¹

¹Sir Charles Gairdner Hospital, Perth, Australia

The presentation will cover several topics including information on key factors for maintaining outpatient transplants.

Topics include the History of outpatient Autologous transplants in WA, show site specific information and include how many transplants are carried out at our site and outpatient regimens used. The presentation will also discuss our admission rate, time to admission, length of stay comparisons.

The presentation will then go on to discuss the timing of symptom onset will be discussed to show we can initiate care before they happen.

The infrastructure developed to ensure outpatient transplants involving the clinical support during their outpatient time will also be identified

The presentation will also include the results of a qualitative descriptive analysis of patient's experiences while undergoing a stem cell transplant.

250. How to help your haematology patients die at home

Lukin B¹

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In this session Dr Lukin will discuss issues around haematology patients dying at home. While there are many commonalities with other patients dying at home there are a few challenges that are unique to haematology. The complex relationship between treating clinicians and the patient will be discussed along with the topic of ceasing product support. The relationship with the local palliative care service is also of paramount importance. An ideal model of care will be discussed.

251. Clinical leadership in haematology

Zitella L¹

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This session will focus on professional career development in haematology nursing. Highlights include how to publish in a peer-reviewed journal, present a professional lecture, serve on national committees, and contribute to evidence-based guidelines and hospital-based quality improvement initiatives.

252. Nursing leadership in cancer care

Yates P¹

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We live at a time of unprecedented change to the way in which health care is delivered. Increasingly, the importance of nurses' contribution to ensuring safe and quality health care in this rapidly changing environment is recognised. Realising nursing's potential for improving health care outcomes now and in the future requires strong nursing leadership. This presentation will review a series of case studies to illustrate ways in which nursing leadership at policy, health service, and professional levels have improved the health of people with cancer. The examples will highlight the importance of building the leadership capabilities of all cancer nurses.

255. How important are gut bacteria in determining BMT outcomes?

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The impact of the microbiota on intestinal graft-versus-host disease (GVHD) in patients undergoing an allogeneic hematopoietic cell transplantation (allo-HCT) was first described decades ago, but the exact relationship is still not well understood. In recent years, extensive studies have been performed in mice and patients to assess the role of intestinal flora changes in the pathophysiology of all three major complications of allo-HCT: infections, GVHD, and relapse, as well as hematopoietic reconstitution. Using next-generation sequencing of the bacterial 16S ribosomal RNA (16S rRNA) gene, we examined the intestinal microbiota of allo-HCT patients and found a post-transplant “microbiota injury” characterized by loss of diversity and a dramatic expansion of potentially pathogenic bacteria that precedes bacterial sepsis with the same organisms. This dysbiosis is likely due to the combined effects of (a) conditioning regimen (radiation and/or chemotherapy), (b) broad-spectrum antibiotics for the treatment of post-transplant febrile neutropenia, as well as other drugs and (c) the profound nutritional alterations experienced by these patients. We found an inverse relationship between GVHD mortality and post-transplant a) loss of diversity of the intestinal microbiota, and b) lower abundance of the genus *Blautia*. Broad-spectrum antibiotics that target the anaerobic commensal flora were particularly associated with increases in GVHD-related mortality in allo-HCT patients and worsened intestinal GVHD in our animal model. In addition, we found both in preclinical models and allo-HCT patients an association between higher abundance of *Enterococcus* and greater risk of GVHD. We have also found an inverse relationship between the abundance of the anaerobe commensal bacterium *Eubacterium limosum* and relapse. Finally, we found that the intestinal microbiota are important for post-transplant lymphoid reconstitution through its role in processing of starches into short chain fatty acids and monosaccharides necessary for calorie uptake from nutrition. In conclusion, the intestinal microbiota play an important role in overall survival, GVHD, infections, relapse and lymphoid reconstitution after allo-HCT. Strategies to prevent or treat post-transplant intestinal dysbiosis could improve outcomes in patients undergoing an allo-HCT.

256. CAST – A randomised phase 3 trial of cyclophosphamide after sibling allogeneic haematopoietic stem cell transplant (ALLG BM12)

Curtis D¹

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Allogeneic peripheral blood stem cell (PBSC) transplant remains an important curative treatment for haematological malignancies. Despite improvements in donor selection, conditioning regimens and supportive care, chronic graft versus host disease (cGVHD) is an increasing cause of mortality (20% of all transplants) and morbidity, with impaired quality of life of many long-term survivors. Better strategies to prevent cGVHD are urgently needed. Cyclosporin A (CsA) plus methotrexate (MTX) has been the gold standard for GVHD prophylaxis since the late 80s. In the last 5 years, an alternate strategy using high dose cyclophosphamide on days 3 and 4 following stem cell infusion (so-called post-transplant cyclophosphamide, PT-Cy) has enabled HLA mis-matched transplantation with low rates of cGVHD. Single arm studies suggest that PT-Cy may also be effective for matched PBSC transplants. However, PT-Cy has never been directly compared with other methods of prophylaxis and therefore, we have initiated the first randomised phase 3 study comparing standard of care (CsA + MTX) with PT-Cy + CsA for the prevention of clinically significant GVHD in matched sibling PBSC transplant for patients with acute leukaemia or myelodysplasia. This national study of 134 patients will have an 80% power to detect an improvement in a composite endpoint of GVHD and relapse-free survival from 28% to 50% (Hazard Ratio 0.54). Major secondary endpoints include quality of life and health economic impact. In addition, this trial will collect tissue samples for subsequent correlative studies to determine the effect of PT-Cy on immune activation, reconstitution of pathogen specific immunity and elimination of minimal residual disease. This will be the largest multi-centre randomised trial of bone marrow transplantation in Australia and the first of PT-Cy, and if successful, may change international practice.

257. Homegrown CAR T-cells for B-cell malignancies and beyond

Micklethwaite K¹

¹Westmead Hospital, Sydney, Australia

Chimeric antigen receptor T-cells (CAR T-cells) have received regulatory approval for the treatment of B-cell malignancies in the United States and Europe, but questions remain regarding their pricing and the limitations of a centralized model of production. We have instituted CAR T-cell trials for relapsed and refractory B-cell malignancies using our locally developed novel production methods. Early results are consistent with those seen in other trials to-date. We are continuing to refine our production methodology and developing new tools to enable ease of production of CAR T-cells. We intend to use this technology as a platform for the development of CAR T-cells for a variety of malignancies. We hope that our technology will contribute to the wider application of CAR T-cells across Australia, providing patients with timely access to this revolutionary new therapy.

258. TCR $\alpha\beta$ /CD19 depleted haploidentical transplantation: Australian experience and future directions

Fraser C¹

¹*Lady Cilento Children's Hospital*

TCR $\alpha\beta$ /CD19 cell depletion is an emerging technique for ex vivo graft manipulation in haploidentical haematopoietic stem cell transplantation (HSCT). Australian paediatric transplant centres have adopted this platform for haploidentical transplantation for malignant and non-malignant diseases and have recently opened a prospective clinical trial to compare the efficacy and cost effectiveness of this strategy to other alternative donor sources. This presentation will provide some background regarding the technology and discuss outcome data for the initial clinical experience in Australia.

259. Making the grade for pathogen and tumour specific T cells

Leighton C¹

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The recent clinical success of gene modified T cells to treat chemotherapy resistant B cell malignancies has highlighted the therapeutic potential of adoptive T cell therapy. For more than 15 years the Cellular Therapies Group at Westmead Hospital have been developing a platform for the delivery of T cell therapies to patients. Our trials program has now evolved to include several different studies that aim to treat haematological malignancies or to treat common infections that occur in immune compromised blood and marrow transplant recipients. This talk will give an overview of the methods employed by our laboratory to manufacture pathogen specific and chimeric antigen receptor T cells.

260. Keeping up appearances – maintaining accreditation

O'Ryan N¹

¹Metro North Hospital and Health Service, Brisbane, Australia

The Royal Brisbane and Women's Hospital in Brisbane provides related and unrelated allogeneic and autologous bone marrow transplantation to around 130 recipients per year. Back in 2007 the Royal Brisbane and Women's Hospital (RBWH) and Royal Children's Hospital (RCH (now LCCH)) decided to achieve and promote a system that ensured that the quality of clinical care for the collection, cell processing, and administration of cellular therapy products was the best it could be. The leadership teams at the RBWH and RCH were more than ready to support the changes necessary to achieve and maintain this high standard, and they understood that a great level of commitment to quality management would be required to obtain and maintain this standard.

Being the first centre in the Southern Hemisphere to be awarded accreditation was a huge achievement. Roll forward 12 years and we have recently received our fourth letter of congratulations from the Foundation for the Accreditation of Cellular Therapy (FACT) Board. The great success in obtaining the accreditation 'pass', often followed by a period of relative calm and perhaps some relief that it is all over for another 3 years, is a marker of the huge effort the multidisciplinary teams at both sites have put in during the lead up to the inspection. However as everyone working closely with the quality management team knows, this is only half the story. There is an obvious requirement for constant oversight of the program to ensure compliance with standards, for updates, for continual monitoring of the processes in place, of document review and revision, and of errors, incidents, adverse events and product recall. In addition, changes to location, services, and program and facility directors must be communicated. Minimum numbers of procedures must be achieved for each facility, compulsory annual audits completed, management review, and the annual report, or on line surveillance audit submitted.

At our centre there is a constant cycle of accreditation in cell therapy with regular on-site visits from FACT, NATA, ACHS and the Centre for International Blood and Marrow Transplant Research (CIBMTR), along with on-line submissions from the ABMDR. Maintaining accreditation can sometimes feel like we are keeping up appearances.

261. The BMT network centralised quality management system

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Background

The national standards *ISO15189 Medical Laboratories –Requirements for quality and competence* and *NPAAC Requirements for Procedures Related to the Collection, Processing, Storage and Issue of Human Haemopoietic Progenitor Cells* require the implementation of a quality management system (QMS) in BMT programs. These standards, however, do not prescribe the model in which this is undertaken. Whilst the traditional method of a quality manager per individual BMT program may appear advantageous due to daily face to face interaction, a centralised system may also achieve adequate contact with a number of BMT programs with the added advantages of independence and harnessing of shared experience.

Method

NSW performs the largest number of HPC transplants of any state in Australia with total of 589 autologous and allogeneic transplants in 2016 (an increase by 22% over the previous 5 years). In 2008 a centralised QMS was established unifying 12 clinical/ collection units and 7 processing laboratories as the BMT Network QMS. This included the use of quality management software configured to BMT requirements, working groups to harmonise practices and procedures and project groups to implement clinical initiatives and educational resources.

Results

This statewide initiative has been successful in:

- Sharing of highly specialised clinical and laboratory expertise
- Standardised procedures and forms
- Centralised ordering of consumables
- Cost effective staffing
- Independent auditing and collaborative implementation of quality improvements
- Benchmarking programs e.g. inter-laboratory frozen CD34 comparison
- Multi-centre validations of quality indicators (cell yield, engraftment, survival) using extensive transplant data.
- Comprehensive education program including webinars, forums and training resources
- Patient experience systems and patient resources

Conclusion

The implementation of the BMT Network QMS has facilitated continued accreditation with the additional benefits validating and comparing practices based on extensive data-sets, addressing opportunities for improvement across hospital BMT programs and developing education tools as a team. The patient is the primary focus with improvements and resources development aimed at maximising product quality whilst assisting quality of life.

P001. Case Report: Congenital Acute Lymphoblastic Leukaemia

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Background

Congenital acute lymphoblastic leukaemia (CALL) presenting within the first 4 weeks of life is a rare haematological malignancy. This presentation details our local experience in the management of a patient diagnosed with CALL with KMT2A (MLL) re-arrangement on day 3 of life.

Case Presentation

A 3 day old term neonate with an unremarkable antenatal and perinatal course, had a full blood count performed in the setting of hyperbilirubinemia, revealing a WCC of 136, ANC of 0.00 and peripheral blast count of 98%. Peripheral blood flow cytometry demonstrated a phenotype of CD10/CD19/CD34/HLA-DR/CD58/CD123, consistent with a diagnosis of precursor B acute lymphoblastic leukaemia (B-ALL). Cytogenetics revealed 47XX, t(4;11) q21 q23, t(7;11), +8. FISH demonstrated rearrangement of KMT2A (MLL). Diagnostic CSF analysis confirmed CNS involvement. Interfant 06 was commenced at reduced doses for age with numerous significant toxicities in induction including Vincristine related SIADH, autonomic and peripheral neuropathy. Bone marrow performed post induction treatment demonstrated a hypocellular marrow with preserved myelopoiesis, erythropoiesis with an overall reduction of megakaryocytes. The presenting phenotype was not identified on flow cytometry (< 0.1% sensitivity). MRD marker MLL-AFF1 was detected at 5×10^{-3} . Given previous toxicities and in view of the proven KMT2A re-arrangement, Azacitidine was commenced at 2.5mg/kg for 5 days as bridging therapy to multi-agent chemotherapy.

Discussion

CALL is rare, with a reported incidence of 1 per 5 million live births. It is strongly associated with KMT2A (MLL) gene translocations at chromosome 11q23, chemotherapy resistance and poor outcomes. Azacitidine monotherapy, a DNA methyltransferase inhibitor (DNMT1), has been found effective in case reports of CALL, with reduced toxicity compared to intensive chemotherapy.

Conclusion

CALL is a rare entity with minimal data available for toxicities and treatment. Azacitidine is a targeted agent against MLL rearrangement and can be considered for bridging therapy in patients who suffer toxicities or failure to conventional chemotherapy.

P003. Assessment of FLT3 Variant Allele Frequency (VAF) by Capillary Electrophoresis and Next-Generation Sequencing in Gilteritinib Treated FLT3mut+ R/R AML Patients

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Aim

Analyze VAF in *FLT3*^{mut+} R/R AML patients who were treated with gilteritinib, a novel FLT3/AXL inhibitor, using capillary electrophoresis (CE) and next-generation sequencing (NGS).

Method

Bone marrow and blood samples were analyzed using the CE (LeukoStrat[®] CDx) *FLT3* mutation assay and the capture-based NGS assay to detect *FLT3*-ITD and D835/I836 *FLT3*-TKD mutations. For the CE assay, loci were amplified using PCR. The NGS assay targeted mutation loci in all *FLT3* exons; target fragments were sequenced (Illumina[®] MiSeq). Overall survival (OS) was determined for patients who received ≥ 80 mg/day gilteritinib and were *FLT3*-ITD[±]*FLT3*-TKD and those with *FLT3*-TKD only. The VAFs were stratified by whether they were \geq or less than the median value. Furthermore, OS of *FLT3*-ITD⁺ patients was stratified using a $\geq 5\%$ VAF threshold by NGS.

Result

Samples from 241 patients were analyzed. *FLT3*-ITD detection by CE or NGS showed a strong concordance in 98.8% of samples, including those with multiple ITDs; strong correlation between both assays was observed for mutation frequencies ($R^2=0.987$). *FLT3*-TKD concordance was observed in 98.3% of samples, with a strong correlation between mutation frequencies ($R^2=0.906$). The OS in *FLT3*-ITD[±]*FLT3*-TKD patients who received ≥ 80 mg/day gilteritinib with VAFs \geq or less than the median value were similar across both assays. Patients with *FLT3*-TKD only and VAFs \geq the median value had longer OS than those with VAFs less than the median value; *FLT3*-TKD only patients with VAFs \geq the median value had OS durations similar to *FLT3*-ITD⁺ patients. By NGS, *FLT3*-ITD⁺ patients with VAFs $< 5\%$ had similar OS as patients with VAFs $\geq 5\%$.

Conclusion

The CE and NGS assays were highly concordant and resulted in similar OS stratified by *FLT3* mutation burden in R/R AML patients treated with gilteritinib. Our results suggest that *FLT3*-ITD⁺ R/R AML patients may benefit from gilteritinib, regardless of *FLT3* mutation burden.

P004. Blinatumomab maintenance therapy in adults with r/r Ph- B-precursor ALL: an exploratory OS analysis from a phase 3 trial

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Introduction

We examined OS for patients who received blinatumomab maintenance and compared outcomes with data pooled from patients who did not receive maintenance in the phase 2&3 blinatumomab trials.

Methods

Patients with bone marrow blasts <5% after two induction/three consolidation cycles were eligible for up to an additional 12 months of maintenance (4 weeks on therapy, 8 weeks off). Cumulative probability of OS over time was estimated using the Simon-Makuch method; the effect of maintenance was analysed using the Mantel-Byar method. OS: measured from the start of maintenance therapy for patients who were in remission until the start of Cycle 6 (for those who received maintenance) or at Day 211 (landmark date for those who didn't receive maintenance). Data from the phase 3 study and an earlier phase 2 study in which maintenance was not offered were pooled to increase the sample size for this analysis.

Results

119/271 (43.9%) blinatumomab patients achieved best response of CR/CRh/CRi within two treatment cycles, and 27 patients continued to maintenance (primary analysis cutoff). Three patients completed maintenance, 4 transitioned to HSCT, one discontinued due to AEs. Twenty-one (77.8%) patients maintained a best response of CR during maintenance, 1 (3.7%) patient each had CRh or blast-free hypoplastic or aplastic bone marrow, and 2 (7.4%) patients each had haematologic relapse/were not evaluable. A 41% reduction in the risk of death was associated with maintenance therapy (p=NS; Mantel-Byar analysis, Figure). Among maintenance patients, incidence of AEs of interest generally was less versus the incidence during the induction or consolidation phases.

Conclusions

High response rates with blinatumomab were maintained from baseline (beyond cycle 5), with longer OS versus patients receiving no maintenance. No new safety concerns were identified. A lower incidence of AEs of interest was seen during maintenance, versus events recorded during the induction/consolidation phases of this, and prior blinatumomab studies.

P005. Poor Correlation Between Peripheral Blood Cytopenias and Degree of Bone Marrow Infiltration in AML

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Aim

Patients with Acute Myeloid Leukaemia (AML) often present with clinical features of peripheral blood cytopenias. However, the pathogenesis of peripheral blood cytopenia remains unclear. This has traditionally been hypothesized to be related to AML blast cells causing displacement of nonleukemic haematopoiesis from the bone marrow. We aim to examine this hypothesis by correlating peripheral blood indices and the degree of bone marrow blast infiltration at diagnosis.

Method

Clinical and laboratory data of 374 patients with newly diagnosed AML between 2003 – 2016 in Western Australia, were retrospectively studied. Information regarding full blood count indices (Haemoglobin, white cell count, platelets, neutrophils) were compared against the degree of bone marrow blast infiltration (by bone marrow aspirate morphology). The SPSS software was used for analysis.

Results

Poor correlations were observed between all peripheral blood indices and bone marrow aspirate blast percentage. The R values for the following peripheral blood indices against blast percentages are as follows: Haemoglobin 0.149, neutrophil 0.025 and platelet -0.034.

Discussion

Our study findings do not support the prevailing assumption that the displacement of normal haematopoietic cells reflects the severity of peripheral blood cytopenias. Although the mechanism for peripheral blood cytopenias remains uncertain, a recent study has indicated the potential role of MPL, the thrombopoietin receptor present on blast cells, on the degree of cytopenia in AML¹.

Conclusion

Our study findings suggest that peripheral blood cytopenia in AML is independent of bone marrow blast content.

References

Rauch P.J., Ellegast J.M., Widmer C.C et al. MPL expression on AML blasts predicts peripheral blood neutropenia and thrombocytopenia. *Blood*. 2016; 128(18):2253-2257

P006. Plasmablastic lymphoma presenting as dermatomyositis

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Plasmablastic lymphoma is a rare and aggressive lymphoma, commonly associated with immunodeficiency disorders, with only a median survival rate of 9 months¹. Given the rarity of the disease, there is currently no accepted protocol for its treatment. We present a case in a patient with a first onset of dermatomyositis, based on an elevated creatinine kinase level >10,000, a positive skin biopsy, raised ANA and MRI findings supportive of myositis. As there is a 5-7 times increased risk of malignancy associated with dermatomyositis², a search for an underlying malignancy revealed multiple sites of lymphadenopathy, most significant in the mesentery and areas of extra-nodal disease. Biopsy of a mesenteric lymph node returned positive for plasmablastic lymphoma (Negative CD45, CD19 & CD20, Ki67 100%). Based on several case series, outcomes have been very positive for patients treated with EPOCH (etoposide, prednisolone, vincristine, cyclophosphamide and vincristine) combined with bortezomib. The largest cohort study by Dittus et al reported a CR rate of 100% & PFS of 2 years in 50% of patients (n=8) in the frontline setting³. Bortezomib, a proteasome inhibitor, traditionally used in multiple myeloma, may be effective as the plasmablast has a unique immunophenotype with loss of traditional B cell markers and expression of classic plasma cell markers³. Our patient was treated similarly, and is currently undergoing 6 cycles of DA-EPOCH with bortezomib given on days 3 and 6. Treatment success with this regimen may pave a way as a guide to future management of this disease in Australia.

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P007. Cytogenetic clonal evolution in relapsed acute myeloid leukaemia patients and the impact of accrual of additional chromosomal abnormalities on survival

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Aim

To retrospectively investigate the effect of cytogenetic clonal evolution (CCE) on the survival of relapsed acute myeloid leukaemia (AML) patients.

Background

The acquisition of additional chromosomal aberrations in a stemline clone or a subclone is consistent with clonal evolution of cells at a cytogenetic level and can be seen in approximately 40% of relapsed AML patients. CCE at diagnosis has been shown to have a negative impact on prognosis however the effect of evolution at first relapse is still to be established.

Methods

A cohort of 141 relapsed AML patients from a 10-year period (2008 – 2017) at PathWest RPH/FSH were followed up from diagnosis to date of death or last review. Conventional analysis and fluorescence in situ hybridization techniques using a panel of AML probes were performed on all samples and the relapsed karyotypes were compared to diagnostic results for the presence of CCE. The date from first relapse to death or last review was determined as the interval for overall survival (OS). A multivariate analysis comparing the effect of; karyotypic evolution, Medical Research Council (MRC) cytogenetic risk groups and curative treatment protocols on OS, was performed using the Kaplan-Meier method and log-rank test.

Results

In the non-clonally evolved group, there was a significant difference in OS according to the MRC risk groups ($p=0.001$). Sixty one (43%) of 141 patients demonstrated CCE and when OS was compared with the non CCE cohort, there was no significant difference ($p=0.08$). Likewise there was no prognostic difference when comparing these 2 groups with consideration to the status of curative treatment ($p=0.79$). The patient numbers were too small to show a significant difference between the CCE MRC risk groups ($p=0.31$).

Conclusion

Our findings demonstrate that CCE at first relapse in AML patients is not an independent poor prognostic factor compared to the MRC groups alone.

P009. A collaborative approach to acute leukaemia care at home

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A project developed between an Inpatient Haematology department and a Hospital in the Home (HITH) service to expand on the care already provided by HITH to include further opportunities for acute leukaemia patients undergoing consolidation treatment to receive chemotherapy and supportive care whilst at home.

3 chemotherapy protocols and 2 supportive care protocols were developed for the patient cohort. Chemotherapy regimens developed are a hybrid mode of care where treatment is started as an inpatient but then taken over by HITH to complete. Neutropenic monitoring also encompassed other post chemotherapy complications including monitoring for fevers, mucositis and electrolyte abnormalities which were managed with an admission to HITH on Day 9-10 post treatment. These patients were managed collaboratively by Haematology and HITH nursing and medical staff at home, unless they developed further complications necessitating an in-hospital admission, or alternatively were discharged once counts recovered. Utilising a risk stratification score to determine neutropenic patients who had a fever that could be discharged early via HITH with intravenous antibiotics was also developed. Patients were required to meet the following eligibility criteria for home based care; haematologist approval, no ICU admission during induction, no significant comorbidities, adequate home support and no behavioural barrier to participation.

To date, 14 patients have been admitted to HITH with 30 admissions saving a total of 116 bed days. Recruitment of patients into the neutropenic monitoring cohort has save 112 days; of those 50% developed a fever, 43% had no complication, whilst 7% of patients were admitted for other treatment related complications. Chemotherapy administration has saved 4 bed days for 1 patient.

With ever increasing demand for inpatient beds the need to be innovative in providing timely care to patients is paramount. Economically this allows for an increase in service provision without added costs of inpatient beds and services.

P010. Acute Lymphoblastic Leukaemia outcomes in adults at Gold Coast University Hospital (GCUH)

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Aim

ALL is a rare malignancy, with 25 adult Queenslanders diagnosed each year. This audit seeks to assess our local outcomes of ALL patients who were given intensive chemotherapy.

Method

This was a single centre, retrospective chart review on patients that underwent chemotherapy for ALL between May 2009 and May 2018 with minimum follow up of 6m (or until death). Patients were stratified according to treatment regimen. Our patients <25yrs receive BFM, 25-60yrs UKALLXII, and >60yrs HyperCVAD +/- TKI, with fluconazole for antifungal prophylaxis. Data was censored at June 2, 2018.

Result

Twenty-five patients (18/25 male) underwent chemotherapy for ALL with a median age of 39yrs (18-76yrs). Across all groups: 4 (16%) needed ICU; 6 (24%) had fungal infections and 11 underwent allograft.

Seven patients received BFM (median 21yrs (18-26yrs). Two patients in CR1 received allograft. Five patients had maintenance with median cycles completed of 15 (range 5-24). One patient relapsed at 24months and received an allograft in CR2. Median OS was 30m (12.2-79.6), DFS 28.0m (10.1-78.6), and PFS 29.2m (12.2-79.6). All are alive and in CR at follow-up.

Nine patients received UKALLXII (median 37yrs (26-57). Seven patients completed the protocol and proceed to allograft. There was 1 TRM. Median OS was 25.7 (0.6-76.4), DFS 27.4m (6.2-75.3), and PFS 25.7m (0.6-76.4). 6 patients are alive at follow-up and in CR, 2 died during allograft.

Nine patients received HyperCVAD (median 67yrs (54-76). Only 1 patient completed all 8 cycles (median 3/8). There was 1 TRM. Median OS was 8.4m (0.7-106.9), DFS 15.6m (1.4-106.1), and PFS 8.2m (0.7-106.9). 3 patients are in CR at follow-up.

Our 12-month survival is comparable to Queensland registry data at 76% vs 75%.

Conclusion

As expected, survival outcomes and chemotherapy tolerance are reduced with increased age, however our overall outcomes are comparable to registry data. The use of fluconazole to prevent fungal infections appears suboptimal

P011. The Good, the Bad and the Ugly...Auckland's AYA access to paediatric trials project

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Aim

There is widespread acknowledgement that outcomes for AYA patients in some malignancies are poorer than those for both younger and older patients. In some diseases (eg ALL) there is evidence that treating AYA on paediatric protocols improves outcomes, particularly within a clinical trial. Access to paediatric protocols and trials is limited for most AYA, once they are more than 18 years old.

'The Ugly': case presentation of Starship/ Auckland City Hospital's (ACH) first unsuccessful attempt to enrol an AYA patient treated in an adult oncology service onto a paediatric clinical trial.

Objective of project

To successfully treat AYA patients within adult haematology/oncology services on paediatric clinical trials/ protocols.

Approach

Negotiations with key trials groups (particularly Children's Oncology Group)

Agreement on an institutional SOP for AYA access to clinical trials – current upper age 25 years

Across service planning meetings to attempt to pre-empt and avoid hurdles – endless ('the Bad')

An 'off study – on study' pilot patient to test the clinical and communication processes

Enrol first patient on study, then treat future patients on study or as per protocol off study

Joint MDT presentations /AYA group meetings with professional advice flowing between adult and paediatric teams

Results

'The Good': case presentation of our first patient successes

All subsequent eligible patients have been treated on study, or 'as per' (during study closures)

Ongoing review of treatment choice, patient disease outcomes and morbidity/mortality is underway although early in process

Conclusion

This 'proof of principal' at Starship/ACH has shown that it is possible in the New Zealand environment to meet our objective. The success of this project has led to adult oncology centres outside of Auckland seeking to send their patients to Auckland City Hospital for treatment, to allow access to paediatric trials. This will support equity of access for AYA patients, across the country, with the aim of improving disease outcomes for this group.

P012. Two paediatric cases of a rare type of T-cell leukaemia

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T-lymphoblastic leukaemia accounts of approximately 15% of paediatric lymphoblastic leukaemia (T-ALL) and approximately 25% of adult T-ALL. Gamma-delta ($\gamma\delta$) T-ALL is associated with a cytogenetic rearrangement between the MYC locus (8q24.1) and TRAD locus (14q11.2), and is rare with an estimated incidence of 2% of all lymphoblastic leukaemias.

Here we report the characteristics and clinical outcomes of two cases of paediatric T-ALL, of similar age but with significantly different clinical courses. Cytogenetics confirmed $\gamma\delta$ T-ALL in both cases.

The first patient is a 21-month-old previously well female, who presented with a one-two week history of fever and stridor, and was found to have a leucocytosis and circulating lymphoblasts on peripheral blood film. Imaging revealed bilateral tonsillar enlargement. The patient was diagnosed with $\gamma\delta$ T-ALL based upon bone marrow aspirate and trephine examination. She commenced on an intermediate-risk chemotherapy protocol, and was found to have persistent leukaemia on bone marrow examination at the completion of induction therapy. Pending further progress at the end of consolidation therapy, a bone marrow transplant was planned if the patient achieved remission, however the patient unfortunately deceased from chemotherapy-related toxicities including fungal sepsis prior to this time.

The second patient is a 22-month-old previously well female, who presented with a one-two week history of fevers, mild respiratory distress, reduced oral intake and non-specific oral pain. She was found to have leucocytosis and circulating lymphoblasts on peripheral blood film. Bone marrow aspirate and trephine examination confirmed the diagnosis of $\gamma\delta$ T-ALL. Upon completion of induction chemotherapy, the patient had persistent leukaemia on repeat bone marrow examination. Her chemotherapy regime was intensified, and she achieved remission. Subsequently she underwent an unrelated umbilical cord blood transplant (UCBT) and remains in the early stages post-transplant, with well managed toxicities.

These cases demonstrate the difficulties in managing $\gamma\delta$ T-ALL, compounded by the rarity and diversity of the disease.

P013. To determine the prognostic significance of monosomal karyotypes in adults with acute myeloid leukaemia

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Aim

To determine the prognostic significance of monosomal karyotypes in adults with acute myeloid leukaemia (AML) in comparison with the Medical Research Council (MRC) prognostic cytogenetic risk groups, in particular the adverse risk group.

Background

The prognostic significance of the karyotype in AML has been well established by the MRC, with favourable, intermediate and adverse risk groups being well defined.

A monosomal karyotype is defined as the presence of at least one autosomal monosomy and either a second autosomal monosomy or at least one structural abnormality (excluding good prognostic markers). Due to the poor outcomes of a monosomal karyotype in AML it has been classified into a prognostic category, namely very poor (Breems et al 2008).

Methods

This is a retrospective study using a database of 455 de novo AML patients from PathWest RPH/FSH (2008 to 2018). All patients had conventional karyotyping performed and fluorescence in situ hybridization (FISH) studies carried out for further investigation. Karyotypes were classified into favourable, intermediate and adverse risk groups as per the MRC prognostic classification system.

Survival times were calculated from the date of diagnosis till the date of death using Kaplan Meier graphs and probability values were compared to determine the clinical relevance of a monosomal karyotype.

Conclusion

Of the 455 cases, 52 patients (11%) had a monosomal karyotype, 84 (18%) had a favourable karyotype, 269 (59%) had an intermediate karyotype and 50 (11%) demonstrated an adverse karyotype. There was a significant difference in the survival between patients with a monosomal karyotype and patients with an adverse karyotype ($p=0.05$). Our results further support the literature of a very poor prognosis of AML patients with a monosomal karyotype.

P014. Case study of cutaneous blastic plasmacytoid dendritic cell neoplasm and a brief review of management

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A previously well independent 58year old man was referred to our plastic surgery service to investigate a rapidly growing facial mass. The mass initially appeared as a small raised non-tender lesion four months prior and was thought to be secondary to trauma, this lead to a diagnostic delay. He had no systemic symptoms or any other clinically evident disease. The mass quickly grew to a 5 x 3 cm impressive large non-fixed, non-tender, violaceous lesion on the left temporal aspect of his face. On examination he also had a small 1x2cm lesion developing in the right maxilla region.

A punch biopsy indicated a diagnosis of blastic plasmacytoid dendritic cell neoplasm (BPDCN). The immunohistochemistry was positive for CD4/CD56/BCL2/CD99/CD43/BCL6, and CD123 with a Ki67 index of 70%. It was negative for TdT, CD68 and EBER. A bone marrow aspirate and trephine showed interstitial infiltration with blastic plasmacytoid dendritic cells (60%). Flow cytometry confirmed that 26% of cells had the following immunophenotype CD34-/CD117-/CD4+/CD56+/CD45+/CD15-/TdT-. His blood counts were within normal range. Staging PET-CT scan revealed multiple lesions including a moderately FDG avid 54x20mm subcutaneous mass over the left zygomatic arch, a 25x12x48mm left pre auricular mass which infiltrated the parotid gland and extended behind the carotid artery and anterior to jugular vein; and an additional area of FDG avidity in distal sternum with signs lytic changes.

BPDCN is a rare and aggressive neoplasm for which there is no consensus on optimal therapeutic approach. Approaches include chemotherapy regime ranging from HyperCVAD to RCHOP as well as conventional AML type therapy. While reasonable responses have been reported, relapse is common and most guidelines suggest consolidation with an allogeneic hematopoietic stem cell transplant. To date, our patient has declined any chemotherapy and is considering localised palliative radiation therapy.

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P015. Evaluation of diagnostic testing for IDH1 and IDH2 variants in acute myeloid leukaemia

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Aim

Acute myeloid leukaemia (AML) is a heterogeneous disorder with 20% of patients being found to carry isocitrate dehydrogenase (IDH) genetic variation. The prognostic significance of *IDH1/IDH2* gene variation remains uncertain, given that *IDH1/IDH2* variants coexist with other gene loci sequence variations. However, inhibitors of *IDH1/IDH2* mutant enzymes are entering clinical practice. The identification of DNA variation in these two genes is therefore of therapeutic significance. To assess inter-laboratory performance, an external quality assurance (EQA) program was developed to monitor laboratories for their ability to detect *IDH1/IDH2* gene variants associated with AML.

Methods

A total of 81 DNA samples were distributed to 15 laboratories over the 2017-2018 survey period. Identical sets of samples were sent to each laboratory for *IDH1/IDH2* gene testing. Laboratories were requested to identify specific *IDH1/IDH2* gene variants and report the findings. Laboratories were also requested to report their specific testing methods used. For 2018, laboratories were additionally requested to clinically interpret the gene variants detected.

Results

All EQA genotyping data from the two-year survey period are presented here. A comprehensive individual qualitative report was generated including laboratory performance for *IDH1/IDH2* genotyping. Overall, approximately 93% of laboratories correctly detected the common c.394C>T (p.Arg132Cys) and c.395G>A (p.Arg132His) variants found in *IDH1*. All laboratories were concordant in the detection of the *IDH2* variant c.515G>A (p.Arg172Lys); with 93% of laboratories correctly detecting c.419G>A (p.Arg140Gln). The testing methods performed by each laboratory for *IDH1/IDH2* genotyping are presented here. The most common assay used for genotyping was PCR and Sanger Sequencing.

Conclusion

Participation in an EQA is essential to ensure that testing and reporting standards are maintained. Overall, laboratories consistently demonstrate good accuracy in genotype determination. Identified areas for improvement and analytical challenges will be discussed.

P016. Phase 3 Trial of Gilteritinib as Maintenance Therapy after Allogeneic Hematopoietic Stem Cell Transplantation in Patients with FLT3-ITD+ AML: Trial-in-Progress

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Aim

Fms-like tyrosine kinase 3 internal tandem duplication (*FLT3*-ITD) mutations in acute myeloid leukemia (AML) are a common indication for allogeneic hematopoietic stem cell transplant (HSCT) in first complete remission (CR1). The use of *FLT3* inhibitors as post-HSCT maintenance therapy has not been prospectively evaluated. Gilteritinib is a highly selective, potent oral *FLT3*/AXL inhibitor with demonstrated antileukemic activity and favorable tolerability in patients with relapsed/refractory AML. A phase 3 trial was designed to compare the safety and efficacy of 2-year maintenance therapy with gilteritinib versus placebo in patients with *FLT3*-ITD⁺ AML in CR1 after allogeneic HSCT.

Method

This phase 3, randomized, double-blind, placebo-controlled trial (NCT02997202; Blood and Marrow Transplant Clinical Trials Network Protocol 1506), conducted at 149 sites worldwide, will enroll 532 adult subjects with *FLT3*-ITD⁺ AML in CR1 who are ≥30 days and ≤90 days from scheduled allogeneic HSCT. Of these 532 subjects, 346 subjects who have achieved successful engraftment without uncontrolled graft-versus-host disease (GVHD) or other serious toxicity will be randomized (1:1; stratified by conditioning regimen intensity, time from HSCT [Day 0] to randomization [30–60 days vs 61–90 days], and presence of minimal residual disease [MRD] in the pre-transplant bone marrow sample) to receive oral gilteritinib (120 mg/day) or matching placebo as maintenance therapy for 2 years. The primary endpoint is relapse-free survival (RFS) in the two treatment arms; RFS will be assessed from the time of randomization to the time of death or morphologic leukemia relapse. Overall survival is a key secondary endpoint. Other endpoints include safety/tolerability, non-relapse mortality, event-free survival, and incidences of acute/chronic GVHD and MRD.

Result

Recruitment for this trial is underway and the study will be completed in 2024.

Conclusion

Findings from this trial will determine the clinical benefit of gilteritinib as post-transplant maintenance therapy in patients with *FLT3*-ITD⁺ AML.

P017. A regional single-centre experience of the BCL-2 inhibitor, venetoclax, in elderly acute myeloid leukaemia

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Background

Elderly patients with acute myeloid leukaemia (AML) have poor outcomes and no current effective standard-of-care therapy exists. Venetoclax is a selective oral anti-apoptotic B-cell lymphoma-2 (BCL-2) protein inhibitor which has demonstrated efficacy in AML. The Townsville Hospital has been utilising venetoclax in AML in both the upfront and relapsed setting since 2017 in elderly patients not fit for induction chemotherapy.

Aim

The aim of this study was to assess our institutional outcomes including response rates, duration of use, adverse effects and reason for cessation.

Method

Data was retrospectively collected on all patients who were commenced on a combination of venetoclax and azacitidine or low-dose cytarabine at the Townsville Hospital.

Results

9 patients with median age 72 (range 58-82) were treated with venetoclax for AML with a combination of azacitidine (n = 7, 77%) or low-dose cytarabine (n = 2, 23%). Dosing schedules followed the Royal Prince Alfred Hospital protocol; oral venetoclax with a dose ramp-up stage of 100mg D1, 200mg D2, 400mg D3 and 100mg day 4-14 in combination with posaconazole 300mg for a 28-day cycle. The median number of treatment cycles was 2 (range 1-7). Bone marrow biopsy was performed after 1 cycle. 5 of 7 patients (71%) achieved an objective response (CR+CRi+PR), 2 have yet to be assessed at the time of writing. Of these patients, 4/7 (57%) had a CR/CRi. All patients suffered grade 4 cytopenias and 3 patients (33%) experienced febrile neutropenia with 2 episodes of sepsis. 2 patients had progressive disease and died.

Conclusion

Venetoclax in combination with azacitidine or low dose cytarabine demonstrates objective responses in over 70% of patients. Neutropenia and infective complications are important adverse events that require management. Venetoclax use in a regional centre is a safe and viable option.

P019. Relapsed Myeloid Sarcoma: Prolonged clinical remission with FDG-PET directed palliative radiotherapy

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Introduction

Myeloid Sarcoma is a rare clonal malignant disorder associated with a poor prognosis. Treatment typically involves systemic chemotherapy, with radiotherapy reserved as adjuvant therapy in selected cases.

Case Record

A 72 year old woman presented with dyspnoea and a right sided breast lesion, and was found to have multifocal myeloid sarcoma. Induction chemotherapy was commenced with daunorubicin and cytarabine ("7:3"), followed by two consolidation cycles with cytarabine, which resulted in complete clinical remission. There was early relapse within 4 months of completion of therapy with multiple new Fludeoxyglucose-Positron Emission Tomography (FDG-PET) avid lesions seen (**Figure 1**). Palliative radiotherapy using 20 Gray in 5 fractions encompassing 5 separate cutaneous lesions resulted in complete clinical response with minimal toxicity. The patient remained in remission for 12 months, until new, palpable, bulky, FDG-PET avid lesions developed. Sequential radiotherapy again using 20 Gray in 5 fractions covering 7 cutaneous and 1 deep lesion resulted in complete response without significant toxicity. The patient remained asymptomatic, with a final PET 6 months following treatment demonstrating ongoing complete metabolic response. 6 months later the patient presented with fulminant septicaemia. She died rapidly whilst still in clinical and laboratory remission 36 months following initial diagnosis.

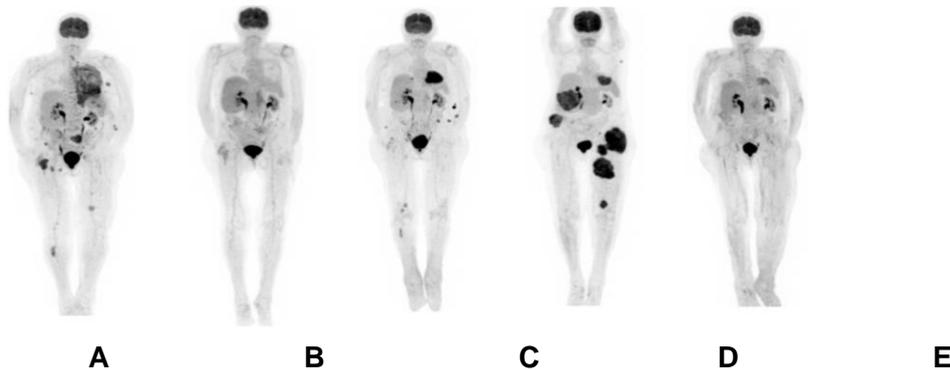


Figure 1: Serial FDG-PET studies tracking extra-medullary lesions. **A:** At diagnosis. **B:** 4 months following diagnosis and completion of chemotherapy. **C:** Early relapse 8 months post diagnosis. **D:** Second relapse 24 months post diagnosis. **E:** Complete metabolic response following final radiotherapy course.

Discussion

This case graphically demonstrates the excellent response myeloid sarcoma lesions can have to palliative radiotherapy, which can be directed and monitored with FDG-PET. This approach can provide meaningful and relatively durable symptomatic remission to a subset of patients with primarily extra-medullary disease, even when the lesions are numerous, large and multiply relapsed.

P022. The Australasian Leukaemia and Lymphoma Group National Blood Cancer Registry: report of the first 1,000 patients with Acute Myeloid Leukaemia

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Background: The NBCR was established by the ALLG in 2012 to collect information on AML clinical practice and as a pathway for registration to ALLG investigator initiated clinical trials.

Methods: Patients provide informed consent for the collection of clinical and laboratory data and the optional provision of biobanking blood and bone marrow samples. Data regarding baseline demographics, AML diagnosis, treatment, response, transplantation and clinical outcomes are entered via a web-based electronic data platform.

Results: Based on data cut-off of 1st May 2018, 1110 patients with AML treated at 32 centres have so far been registered (Figures 1 and 2). The median age is 59 years (range 16-92). WHO 2018 and MRC 2010 cytogenetic classification are verified by central medical monitors using de-identified FBE, bone marrow morphology, flow cytometric, cytogenetic and molecular reports scanned into the NBCR. A review of selected data fields revealed the following: WHO classification (available for 69%), cytogenetics (available for 76%; 16% favourable, 64% intermediate, 20% adverse), *FLT3*-ITD (available for 71%; positive in 23% and ≥ 0.5 in 46%), *NPM1* (available in 56%; mutant in 35%) and *IDH1/2* (available in 16%, mutant in 29%). Excluding acute promyelocytic leukaemia, treatment regimen (available in 87%) included induction chemotherapy (68%), clinical trials (24%) and others (e.g. azacitidine, palliation etc.). The commonest induction approaches were 7+3 (58%) and higher dose cytarabine based induction (39%). At least one follow up time point was available for 66% participants. Allogeneic stem cell transplantation was undertaken in 14% of patients receiving induction. Median follow up for the survivors was 24 months; 32% has follow up >2 years. A baseline sample is biobanked in up to 50% of cases.

Conclusion: The ALLG NBCR represents the largest database of clinical, diagnostic (cytogenetic and molecular), treatment practice and patient outcomes ever collected on Australian patients with AML.

Figure 1. Participating NBCR sites

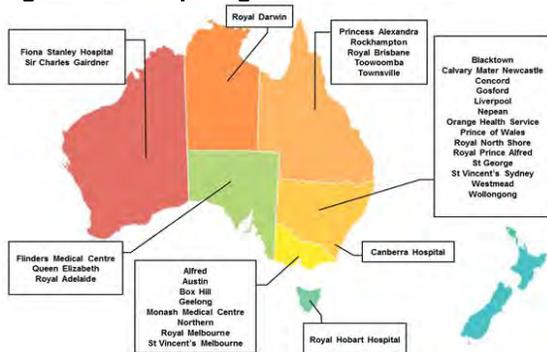
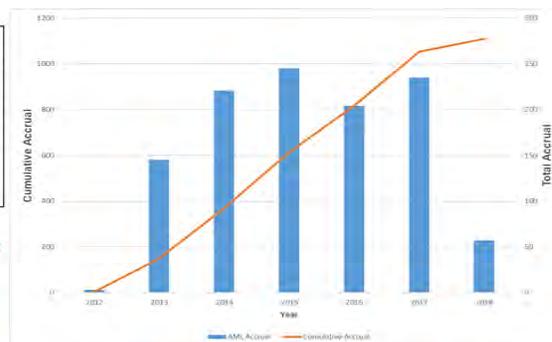


Figure 2. NBCR patient accrual.



P024. Case Report: LSD1 Inhibitor in Acute Myeloid Leukaemia

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The role of epigenetic dysfunction in cancer has been increasingly appreciated in recent years. Lysine Specific Demethylase 1 (LSD1) is a histone demethylase that modifies chromatin through covalent modification of histone tails, to either facilitate or impair translation of genes. It has important roles in mammalian biology including haematopoietic differentiation, and has been found to be over-expressed in multiple types of cancer including Acute Myeloid Leukaemia (AML). Recent studies in murine models have shown LSD1 inhibitors to significantly reduce blast counts and prolong survival rates in AML and there are several pharmacological inhibitors in phase I clinical trials currently.

Our patient is a 78-year-old female from Rockingham with AML transformed from Essential Thrombocythaemia, who had previous therapies including Busulfan and Hydroxyurea. On this trial, she was commenced on LSD1 inhibitor IMG-7289 in February 2017. Remarkably, for such a case with a historically poor survival with secondary AML in an elderly patient, she remains alive and well at 16-months post commencement of therapy. The blast cells have reduced on marrow morphology and flow cytometry, with increased monocytoid precursors. She has had regular transfusions of red cells and platelets, and two hospital admissions for infections from which she recovered with an associated significant rise in neutrophils. We present her case for interest, as an example of an exciting future agent in haematological malignancies.

P025. Invasive mold diseases in malignant haematology patients: Unlocking 8 years of data using artificial intelligence

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Aim

Traditional surveillance methods for invasive mold diseases (IMD) are arduous, often relying on pharmacy reporting of antifungal use. This study aims to demonstrate the value of natural language processing (NLP), a computational method of analysing human language based on machine learning, to audit the institutional burden of IMD and use of antifungal prophylaxis across all malignant haematology patients.

Methods

We identified malignant haematology and haemopoietic stem cell transplant (HSCT) patients with IMD at Alfred Health by screening >5000 chest CT reports from September 2008 to December 2017 with NLP. Positive reports underwent manual review for presence of IMD according to international criteria, characteristics of underlying haematologic disease, antifungal use and clinical outcomes.

Results

We identified 247 IMD-episodes in 229 patients being probable/proven in 35%. *Aspergillus* species accounted for 62% of isolates and non-*Aspergillus* molds 38%, in microbiologically confirmed cases. Underlying disease included acute myeloid leukaemia (56%), acute lymphoblastic leukaemia (13%), lymphoma (13%), multiple myeloma (7.7%), myelodysplastic syndromes (3.2%), and chronic lymphocytic leukaemia (2.8%). Grade IV neutropenia lasting \geq 10 days in the month preceding diagnosis was present in 52%. There were 83 HSCT recipients (23% autograft and 77% allograft, with median time to IMD diagnosis of 21 and 157 days respectively post HSCT). Breakthrough IMD despite antifungal prophylaxis occurred in 139 episodes (57%). There were 38 episodes post-HSCT without antecedent antifungal prophylaxis, of which 61% occurred >100 days post allograft. Overall mortality at 6 and 12 weeks was 29% and 38% respectively.

Conclusion

NLP is a scalable technology with an inclusive approach that can facilitate surveillance and clinical audit among all haematology patients, highlighting gaps in practice and specific risk groups who may benefit from preventive strategies. Our real-world experience with NLP sets a precedent for its use in the haematology setting.

P027. Graft quality after Plerixafor and G-CSF mobilisation

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Plerixafor is used in patients who fail to mobilize adequate stem cell numbers for autologous transplant after stimulation with granulocyte – colony stimulating factor (G-CSF). We aimed to determine whether graft quality after G-CSF with Plerixafor mobilisation is equivalent to G-CSF alone.

Data collected from all patients with myeloma or lymphoma who received Plerixafor in combination with G-CSF as part of a stem cell mobilisation regime at Fiona Stanley Hospital between 2016 and 2018 was compared to data from 52 patients with myeloma or lymphoma consecutively collected in 2017 who received only G-CSF.

Plerixafor was used in 11 cases due to either failed mobilisation (peripheral CD34+ cell counts < $10 \times 10^6/L$) or failed collection (< 2.0×10^6 CD34+ cells/kg). A further 42 collections were performed without Plerixafor during this period. There was no significant difference in peripheral blood CD34+ cell count between groups prior to collection. Grafts collected after Plerixafor had a higher mean total nucleated cell count (14.2 vs 6.9×10^{10} , $p < 0.001$) and higher volume (481ml vs 356ml, $p = 0.007$), reflecting laboratory practice to dilute grafts with higher white cell counts. While mean CD34+ cell viability was very similar prior to cryopreservation (98% vs 99%), significant differences were observed in post-thaw pilot vials for both CD34+ cell viability (74% vs 92%, $p < 0.001$) and CD34+ cell recovery (54% vs 79%, $p < 0.001$).

We observe that grafts collected using Plerixafor have significantly lower post-thaw CD34+ cell viability and recovery. It is uncertain whether this is due to Plerixafor itself or other characteristics of poor mobilisers such as prior therapy, underlying disease or bone marrow milieu. However, our data indicate that lower post-thaw viable CD34+ cell recovery should be expected for poor mobilisers treated with Plerixafor.

P029. Myelofibrosis and allogenic bone marrow transplantation in the era of Ruxolitinib – Single centre experience

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Background

Myelofibrosis is a heterogeneous disorder where allogenic bone marrow transplant (AlloBMT) is the only curative treatment, although its use had been limited due to high rates of transplant related morbidity and mortality. Ruxolitinib is a JAK 1/2 inhibitor that is currently being used as a treatment for both primary and secondary myelofibrosis with improved patient status and reduction in spleen size prior to AlloBMT and is investigated for treatment of graft versus host disease (GVHD).

Method

We performed a retrospective study of consecutive patients who underwent AlloBMT for myelofibrosis (primary and secondary) in our centre from 2008-2018. We obtained data on duration of therapy with Ruxolitinib pre-transplant, incidence of aGVHD, time to engraftment of neutrophil (TEN) and time to engraftment of platelets (TEP).

Results

We reviewed results of 8 patients (N=4 pre-treated with Ruxolitinib and N=4 without pre-treatment) with a median follow-up of 182 days. In the Ruxolitinib pre-treated group, median age was 54 with all patients being transfusion independent at the time of transplantation. Average exposure to Ruxolitinib was 11.2 months. In the non-pre-treated group, median age was 53.8 with all patients being transfusion dependent at the time of transplantation. Overall, median TEN was 20.5 vs 15.5 days and median TEP was 27.5 vs 45.3 days for Ruxolitinib pre-treated and non-pre-treated groups respectively. 1 patient in the pre-treated group restarted Ruxolitinib on Day+8 to Day+13 due to rapidly increasing splenomegaly with excellent response. All patients in the non-pre-treated group developed aGVHD compared to one patient in the pre-treated group.

Discussion

There are ongoing challenges in selecting transplant eligible patients with myelofibrosis especially with apparent improved outcomes with Ruxolitinib. More research and refinement of DIPSS is needed to investigate optimal duration of treatment with Ruxolitinib prior to/ during/post- transplant as well as optimal patient selection and conditioning.

References:

Verstovsek, S., Mesa, R. A., et al (2012). A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *New England Journal of Medicine*, 366(9), 799-807.
Zeiser, R, Burchert, A, Lengerke, C, et al (2015). Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multicenter survey. *Leukemia*, 29(10), 2062.

P030. Cost-effectiveness of letermovir prophylaxis for CMV infection or disease in adult CMV-seropositive recipients of an allogeneic haematopoietic stem cell transplant

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Aim

Clinical trial evidence demonstrated that letermovir prophylaxis is superior to placebo for the prevention of cytomegalovirus (CMV) infection or disease in adult CMV-seropositive recipients [R+] of an allogeneic haematopoietic stem cell transplant (HSCT). Letermovir was shown to prevent the development of CMV infection and associated complications, including reduced re-hospitalisations and improved survival. The aim of this study was to evaluate the cost-effectiveness of letermovir in an Australian patient population receiving HSCT to determine if letermovir is cost-effective when compared with placebo from an Australian healthcare system perspective.

Method

A Markov model was developed to capture clinically relevant disease states following allogeneic HSCT, including CMV infection, CMV disease, acute and chronic graft-versus-host disease (GvHD) and death. The time horizon was 10 years with costs and outcomes discounted at 5% annually. The transition probabilities between health states were calculated from the pivotal phase 3 trial evidence over the trial period (48 weeks follow-up). Mortality beyond the trial period was extrapolated using a validated statistical model, with consistent extrapolation assumptions applied to both treatment arms. Costs of managing post-transplant outcomes were estimated from published hospital costs and drug costs. Quality of life data were obtained from published literature. Univariate sensitivity analyses were conducted.

Result

Compared with placebo, patients receiving letermovir prophylaxis gained 0.52 additional quality adjusted life years per person, at an incremental discounted cost of AU\$14,213. This resulted in an ICER of AU\$26,960/QALY.

Conclusion

Letermovir is a cost-effective option for preventing downstream morbidity and mortality associated with CMV infection post allogeneic HSCT.

P031. Neurologic complications after allogeneic hematopoietic stem cell transplantation: risk factors and impact

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Background

Allogeneic haematopoietic cell transplantation (HCT) is a potentially curative treatment for patients with haematological malignancies and genetic disorders. Despite advances in recent decades, HCT is still complicated by significant toxicity and transplant-related mortality. Neurologic complications may be a significant source of morbidity and mortality after HCT.

Methods

We performed a retrospective study of 263 consecutive patients undergoing allogeneic HCT to determine the incidence, risk factors, and clinical impact of central nervous system (CNS) complications and peripheral neuropathy in the first five years after HCT. CNS complications included: infection, intracranial haemorrhage, ischaemic stroke, metabolic encephalopathy, posterior reversal encephalopathy syndrome (PRES), and seizure.

Results

50 patients experienced 66 neurologic complications – 37 early (\leq day +100), 21 late (day +101 to 2 years) and 8 very late (2 years to 5 years). The 1- and 5-year cumulative incidences of all neurologic complication were 15.6% and 19.2%, respectively, and of CNS complication were 12.2% and 14.5%. Risk factors for CNS complication were age (HR=1.06 per year, $p=0.0034$), development of acute GVHD grade III-IV (HR=2.78, $p=0.041$), and transfusion-dependent thrombocytopenia (HR=3.07, $p=0.025$), and delayed platelet engraftment ($>90^{\text{th}}$ centile) (HR=2.77, $p=0.043$). CNS complications negatively impacted progression-free survival (HR=2.29, $p=0.0001$), overall survival (HR=2.63, $p<0.0001$) and non-relapse mortality (HR=8.51, $p<0.0001$).

Conclusions

Neurologic complications after HCT are associated with poor outcomes, and usually occur early after HCT. Strategies to reduce the risk of CNS complication might focus on supportive care through the period of thrombocytopenia, as well as improving prophylaxis regimens to reduce the risk of severe acute GVHD.

P032. Blinatumomab is a safe and effective therapy following allogeneic stem cell transplantation for B-ALL: a case series

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Blinatumomab is a bi-specific T cell engaging antibody which associates cytotoxic T cells and CD19+ cells resulting in the clearance of malignant and normal B cells. As a bridge to allogeneic stem cell transplantation (alloSCT), blinatumomab has shown impressive results in patients with relapsed/refractory B-acute lymphoblastic leukaemia (B-ALL). However, the role of blinatumomab as salvage therapy following alloSCT has not been established.

We report herein a case series of three patients who received blinatumomab following alloSCT – two patients with Philadelphia chromosome negative disease (Ph-ve) and one patient with Ph+ve disease. Minimal toxicity was observed with only one patient manifesting mild chronic graft versus host disease. All patients achieved complete remission, with two patients achieving minimal residual disease (MRD) negativity. Blinatumomab was used as a bridge to a second alloSCT in the two Ph-ve patients, and continued as consolidation therapy in one of these patients. Two patients relapsed whilst on blinatumomab and responded successfully to subsequent novel agents, whilst the other patient relapsed over 6 months following discontinuation of blinatumomab and responded successfully to rechallenge. We further characterised the response of the innate B cell compartment. We show, using highly sensitive flow cytometric techniques, the clearance of B-ALL blasts and marked expansion of normal progenitor B cells in the periods between cycles of blinatumomab. In this case series, we therefore demonstrate that blinatumomab is a safe and effective therapy that still allows normal immune reconstitution even following alloSCT.

P033. First case of successful non-myeloablative allograft in a young adult with erythropoietic protoporphyria following two liver transplantations

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Background

EPP is a rare but serious autosomal recessive inherited condition with an incidence of 1 in 75,000 births. It manifests as a painful cutaneous porphyria with a non-blistering rash and is usually diagnosed in childhood after sunlight exposure. The phenotype results from a deficiency of the enzyme ferrochelatase causing accumulation of protoporphyrins leading to cutaneous photosensitivity. Fulminant hepatic failure is reported in up to 5% of cases. Regular plasma exchange and/or red cell exchange has been used but this is often insufficient to prevent hepatotoxicity and eventual requirement for liver transplant which is non-curative. Ongoing re-accumulation of porphyrins leads to further liver failure and eventually death.

Case Report

We describe a 28-year-old female diagnosed with EPP in her childhood who underwent her first liver transplant secondary to porphyrin accumulation and liver failure in 2011. Rapid hepatic porphyrin re-accumulation within six months of liver transplant led to regular red cell/plasma exchanges for six years. She developed severe liver failure and underwent a second liver transplant in March 2017. A planned ABO-incompatible non-myeloablative (fludarabine/ low-dose cyclophosphamide) with T-cell depletion using thymoglobulin unrelated peripheral blood (PB) stem cell transplant was carried out five months later. However, progressive loss of partial donor chimerism occurred within the first 100 days resulting in early graft failure and recurrence of EPP. She underwent a second PB allograft with the same donor using fludarabine and melphalan (100mg/m²) conditioning without T-cell depletion in February 2018. She achieved 100% donor chimerism by day 14 with graft-versus-host disease (GVHD) prophylaxis. There was no veno-occlusive disease or acute GVHD observed during follow-up. Full donor chimerism remained at Day 145+. To date, plasma porphyrin levels have been normalised post engraftment suggesting a successful therapy for EPP and potential cure.

P034. Assessing the potential impact of a clinico-genomic algorithm on decision-making about allogeneic transplantation in AML

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Aim

To determine whether a published prognostic algorithm incorporating extended genomic data could contribute to decisions about the timing of allogeneic transplantation in AML.

Method

Retrospective analysis was performed of data from consecutive patients with newly diagnosed AML who had extended genomic NGS performed and who were treated with curative intent at our centre between 01/2016-03/2018. Survival estimates at 3 years from diagnosis and first complete remission (CR1) for each patient were calculated using a research algorithm (Gerstung et al., Nat Genet. 2017) which included standard clinical, pathological (cytogenetics, FLT3-ITD, NPM1, CEBPA) and 55 additional genomic variates. Estimates simulated survival based on either elective allograft in CR1 or with transplant reserved until after relapse. For this analysis it was assumed that transplant would be recommended if the algorithm predicted $\geq 5\%$ gain in 3-year survival compared to no transplant in CR1. The recommendation inferred from the algorithm was compared with the actual treatment decision.

Result

64 patients were included (33 transplanted in CR1, 6 transplanted post-relapse, 25 never transplanted). Use of extended genomic data reclassified prognosis at diagnosis in over one-third of patients compared with standard ELN classification. 19/33 (58%) patients allografted in CR1 were estimated to have derived $< 5\%$ gain in 3-year survival compared to transplantation beyond CR1. Similarly, 8/20 (40%) patients with donors not transplanted in CR1 were predicted to have benefited from early transplant ($\geq 5\%$ gain). Incorporation of extended genomic data into decision-making and accepting the $\geq 5\%$ gain threshold may have altered clinical practice in 27/64 (42%) patients ($p=0.032$, Chi-squared test) and resulted in fewer transplants in CR1.

Conclusion

Inclusion of extended genomic data can potentially inform decision-making about preferred timing of allograft for AML patients. However, further validation of this algorithm including consideration of uncertainties and thresholds is first required, and additional clinical factors must be considered.

P035. Outcomes of Mantle Cell Lymphoma following upfront Autologous Stem Cell Transplant after Nordic MCL2 Induction in a Tertiary Level Hospital

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Aim

Mantle cell lymphoma (MCL) is a rare and incurable form of non-Hodgkin Lymphoma with traditionally poor clinical outcomes. The Nordic MCL2 Protocol which consists of rituximab (R), cyclophosphamide, vincristine, doxorubicin and prednisolone (R-maxiCHOP), alternating with R and high-dose cytarabine followed by BEAM (carmustine, etoposide, cytarabine and melphalan) autologous stem cell transplant (ASCT) has yielded durable remission rates and improved overall survival.

Method

The study was a retrospective clinical audit of all patients undergoing upfront ASCT following Nordic MCL2 induction at The Canberra Hospital between January 2009 and January 2018. Demographic information, disease characteristics and survival were analysed.

Results

A total of 18 patients underwent upfront BEAM ASCT following Nordic MCL2 induction during the study period. Males were over-represented (83.3%) and the mean age of diagnosis was 75.1 years. The vast majority of patients (88.9%) were Stage III or IV at diagnosis. Splenic involvement was seen in 33.3%. The Mantle Cell Lymphoma International Prognostic Index (MIPI) was calculated – low (27.8%), intermediate (38.9%) and high risk (33.3%), respectively. The Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) score calculated was 0 (77.8%), 1 (16.7%) and 2 (5.6%) in our patients. Following the Nordic MCL2 induction, the overall response rate (ORR) was 88.9% (66.7% complete response [CR], 16.7% partial response [PR] and 16.7% unknown). All patients underwent ASCT and hereof, 83.3% obtained CR and 11.1% obtained PR. At time of submission (mean follow up of 46 months), 77.8% remain in remission and 22.2% developed progressive disease.

Conclusion

In this single centre retrospective audit, a durable short-term response following ASCT after Nordic MCL2 induction can be obtained. Long-term follow up of this cohort will be required to determine further treatment efficacy.

P036. Assessment of Cell Composition of Grafts in Allogeneic Hematopoietic Stem Cell Transplantation

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Aim

The role of different cell populations in grafts to determine the outcome of allogeneic stem cell transplant (AlloHSCT) has not been well established. We postulate that grafts from different donors and sources have variable cell composition, which may have an impact on the clinical outcomes of patients after AlloHSCT.

Method

164 patients who underwent AlloHSCT at St Vincent's hospital, Sydney from March 2013 to November 2017 were included in this study. 137 patients received peripheral blood stem cell (PB) grafts and 27 patients had bone marrow (BM) grafts. We prospectively assessed the proportion and dose of cells in fresh grafts, including CD34+ stem cells and putative myeloid and lymphoid progenitor subsets (CD34+CD38+CD117+ cells and CD34+CD7+ cells) as well as B cells, NK cells, CD3, CD4, CD8 and regulatory T cells (Treg) by flow cytometry in addition to routine stem cell enumeration and viability assessment. Statistical analysis was performed to determine the correlation between graft composition and post transplant clinical outcomes.

Result

The median viable CD34+ cells dose in BM grafts was $2.02 \times 10^6/\text{kg}$ (0.21-5.99), compared to the median dose of $4.5 \times 10^6/\text{kg}$ (1.1-6.01) in PB graft. However, median stem cell subsets (CD34+CD38+CD117+ and CD34+CD7+) numbers in BM and PB grafts were similar. The median CD3 and Treg dose in PB grafts were $295.83 \times 10^6/\text{kg}$ (41.58-999.22) and $10.51 \times 10^6/\text{kg}$ (0.02-41.46), 8-10 times higher than those in BM grafts. The incidence of acute and chronic GVHD was higher in patients who received BM [48%(BM) vs 39%(PB) for acute GVHD, and 73%(BM) vs 49%(PB) for chronic GVHD], which may be related to lower Treg in BM grafts. Overall survival of the whole cohort was 57%.

Conclusion

Considerable variation in cell composition of different grafts was identified, which may prove useful in predicting outcomes and assist in guiding future trials for novel management strategies in AlloHSCT.

P037. De novo acute myeloid leukaemia (dnAML) versus secondary AML (sAML): Comparison of allogeneic transplant outcomes at two Australian transplant centres

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Background: Acute myeloid leukaemia (AML) can arise either de novo (dnAML) or secondary to a myelodysplastic syndrome or myeloproliferative disease (sAML). While sAML is associated with inferior outcomes compared with dnAML, direct comparison of transplant outcomes in dnAML versus sAML has not previously been made in Australasia.

Aim: To examine and compare allogeneic transplant outcomes in patients with dnAML and sAML.

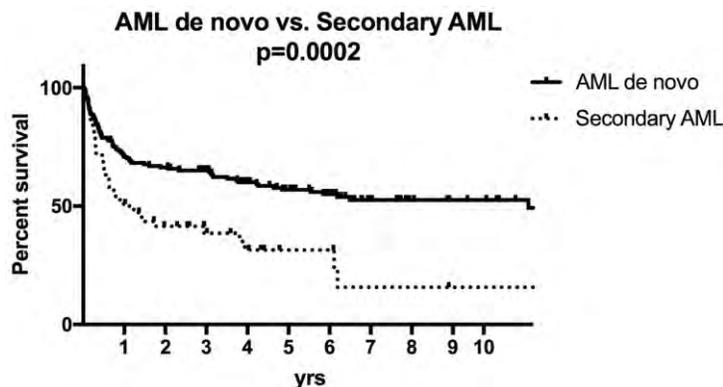
Methods: A retrospective cohort study of all AML cases ≥ 16 years undergoing allogeneic stem cell transplant at St Vincent's Hospital (SVH) and Royal North Shore Hospital (RNSH) in NSW Australia between 1998-2015 was conducted. Included cases were identified from the ABMTRR. Patient and donor demographics, disease characteristics including disease risk index (DRI), cytogenetics and outcome data were ascertained. Study outcomes included overall survival (OS), disease-free survival (DFS), transplant-related mortality (TRM) and relapse-related mortality (RRM). Descriptive statistics and overall outcomes of AML cases were assessed and then compared between dnAML and sAML cases using log-rank statistics.

Results: 148 patients were transplanted for AML, 91 (61%) with dnAML and 57 (39%) with sAML. The median age at transplant was 47 years for dnAML and 55 years for sAML and 55% of cases were male. The median OS was 1135 days for dnAML versus 372 days for sAML with almost twice as many dnAML patients being alive compared to sAML patients at last assessment of survival status (65% vs 33%- see Fig1). TRM was higher for sAML compared to dnAML patients at both 100 days (16% vs 9%) and 365 days (28% vs 17%). The relapse rate was higher in sAML vs dnAML patients (28% vs 13%).

Conclusion: When compared to patients with dnAML, patients with sAML are older and have inferior outcomes at allogeneic transplant including shorter OS, higher TRM at both 100 and 365 days, and a higher relapse rate.

Total: 295 (see Fig 1 below)

Figure 1: Overall survival: de novo AML (dnAML) vs secondary AML (sAML)



P038. The evaluation of hyperhydration for high dose melphalan in stem cell transplantation

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Aim

This study aimed to evaluate the benefits and adverse effects of hyperhydration given with high dose melphalan (HDM) in haematopoietic stem cell transplantation (HSCT).

Method

It was a retrospective cohort study comparing patients' outcomes between institutes using hyperhydration and not using hyperhydration. A chart review was performed on patients who had received HDM autologous HSCT for myeloma between January 2015 and September 2017 at the two different hospitals in Australia. These institutions were selected based on the similar in-patient treatment provided to HSCT patients with different amount of fluid administered with melphalan (6L vs 2L). Patients' demography, daily creatinine (Cr) and weight were collected from admission to day 7 post HSCT. Additionally, fluid overload (O/L), frusemide use, acute pulmonary oedema (APO), sepsis and antibiotic use were recorded from the medical record. Data was analysed using Student t-test or Fisher's exact test.

Results

The total sample was 88: 54 patients with hyperhydration and 34 patients without hyperhydration. Patients' demography and baseline Cr were comparable. Mild acute kidney injury (Cr of 1.5-1.9 times baseline or 26 micromol/L increase) was observed in 6/54 patients (11%) and 2/34 patients (6%) with and without hyperhydration respectively ($p=0.48$). The change in Cr from baseline (maximum Cr / baseline Cr) was larger in the hyperhydration cohort (1.14 vs 1.03, $p<0.01$). In the observation period, 5/54 patients with hyperhydration (9%) and 2/34 patients without hyperhydration (6%) experienced clinical O/L ($p=0.7$). There was no record of APO in either group. The early weight gain was larger in hyperhydration cohort but not significantly (1.79kg vs 1.15kg, $p=0.09$).

Conclusions

In this small study hyperhydration (6L) did not show benefits in protecting the kidney or statistically significant increases in adverse effects such as O/L or APO compared to the normal hydration (2L). It appears hyperhydration is not required with HDM

P039. Ultrasound guided peripheral venous access reduces the number of central venous access devices in autologous haemopoietic progenitor cell collection

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Aim

To describe Austin Health's experience in reducing the number of central venous access devices (CVAD) inserted in patients for autologous haemopoietic progenitor cell (HPC) collections following the implementation of ultrasound guided peripheral venous line insertion.

Method

HPC collections at the Austin Hospital are performed on approximately 80 patients per year, using a dual access cell separator. Access is required either peripherally or centrally to maintain blood flow rates of 50ml/min. Ideal access is peripheral due to the associated risks and complications of CVADs. SonoSite NannoMax ultrasound guided peripheral line insertion was implemented in 2016. Staff training took place using simulated practical learning. Retrospective analysis of venous access used in autologous HPC collections was obtained over a four-year period from 2014 to 2017, existing CVAD's were excluded.

Results

In 2014 and 2015 ultrasound guidance was not in use. There was 72% CVAD insertions and 28% peripheral access. In 2016 and 2017 ultrasound guided peripheral line insertion was commenced and CVAD insertions were reduced to 24% and peripheral insertions increased to 76%. Reduction of CVAD insertions resulted in decreased length of hospital stay, and significant cost savings. There was no evidence of a decrease in the quality of the HPC product when peripheral access was used as 2-3 blood volumes were still able to be processed.

Discussion/Conclusion

There are significant risks associated with the insertion of a CVAD as discussed by Salazar et al. (2017). Peripheral venous access for HPC collection is preferred and with adequate training in the use of ultrasound this can be achieved. Our results demonstrate that implementation of US guidance reduced CVAD's by 42% with benefits of minimising complications known to be associated with central access as well as reduced cost and admission time.

Reference:

Salazar, E., Garcia, S., Miguel, R., Segura, F. J., Ipe, T. S., & Leveque, C. (2017). Ultrasound-guided peripheral venous access for therapeutic apheresis procedures reduces need for central venous catheters. *Journal of Clinical Apheresis*, 32, 266-269.

P040. Multi-modal treatment in disseminated Fusariosis: a case report of survival in allogenic bone marrow transplant for aplastic anaemia

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Introduction

Fusarium is a ubiquitous fungus, emerging as a deadly pathogen amongst immunosuppressed patients, including those with neutropaenia and stem cell transplant recipients. In this cohort, disseminated infection carries a high rate of mortality and is challenging to treat. Currently, the evidence base for optimal treatment is limited. Here we describe a rare case of survival in a patient with disseminated fusarium following allogenic bone marrow transplant for aplastic anaemia.

Case Presentation

An 18 year old gentleman with aplastic anaemia, underwent sibling matched allogenic bone marrow transplant. 1 week into transplant he developed disseminated fusarium with widespread ulcerative skin lesions, fungaemia, pulmonary nodules and ophthalmic lesion. Rapid diagnosis of *Fusarium solani* species was achieved through skin biopsy as well as BD BACTEC™ FX blood culture system with PCR enabling identification at 3 days.

Following engraftment, he had initial response with voriconazole and liposomal amphotericin in combination. With attempts to use each agent in isolation, he had relapse of disseminated infection with worsening fungal pneumonia and splenic lesions. Consistent response and infection control was only re-established with both voriconazole and liposomal amphotericin in combination. Positron Emission Tomography (PET) scan revealed resolution of fusarium except for multiple splenic lesions that persisted despite maximal antifungals. A splenectomy was performed confirming fungal abscesses. Antifungals were continued for a further 3 months; 11 months in total. Subsequent PET scan showed complete resolution. He is now at 2 years survival post transplant in good health.

Discussion

Resolution was achieved through prompt diagnosis and initiation of antifungals, prolonged treatment with combination of liposomal amphotericin and voriconazole, as well as splenectomy for residual infection unresponsive to medical therapy. This case highlights the success of an individually tailored approach. This case also illustrates the utility of positron emission tomography (PET) in evaluating disseminated fusarium and directing these treatment decisions.

P042. Diffuse Alveolar Haemorrhage in the autologous stem cell transplant setting

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Diffuse alveolar haemorrhage (DAH) complicates approximately two percent of autologous stem cell transplants and setting carries a high mortality risk.

DAH is associated with infective and non infective causes as demonstrated in this case report.

DAH is characterized by progressive dyspnea, hypoxia, cough, diffuse consolidation on chest CT and characteristic bronchoalveolar lavage finding of hemorrhagic lavage aliquots.

Six month survival rate of patients with DAH in the stem cell transplant setting was 38% in a retrospective review by *Gupta et al.* Isolation of a microbial organism on bronchoalveolar lavage predicted an even poorer outcome. (1)

Case report

72 year old lady with Stage IVA Mantle Cell lymphoma underwent Stanford BCNU autologous stem cell transplant (Carmustine, Etoposide and Cyclophosphamide) in first remission. Fevers occurred early in the non neutropenic transplant period following carmustine infusion.

Day eight she developed dyspnea, hypoxia and generalized deterioration on top of ongoing high fevers in the setting of neutrophil recovery. CT chest demonstrated extensive perihilar ground glass opacity.

Bronchoscopy on day eleven revealed diffuse alveolar hemorrhage with bright blood in proximal airways. She was commenced on 1mg/kg of prednisolone and remained afebrile day twelve to sixteen.

Ferritin peaked at 27000 µg/L and bone marrow biopsy revealed occasional hemophagocytosis however not sufficient for diagnosis of Hemophagocytic Syndrome.

On bronchial washing PCR revealed cytomegalovirus (CMV). Cytology was negative for inclusion bodies and CMV viral load peaked at 440 IU/ml.

In the setting of prednisolone wean on day 16, fevers and hypoxia reoccurred. The patient was commenced on 1 gram of IV methylprednisolone and treatment dose ganciclovir for possible CMV. Drastic clinical improvement was seen.

Discussion

This case highlights the rare case of DAH in the autologous transplant setting that coincided with timing of neutrophil recovery and was triggered by either Carmustine or CMV. CMV disease could not be definitely proven as a biopsy was not performed. It emphasises the importance of early bronchoscopy and prompt treatment of infectious and non infectious causes to decrease transplant related mortality.

References:

Gupta S, Jain A, Gupta A, Warneke SG, Eapen G. Outcome of Diffuse Alveolar haemorrhage in Haematopoietic Stem Cell transplant recipients. *Blood* 2006 108:2967

P048. Safety and feasibility of outpatient autologous stem cell transplant – The Royal Hobart Hospital experience

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Background: Outpatient autologous stem cell transplants (ASCTs) at Royal Hobart Hospital (RHH) have been performed successfully since early 2000, following data from international centres showing that this is safe^{1,2}. Currently, outpatient ASCT includes daily pathology and clinical review. We hypothesize that patients require few interventions prior to nadir and would like to explore the feasibility of transitioning to phone reviews in the early post-transplantation period.

Aim:

- 1) Investigate the safety and outcomes of outpatient ASCTs.
- 2) Explore the need for outpatient interventions in the early post-transplant period.

Method:

We conducted an audit of patients who underwent BEAM- (Carmustine/Etoposide/Cytarabine/Melphalan) and melphalan-ASCT from July 2008 to June 2018. Data collected include:

Patient demographics, diagnosis, indication for ASCTs, details of treatment prior to transplant, stem cell dose infused, outpatient versus inpatient

Outcome data: length and indication for hospital admission, timing of and need for intervention such as blood product transfusions, intravenous fluids or electrolyte replacements, parenteral anti-emetics, complications of transplant, 30-day and 100-day mortality rates.

Results:

A total of 232 patients underwent ASCTs during study period. The baseline characteristics of patients are as follows:

	Melphalan-conditioning			BEAM-conditioning		
	Outpatient	Inpatient	p-value	Outpatient	Inpatient	p-value
No. of pts.	85(59%)	58(41%)		63(71%)	26(29%)	
Age(mean in yrs)	60.6	60.7	0.9601	54.5	58	0.1074
Male(%)	64.7%	62.1%	0.8596	65.1%	46.2%	0.1534
Admission length (mean+/-std in days)	8.3+/-5.6	17.8+/-4.3	<0.00001	11.2+/-6.5	22.3+/-5.9	<0.00001
Neutrophil engraftment	11.4+/-1.4	11.3+/-0.9	0.7414	10.5+/-0.8	10.5+/-1.1	0.9203
Platelet engraftment	12.2+/-2.9	13.3+/-2.9	0.0168	15.9+/-7.5	14.6+/-5.4	0.8026

Baseline demographics are comparable; the engraftment details are comparable apart from 1 day delay in inpatient melphalan patients. Further data regarding pre-nadir interventions and outcome will be presented.

Discussion:

There is a significant reduction in admission length with an initial outpatient approach to ASCT. The findings of this audit will allow optimisation of medical care in the early post-transplant period.

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P049. Predictors of mortality in true positive versus discordant gastrointestinal graft versus host disease (GI-GVHD)

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Aim: Clinical assessment plus endoscopic biopsy is the gold standard diagnostic approach for suspected Gastrointestinal Graft *versus* Host Disease (GI-GVHD), however this approach fails to identify 26% of cases requiring treatment. Patients with negative biopsies treated for GI-GVHD (“Discordant GVHD”) show survival inferior to “True Negative” cases but superior to “True Positive” cases (1-yr overall survival 66%, 88% and 48% respectively)¹. We aimed to explore any impact established GI-GVHD prognostic factors may have had on these survival outcomes²⁻⁷.

Method: Patients treated for acute GI-GVHD at our institution between 2011-2016 were retrospectively identified from an existing database. Patients were classified as having True Positive or Discordant GVHD. The following prognostic factors were assessed: baseline serum albumin and bilirubin; baseline performance status (Eastern Cooperative Oncology Group score) and; best response to anti-GVHD therapy (defined by prednisolone >1mg/kg/day). Steroid-responsive GVHD was defined by a partial response (PR) or better without escalation to second-line therapy within 14 days of commencement⁸. The two cohorts were compared, using Fisher’s exact test, to identify any differences in terms of prognostic factors between cohorts.

Result: 74 patients were identified, comprising 55 (74%) True Positive and 19 (26%) Discordant GVHD cases. True Positive, compared to Discordant GVHD cases, were significantly associated with lower baseline albumin (94% vs. 75% respectively; p=0.023) and a lower incidence of steroid responsiveness (47% vs. 89%; p=0.001). There was no significant difference between cohorts in baseline bilirubin or performance status.

Conclusion: Discordant GVHD cases are associated with less hypoalbuminaemia and more frequent steroid responsiveness compared with True Positive GVHD cases. This may reflect over-diagnosis and treatment of suspected GVHD in Discordant patients, or, alternatively, a cohort with a less severe disease. Regardless, improved diagnostic strategies that more accurately identify patients with True Positive GVHD are required, particularly as Discordant GVHD cases still demonstrate inferior survival to True Negative cases.

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P050. Retrospective audit of infection rate during and post-autologous stem cell transplant (ASCT) July 2015-July2016: Gold Coast University Hospital (GCUH)

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Aim

ASCT is part of the therapeutic armamentarium for myeloma and lymphoma. Whilst it's recognised that ASCT results in profound immunosuppression, there is no consensus on the use of prophylactic antiviral, antifungal or antibacterial agents.

This study's aim was to evaluate the number, type and severity of infections during and up to 1-year post ASCT.

Method

Retrospective single centre analysis of lymphoma/myeloma patients receiving an ASCT at GCUH between July 2015-July 2017 was undertaken. Myeloma patients received melphalan 200mg/m² (n= 34)/140mg/m² (n= 4). Lymphoma patients received BEAM. Confirmed infection was defined as fevers with culture positivity, radiology positivity or clear clinical symptoms. Suspected infection was defined as fever that did not meet criteria for confirmed infection. All patients received fluconazole whilst inpatient and valaciclovir daily until 6 months post ASCT. From April 2016 Ciprofloxacin 500mg BD was added from D+4 until engraftment or initiation of parenteral antibiotics.

Results

Thirty-eight myeloma and 18 lymphoma patients were analysed. Two lymphoma patients had 2 attempts at ASCT (n=20 admissions). During ASCT admission, 25/38 (65.9%) of myeloma transplants developed infection; 12-suspected, 13-confirmed. 19/20(95%) lymphoma transplants developed infection; 9-suspected,10-confirmed.

Infection rate before/after adding ciprofloxacin was 80%(8/10) versus 60.7% (17/28) for myeloma and 100% (5/5) versus 93% (14/15) for lymphoma. Intensive care admissions (ICU) before/after adding ciprofloxacin was 10% (1/10) versus 4%(1/28) for myeloma and 60% (3/5) versus 7%(1/15) for lymphoma.

24 myeloma and 13 lymphoma patients were followed till 12 months post ASCT. Eight myeloma patients developed infection; 2 suspected, 6 confirmed. Nine lymphoma patients developed an infection, 1 suspected, 8 confirmed.

Conclusion

Bacterial infection rate during admission for ASCT is notable. Within the limitations of a small retrospective single centre study it appeared that ciprofloxacin reduced ICU admissions.

Valaciclovir use for 6 months post ASCT delayed but did not prevent herpes zoster. Despite no routine trimethoprim/sulphamethoxazole there were no PJP infections.

P051. Donor clonal haematopoiesis of indeterminate potential (CHIP) and implications in allogeneic stem cell transplant

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Introduction

CHIP is defined as acquired somatic mutations that drive clonal expansion in the absence of cytopenia and dysplastic haematopoiesis. CHIP involving DNMT3A, TET2 and ASXL1 mutations are found to be associated with an increased risk of haematologic malignancies, cardiovascular deaths and all-cause mortality. There is limited literature about donor-derived CHIP and implications in allogeneic stem cell transplant (alloSCT) recipient. We present a case of CHIP in donor and emergence of myelodysplasia with donor-derived mutations in recipient following alloSCT.

Case report

A 49-year-old lady was diagnosed with refractory anaemia with excess blasts-2 (RAEB-2) in April 2014. At diagnosis, she had mild macrocytic anaemia with leucoerythroblastic blood film. Bone marrow aspirate revealed 12.5% blasts with dysplastic erythropoiesis. A myeloid next generation sequencing (NGS) panel revealed presence of NPM1 and TET2 mutations. She underwent a myeloablative-conditioning Busulfan/ Cyclophosphamide sibling alloSCT in July 2014. At the time of stem cell collection, the sibling donor had normal haematological parameters including a normal MCV.

Her transplant was complicated by chronic graft-versus-host disease treated with cyclosporine. Immunosuppression was tapered at 12 months. Bone marrow aspirate one year post alloSCT revealed normocellular marrow without dysplasia. She had persistent macrocytic anaemia after immunosuppression withdrawal. Bone marrow aspirate at two years post alloSCT showed morphological dysplasia, ringed sideroblast (MDS-RS) and no excess of blasts. Myeloid NGS panel at this stage revealed the mutations in DNMT3A and SF3B1. The previous NPM1 and TET2 mutations were not detected. The DNMT3A and SF3B1 mutations were confirmed to be donor-derived by sequencing archival samples from the sibling donor. The patient had 100% donor chimerism at 12, 24 and 36 months. She continues to have mild macrocytic anaemia with normal haematological parameters.

Discussion

This case highlights the under-recognised significance of CHIP in allogeneic donors. The incidence of CHIP increases with age and is particularly of relevance as older donors are used for alloSCT. The influence of bone marrow microenvironment and effects of immunosuppression on the manifestation of clonal population are also demonstrated in this case. More studies are required to better understand the implications of CHIP in allogeneic donors.

P053. A modular, 12-color flow cytometry panel for the immunophenotyping of healthy and AML subjects

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Aim

Flow cytometric analysis of the immune system is conventionally used for the characterization of hematologic malignancies. Limited instrument capability often leads to the development of multiple panels for the comprehensive characterization of a subject's immune system. This approach results in increased workflow and limited understanding of complex antigen expression patterns. We developed an 8-color backbone panel for identification of major immune cell subsets and designed such that 4 drop-ins for deeper characterization of a hematological disease of interest could be supplemented. In this study we added 4 drop-ins for the characterization of AML myeloblasts.

Method

An 8-color backbone panel was developed using lineage-specific markers for the detection of monocytes, T, B, and NK cells. Four complementary drop-ins enabled the detection of myeloid blasts and aberrant expression of lymphoid markers. Cells from healthy or AML subjects were stained and acquired on a 12-color flow cytometer.

Result

The backbone panel allowed for clear resolution of CD3⁺ CD4⁺ helper and CD8⁺ cytotoxic T cells, CD19⁺ B cells, CD56⁺CD16⁺ NK cells, and three monocyte subsets differentially expressing CD14 and CD16 in both healthy and AML subjects. The addition of the 4 drop-ins did not alter the resolution of the major subsets and allowed us to further detect CD34⁺ myeloid blasts aberrantly expressing the lymphoid markers CD56 and CD7.

Conclusion

We showed the advantages of a universal 8-color panel for broad immune cell analysis and enumeration coupled with a modular 4-color drop-in panel for deeper characterization of diseases of interest within a single-tube assay. Using this approach, we identified several differences between the phenotypes of healthy and AML specimens using a single sample, thus reducing workflow and cost. From a biological standpoint, the ability to simultaneously analyse 12 parameters provides unique insights into the interplay between different antigens in health and disease.

P053. Real-world efficacy of antifungal prophylaxis in patients treated for acute gastrointestinal graft-versus-host disease (GI-GVHD)

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Aim

Allogeneic progenitor cell transplant (HPCT) recipients who develop acute gastrointestinal graft-versus-host disease (GI-GVHD) are at increased risk of invasive fungal infections (IFI). Randomised control trial data supports the use of mould-active fungal prophylaxis in HPCT patients with grade II-IV GVHD¹. We aimed to assess our unit's use of anti-fungal prophylaxis and describe the incidence and species of breakthrough IFI in patients with GI-GVHD.

Method

We conducted a retrospective audit of patients who underwent HPCT at our institution between 2011-2016 and identified those who were treated for acute GI-GVHD using a minimum of prednisone 1mg/kg or equivalent. For those patients the following details were collected: presence of any prior IFIs, anti-fungal prophylaxis before and after initiation of steroids, and the incidence of new IFIs within 6 months of commencing steroids.

Result

Of the 551 HPCT performed during this period, 74 evaluable patients were treated for GI-GVHD. All patients received anti-fungal prophylaxis prior to steroid commencement (66.2% received fluconazole, 10.8% posaconazole, 20.2% voriconazole and 2.7% other). Post steroids 35.1% remained on fluconazole, 21.6% received posaconazole, 35.1% received voriconazole, and 8.1% received other anti-fungals. Of the 26 patients remaining on fluconazole, 9 were transitioned to mould-active prophylaxis at a later time.

Thirteen patients (17.5%) experienced a breakthrough IFI (7 definite and 6 probable). In the 42 patients receiving posaconazole or voriconazole, 7 (26.2%) experienced breakthrough IFI, compared with 4 (15.4%) in the fluconazole cohort. Two other cases occurred in patients who received caspofungin. Notably, patients receiving mould-active fungal prophylaxis developed mucormycosis, *Fusarium* and *Scedosporium* infections whereas fluconazole lead to invasive aspergillosis and candidiasis.

Conclusion

Despite antifungal prophylaxis, real-world GI-GVHD patients remain at particularly increased risk of developing IFI. Anti-mould prophylaxis is associated with lower incidence of invasive aspergillosis and candidiasis but higher incidence of non-*Aspergillus* mould. Further studies investigating optimal anti-mould strategies are warranted.

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P054. Omission of folinic acid post methotrexate dose in allogeneic stem transplant recipients

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Aim

To determine whether withholding folinic acid post low dose Methotrexate increases the incidence of mucositis and delays engraftment in allogeneic transplant recipients.

Methodology

Prospective audit reviewing 10 patients at Fiona Stanley Hospital, who underwent allogeneic haematopoietic stem cell transplant (allo-HSCT) with the use of methotrexate to prevent GVHD without folinic acid rescue.

Results

The average days until engraftment for the 10 patients audited was 15 days. This is reflective of the mean time till engraftment for AML patients (13-15 days) and MDS patients (19-23 days) receiving allogeneic stem cell transplant.

Most patients (9 of 10) developed mucositis due to the conditioning regime. Two patients developed mild mucositis (WHO grade 1) 5 patients developed moderate mucositis (WHO grade 2-3) and 2 patients developed severe mucositis (WHO grade 4) with the omission of folinic acid rescue. This reflects results from prior studies which report mild mucositis in 7% of patient, and moderate to severe mucositis in 89.5% of patients undergoing allo-HSCT with methotrexate and folinic acid rescue.

No patients recorded toxic methotrexate levels in this study. One patient recorded a mildly elevated methotrexate level (0.99umol/L) secondary to acute kidney injury, subsequent doses were withheld. A second patient received folinic acid after day 11 methotrexate due to an increase in her creatinine over 25% from baseline. Her methotrexate levels remained within the normal range.

Conclusion

Mucositis severity and time till engraftment was not affected by omitting folinic acid post low dose methotrexate. Based on these limited results, folinic acid post methotrexate may be safely omitted without affecting mucositis severity and days until engraftment. The use of folinic acid should be considered if renal function deteriorates. A follow up study to compare the incidence of graft versus host disease with and without folinic acid rescue is planned.

P056. Treating Acquired hypogammaglobulinaemia secondary to haematological malignancy with immunoglobulin through the National Immunoglobulin Governance Program

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Treatments involving immunoglobulin (Ig) offer significant therapeutic benefit to people with haematological disease. However, Ig is a high cost product and the demand for use in Australia, per capita is amongst the highest globally with an average 11% increase in demand annually for at least the last eight years.

For this reason, access to Ig in Australia is provided through specific governance arrangements. Where eligibility criteria are met, Ig is supplied at no direct cost to the patient through the National Ig Governance Program. The cost instead, is met by all Australian governments via a process managed by the National Blood Authority (NBA). Consider the following cases studies:

Patient 1, a 62-year-old male who had recently undergone FCR treatment for B CLL presented with febrile neutropenia without an identifiable infectious source. At admission the patient was found to have an IgG of 4.4g/L. Following antibiotics and G-CSF, a bone marrow examination demonstrated reduced granulopoiesis and an absence of CLL.

Patient 2, an 83-year-old female, was admitted with sepsis and an IgG of 2.9g/L. The patient had undergone treatment with R-CHOP for double hit lymphoma 9 months prior to the current episode of sepsis. She had also been hospitalised several months ago for community acquired pneumonia (*H. influenzae*) which required IV antibiotics.

Do these patients qualify for Ig via the National Ig Governance Program? If yes, what factors allow them to qualify?

Almost 18,000 patients were approved to receive Ig treatment via the Ig Governance Program in 2016-17 at a total cost of over \$532 million. Awareness and understanding of access arrangements through the National Ig Governance Program is paramount to supporting patient access to a valuable, but high cost therapy and ensuring government funds are expended efficiently, effectively and ethically.

P058. Disseminated Nocardiosis Related to Ibrutinib therapy for heavily pre-treated Chronic Lymphocytic Leukaemia

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Nocardia is an aerobic Gram positive, weakly acid-fast bacterium that is commonly found in soil and water. Disseminated Nocardiosis commonly occurs in immunosuppressed individuals, frequently with pulmonary, central nervous system and cutaneous involvement.

We report the second known case of disseminated Nocardiosis related to Ibrutinib, a Bruton's tyrosine kinase inhibitor therapy, in an individual with heavily pre-treated Chronic Lymphocytic Leukaemia (CLL). Our patient is a 72-year old avid gardener who was commenced on Ibrutinib monotherapy in January 2016 for relapsed CLL with known 17p deletion, occurring within 2 months of completing 6 cycles of Rituximab and Bendamustine. His prior therapy included Rituximab, Cyclophosphamide, Vincristine and Prednisolone (RCVP) and Fludarabine, Mitoxantrone and Dexamethasone (FMD).

In February 2017, he was treated with intravenous antibiotics for a left lower lobe pneumonia. Three weeks following this, he developed gradual onset left lower limb weakness. Magnetic resonance imaging of the brain revealed a 13 x 12 x 14mm ring-enhancing lesion in the right frontoparietal junction with surrounding vasogenic oedema and localised mass effect. This was treated as a cerebral abscess with six weeks of intravenous antibiotics, with reduction in the size of the lesion and had complete neurological recovery. He was then commenced on oral trimethoprim/sulfamethoxazole for presumed Nocardiosis.

Whilst on trimethoprim/sulfamethoxazole in December 2017, he developed dyspnoea, fevers and night sweats. Computer tomography (CT) of the chest revealed a 24 x 33mm spiculated right upper lobe lesion. Subsequent biopsy confirmed *Nocardia* species. He was recommenced on intravenous antibiotics with improvement in symptoms and radiological appearance, and was subsequently commenced on suppressive oral antibiotics. He continues to obtain durable disease control on Ibrutinib therapy with no recurrence of Nocardiosis at 7 months.

P059. Progressive multifocal leukoencephalopathy as a complication of ibrutinib therapy for relapsed chronic lymphocytic leukaemia

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Introduction

Ibrutinib, an irreversible inhibitor of Bruton tyrosine kinase in B lymphocytes, is increasingly used for treatment of chronic lymphocytic leukaemia and other B-lymphoproliferative disorders due to its favourable efficacy and safety profile. However opportunistic infections are a recognised complication. Only one small case series and one case report of progressive multifocal leukoencephalopathy in the setting of ibrutinib exist in the literature, most of which were in the elderly.

Case Report

We present a case of a 56 year old woman treated with ibrutinib for chronic lymphocytic leukaemia, who presented with progressive multifocal leukoencephalopathy that was ultimately fatal.

Our patient had been diagnosed with chronic lymphocytic leukaemia more than 7 years ago and had previously received rituximab-based chemoimmunotherapy; she had commenced ibrutinib 3 years prior to presentation. She presented to hospital with rapid onset progressive confusion, expressive dysphasia, hemiparesis and fevers. MRI was suggestive of progressive multifocal leukoencephalopathy, which was confirmed on brain biopsy. She was concurrently diagnosed with *Aspergillus niger* fungaemia and bacterial pneumonia, suggestive of profound immunodeficiency. She subsequently developed seizures and deterioration in her neurological status and eventually passed away.

Conclusion

Ibrutinib may cause profound immunosuppression leading to serious opportunistic infections. Development of fevers and focal neurological signs and symptoms in ibrutinib-treated patients should prompt consideration of progressive multifocal leukoencephalopathy. Patients starting ibrutinib should be counselled on the risk of progressive multifocal leukoencephalopathy

P060. T-cell prolymphocytic leukemia (T-PLL) and megakaryocytic dysplasia: an intriguing tale of blebbed cytoplasm, separated nuclei and chromosomal disarray

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Aims

To describe the clinical, morphological, immunophenotypic and cytogenetic features of a case of T-PLL.

To explore the possible association between T-PLL and Myelodysplasia.

Method

A patient was found to have a marked lymphocytosis on a routine FBC. A presumptive diagnosis of T-PLL was made following film review. A bone marrow biopsy, immunophenotyping, metaphase cytogenetics and FISH for abnormalities of chromosome 14 were performed.

Results

The patient's haemoglobin was 94g/L, Platelets $94 \times 10^9/L$ and WBC count $52 \times 10^9/L$. The abnormal cells were small lymphocytes with mature chromatin and prominent cytoplasmic blebbing. The immunophenotype was: CD3+(weak)/CD4+/CD8-/CD2+CD5+/CD7+. Bone marrow histology revealed a heavy interstitial infiltrate of T-lymphocytes and dysplastic megakaryocytes. A complex abnormal karyotype with multiple structural and numerical abnormalities was detected. Inversion 14q11q32 was identified by FISH.

Discussion

T-PLL is a rare chronic lymphoproliferative disorder. It is a clinically aggressive malignancy with a short median survival and poor response to conventional chemotherapy. Alemtuzumab is the most commonly used treatment, but the outcome remains poor, especially in patients not fit for a consolidative transplant.

The classical presentation is with a marked leucocytosis, hepatosplenomegaly and generalised lymphadenopathy. T-PLL has characteristic morphological and immunophenotypic features reflecting its mature post-thymic T cell origin. Recurrent cytogenetic abnormalities involving chromosome 14, cause dysregulation of the TCL1 oncogene, are unique to T-PLL and are found in approximately 75% of cases. Multiple other abnormalities are commonly identified in T-PLL and the chromosomal changes are often very complex.

There is a described association between T-PLL and hypoplastic myelodysplasia which may explain the unexpected finding of dysplastic megakaryocytes. This association is thought to be related to T-cell mediated autoimmunity and clonal expansion leading to bone marrow failure. In this particular case, this awaits further investigation using FISH and molecular karyotyping to assist in establishing the diagnosis of possible co-existent myelodysplasia.

P061. A case of disseminated cryptococcosis in a patient with chronic lymphocytic leukemia on ibrutinib immunotherapy in rural Australia

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Introduction

Ibrutinib, a first-in-class inhibitor of Bruton tyrosine kinase, has revolutionized the treatment of chronic lymphocytic leukemia (CLL) in high risk and relapsed refractory populations. Its increasing use in clinical practice, however, has seen a rise in reports of opportunistic fungal infections, often with atypical presentations and high mortality.

Case

We report a 59-year-old Caucasian man from rural Tasmanian who developed asymptomatic fevers on a 2-year history of Ibrutinib monotherapy for CLL. Medical history was significant for prior FCR chemotherapy; polymyalgia rheumatica on long term low dose prednisolone; hypogammaglobulinaemia on maintenance immunoglobulin; and previous *Pneumocystis jiroveci* pneumonia. The patient reported no localizing symptoms of infection, with unremarkable clinical examination. Neutrophil count was $1.7 \times 10^9/L$ with a C-reactive protein of 240mg/L. Preliminary cultures were negative. Four days into admission the patient became haemodynamically unstable despite broad-spectrum antibiotics, developing a non-ST-elevation myocardial infarction, and hypoxic respiratory failure. After 4 days of incubation, multiple blood cultures flagged positive with a yeast, subsequently identified as *Cryptococcus neoformans*. The patient was commenced on liposomal amphotericin and flucytosine. Cerebrospinal fluid analysis demonstrated a cryptococcal antigen titre of 1:10, with positive culture. Computed tomography revealed diffuse ground-glass changes throughout both lungs, and a right occipital lobe lesion possibly representing intracranial cryptococcoma. Despite maximal antimicrobial, inotropic and ventilatory support, the patient continued to deteriorate with persisting culture positivity, rapidly rising white cell count, and progressive multi-organ failure, and died on day 10 of admission.

Conclusion

This case, possibly the first of its kind described in Australia, highlights an increasingly frequent and serious complication of ibrutinib therapy. Whilst further evaluation is needed to understand the exact mechanism by which small molecule kinase inhibitors increase risk of opportunistic infection, such cases emphasise the importance of pre-treatment screening for pre-existing risk factors as well as increased vigilance for atypical infection during treatment.

P062. The effect of tyrosine kinase inhibitor, ponatinib in haemostasis, thrombosis and inflammation

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Aims

Determine the effect of ponatinib on platelet function and haemostasis in vitro and the effect of ponatinib on platelet function and haemostasis ex vivo. Also, assess the acute effect of TKI treatment on primary haemostasis, platelet and endothelial activation and thrombus formation in vivo using a C57BL/6 mouse model. Finally determine strategies to ameliorate the prothrombotic effects of ponatinib ex vivo and in vivo thrombus formation in mouse models (calcium channel blockers, statins and anti-platelet agents).

Method

Ferric chloride-induced vascular injury model of mesenteric arterioles and carotid arteries. Thrombin generation measurement. Enzyme linked immunosorbent assay(ELISA).

Result

In vitro treatment of whole human or murine blood with ponatinib highly increased platelet activation comparing with control samples. In addition, treatment of wild type C57BL/6 mice with ponatinib and control for 4 hours increased the thrombus formation. For ex vivo treatment, the growth of thrombus increased with ponatinib treatment compare to control and other tyrosine kinase inhibitors. In addition, the amount of plasma level of inflammatory markers such as soluble P-selectin, TNF-alpha and IL-6 increased compare to normal level of control.

Conclusion

Regarding to our results, we conclude that Ponatinib has a prothrombotic effect that leads to thrombotic complications

P063. Implementing a new BCR-ABL1 assay and giving it the green light

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Aim

Altered referral practices, customer expectations, and economics dictated assessment of an alternate quantitative BCR-ABL1 assay (Cepheid Xpert Ultra). This study describes the extended verification process for the new assay and defines an amended laboratory algorithm for the judicious application of BCR-ABL1 testing methodologies.

Method

Quantitative BCR-ABL1 testing is a component of the laboratory's repertoire of BCR-ABL1 assays. In this study 136 Xpert Ultra test results were compared to either reference sample target values or results determined by the laboratory's existing quantitative BCR-ABL1 assay (Qiagen, Ipsogen ISMMR Dx). Performance metrics examined included assay limits (background, detection, quantitation), reportable range, reproducibility, and measurement uncertainty. Concordance of BCR-ABL detection status and molecular response classification (MR<4.5 v MR≥4.5) was scrutinized. Existing BCR-ABL1 testing workflows were reviewed based on the verification findings and ESMO CML Clinical Practice Guidelines¹. Reporting practices were reappraised against international recommendations and commenting was enhanced for clinical relevance.

Results

Test results (reference samples n=67 tests; patient samples n=69) were analyzed and revealed: substantiation of claimed limits; a linear reportable range from 0.001 - 10% IS; measurement uncertainty was highest (~93%) at low BCR-ABL1 levels (0.001-0.01%); detection accuracy was 92.8%; response classification accuracy was 97.1%; target bias estimates were achieved (patient cohort bias = -1.01; RCPA QAP 5 sample bias = +1.34). The assay's intended use and limitations were also noted. Subsequently the existing qualitative / quantitative workflow algorithm was amended to include the Xpert Ultra assay with the primary classification based on provided clinical history and prior BCR-ABL1 test results.

Conclusions

The Xpert BCR-ABL Ultra assay is a therapeutically relevant test complementing but not superseding qualitative testing. Qualitative BCR-ABL assays have a sentinel role in accurate documentation of BCR-ABL1 transcript type thus determining the applicability of different quantitative BCR-ABL1 assays in a given clinical scenario.

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P064. Surgically treated primary hepatic lymphoma - a case report

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Introduction

Primary hepatic lymphoma (PHL) is a rare malignancy characterised by liver involvement without evidence of extrahepatic disease at presentation. We present an interesting case of incidental PHL treated with surgery alone.

Case study

A 70 year old gentleman was found to have an 18mm single nodular liver lesion on a MRCP scan following a recent episode of pancreatitis. Repeat imaging noted its rapid growth while PET CT, endoscopy and colonoscopy failed to reveal any primary malignancy or lymphadenopathy. The patient underwent a segment 3 liver resection and the histopathology was diffuse large B-cell lymphoma with clear surgical margins. At 8 months post-resection he remains clinically and radiologically (PET CT) in remission.

Discussion

Evidence for the treatment and outcomes of PHL is restricted to case studies and reviews due to the rarity of the disease. A variety of treatment options are seen in the literature, most commonly chemotherapy with or without surgery, a small number of cases have been reported with good outcomes following surgery alone.

P065. Burkitt's Lymphoma Arising Post Previously Treated DLBCL and Advanced Bowel Cancer

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Background: Outcomes for patients with Burkitt's lymphoma has continued to improve with early disease identification and aggressive therapy. However a complication of intensive chemotherapy is increased risk of secondary malignancies including lymphomas. Other complications including cardiotoxicity, such as with anthracyclines, may limit future treatment options.

Method: We performed a review of treatment options available for a 68 year old man with de novo Burkitt's lymphoma that occurred on a background of two successfully treated malignancies which included diffuse large B-cell lymphoma and advanced bowel adenocarcinoma which had required adjuvant chemotherapy. Available publications were reviewed to guide management.

Results: We reviewed a 68 year old man diagnosed with DLBCL in 2009 that was successfully treated with six cycles of R-CHOP chemotherapy. In 2014, he developed a stage IIIB poorly differentiated adenocarcinoma of his ascending colon. He underwent right hemicolectomy followed by adjuvant chemotherapy. In 2018 he presented with abdominal pain due to a large abdominal mass thought to be recurrent bowel cancer. However, histopathology and cytogenetics confirmed Burkitt's lymphoma. Wound dehiscence from his exploratory laparotomy and recurrent infections delayed the onset of chemotherapy. Borderline cardiac function, age, surgical complications and previous chemotherapy made it difficult to decide on the most appropriate treatment regimen. He has received two cycles of R-DHAC chemotherapy with very good response with attempted autologous stem cell collection. Autologous stem cell transplant with BEAM conditioning is proposed.

Conclusion: There are ongoing challenges in managing Burkitt's lymphoma, particularly in the older patient with co-morbidities. The possibility of secondary malignancy post previous therapy may be associated with more aggressive disease and inferior outcomes. Alternatives to anthracycline based therapy are required in patients who have had prior R-CHOP chemotherapy. The role of autologous transplant in Burkitt's lymphoma has been proposed as an option, though it is not standard therapy in de-novo disease.

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P069. The utility of beta2-microglobulin as a prognostic marker in Hodgkin lymphoma

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The role of biological markers in Hodgkin lymphoma and their prognostic utility is uncertain. We aimed to determine whether an elevated beta2-microglobulin level at diagnosis is predictive of worse prognosis in patients with Hodgkin lymphoma (HL).

We conducted a retrospective review of patients diagnosed with HL and treated at the Princess Alexandra Hospital (PAH) between January 2003 and December 2013. Serum B2M was measured routinely with diagnostic blood tests. A serum B2M level of ≥ 2.5 mg/l was considered elevated.

110 patients were included in the analysis. With a median follow up time of 74 months (range 0.98 – 175 months), median event-free survival (EFS) and median overall survival (OS) were not reached. Thirty-two patients (29%) had a B2M ≥ 2.5 mg/l. On univariate analysis an elevated B2M was associated with worse EFS (HR 3.829, 95% CI 1.901 – 7.689, $p < 0.001$). Elevated B2M was also associated with inferior OS (HR 7.081, 95% CI 2.447 – 20.488, $p < 0.001$). Five-year EFS was 53.13% in patients with B2M ≥ 2.5 mg/l vs 83.16% in patients with B2M < 2.5 mg/l ($p < 0.001$). Five-year OS was 70.59% in patients with B2M ≥ 2.5 mg/l vs 94.87% in patients with levels < 2.5 mg/l ($p < 0.001$). On multivariate analysis, B2M was independent of risk group for inferior EFS (HR 1.582, 95% CI 1.271 – 1.969, $p < 0.001$) and OS (HR 2.011, 95% CI 1.539 – 2.628, $p < 0.001$).

We found beta2-microglobulin to be strongly predictive of inferior event free survival and overall survival in patients with Hodgkin lymphoma.

P070. Real-world Experience of Australian and New Zealand Relapsed or Refractory Mantle-Cell Lymphoma Patients on Ibrutinib in a Named Patient Program

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Background

In 2014, a global ibrutinib Named Patient Program (NPP) was opened in multiple countries, including Australia and New Zealand (ANZ) for patients with Mantle-Cell Lymphoma (MCL) who had received at least 1 prior line of therapy.

Aim

To analyse duration on ibrutinib treatment for patients with relapsed or refractory (R/R) MCL enrolled in the NPP in ANZ.

Method

A retrospective cohort analysis was conducted using baseline patient characteristics entered by treating physicians when enrolling patients into the NPP via the Janssen Managed Access portal (MAcWeb). We estimated patient time on treatment using data from resupply requests. Patients were considered to be on treatment until the time of last fill of ibrutinib supply or resupply. Ibrutinib treatment duration in the NPP was compared to time on treatment in the ibrutinib arm of the pivotal clinical trial (MCL3001). Time on treatment was evaluated using Kaplan-Meier (KM) curves, and statistical testing was conducted using the log-rank test.

Result

A total of 291 patients have been treated with ibrutinib in the NPP in Australia and 29 in New Zealand from December 2014 to June 2018. Of these, 75% were male, 75% were 65 years or older, and 46% of patients had received 3 or more prior lines of therapy before commencing on the NPP. The median duration on treatment in the NPP was 15 months which compares to 14 months in MCL3001. There was no statistical difference in the time on treatment between the clinical trial and the NPP ($p=0.36$, $HR=1.11$, $95\% CI=0.86-1.43$).

Conclusion

The ANZ NPP estimates of time on treatment closely tracks the treatment duration in the pivotal phase 3 trial for ibrutinib in R/R MCL. While there are limitations to the NPP data, given that it was based on unmonitored physician declarations, and the duration on treatment was estimated from resupply data, these findings indicate that the MCL3001 trial results on duration of treatment are reproducible in ANZ clinical practice.

P071. Outcomes in relapsed/refractory Hodgkin lymphoma post autologous stem cell transplant and the role of pre-transplant re-staging: A retrospective review in an Australian tertiary centre

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Aim

The primary aim of this study was to assess outcomes in patients with relapsed/refractory Hodgkin lymphoma (HL) who underwent autologous stem cell transplant (ASCT) and assess the impact that positron emission tomography (PET) response post-salvage chemotherapy had on outcomes.

Method

A retrospective review was undertaken of patients ≥ 16 years with relapsed/refractory HL who underwent ASCT at Royal Brisbane and Women's Hospital between September 2001 - December 2016. A list of patients was obtained from the bone marrow transplant database and data was collected through a retrospective review of patient medical records. Statistical analyses including responses, survival and univariate analyses were done with GraphPad Prism.

Results

55 patients were identified. First-line chemotherapy was ABVD for most patients (94.5%). Time to salvage chemotherapy was < 12 months in 45% and salvage was with platinum-based chemotherapy in all patients. The conditioning chemotherapy pre-ASCT was BEAM in 64% followed by MSK protocol (16%). Those who underwent MSK treatment were patients with high-risk disease. With a median follow-up of 86 months, overall survival (OS) and progression free survival (PFS) were 64% and 62.9% at 7 years respectively. 7-year OS based on imaging pre-ASCT was markedly reduced in patients refractory to salvage chemotherapy (OS in CMR 72%, PMR 74%, refractory 20%, $p < 0.001$). The type of conditioning chemotherapy did not demonstrate any significant difference in OS or PFS.

Conclusion

Outcomes from our centre are comparable to published data. Patients with refractory HL post salvage pre-ASCT had significantly reduced OS and PFS regardless of the conditioning regimen. More intensive non-BEAM regimens had similar transplant related mortality, OS and PFS. There was no significant difference in OS or PFS in patients who underwent ASCT in PMR versus CMR. The role of novel agents (e.g. brentuximab vedotin) to improve depth of response prior to ASCT in refractory patients needs to be considered.

P072. Isolated central nervous system relapse of mantle cell lymphoma in enduring remission on Ibrutinib monotherapy

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Central nervous system (CNS) involvement with mantle cell lymphoma (MCL) is a rare and devastating manifestation of an already uncommon variant of non-Hodgkin lymphoma with traditionally poor clinical outcomes. We present a rare case of isolated CNS relapse in an individual with heavily pre-treated MCL who remains in enduring remission on Ibrutinib monotherapy beyond two years follow-up.

A 69 year-old man presented with subacute onset of drowsiness, diplopia and slurred speech. He had a 6-year history of Stage IV MCL and concomitant hairy cell leukaemia after initially presenting with thrombocytopenia and neutropenia. Treatment then included cladribine and four cycles of fludarabine, cyclophosphamide and rituximab (FCR). In the four years prior to his current presentation, he relapsed twice with extra-nodal disease recurrence. His first relapse was in the form of tonsillar involvement, and he was treated with rituximab, cyclophosphamide, vincristine and prednisolone (R-CHOP) and rituximab, dexamethasone, cisplatin and prednisolone (R-DHAP). Eighteen months prior to this current presentation, he relapsed again with nasal polyp involvement and was treated with six cycles of rituximab and bendamustine.

In this presentation, physical examination was significant for disconjugate gaze, diplopia and loss of consensual light reflex. Magnetic resonance imaging (MRI) of the brain was negative for disease involvement and there was no leptomeningeal enhancement. Cerebrospinal fluid analysis performed revealed cytological and immunophenotypical evidence of MCL in the CNS. Serological studies for infectious causes returned negative. Computer tomography of the neck, chest, abdomen and pelvis revealed no evidence of nodal disease and bone marrow biopsy performed was also negative.

He was commenced on dexamethasone and Ibrutinib 560mg daily, with rapid improvement in his neurological status. Dexamethasone was weaned successfully, and he remains in enduring remission beyond two years follow-up on Ibrutinib monotherapy with no neurological deficits.

P073. Cast nephropathy in Waldenstrom's macroglobulinaemia following rituximab therapy

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Background/Aim

Renal complications in Waldenstrom's Macroglobulinaemia (WM) are rare. Moreover, complications mediated by free light chains (FLCs) have been infrequently described, and the role of serum FLC monitoring is without consensus.

We describe a patient with WM who developed cast nephropathy, some months after initiating rituximab therapy.

Case Description:

A 63yr old woman was diagnosed with WM following investigation for persistently elevated ESR. Investigations revealed: IgM paraprotein of 13g/L, kappa FLC of 137mg/L & lambda FLC 7mg/L (K/L ratio 19.57) [Siemens N-Latex FLC assay on BNII Nephelometer.] Bone marrow biopsy demonstrated a monoclonal lymphoplasmacytic infiltrate consistent with WM. Haematological parameters were within normal limits; she was monitored expectantly until a clinical diagnosis of Schnitzler's syndrome was made following the development of persistent urticaria. IgM paraprotein and serum FLC remained stable.

She was treated with rituximab monotherapy resulting in marked improvement in her skin symptoms, without reduction in her IgM or FLC levels.

Ten months later she developed severe acute kidney injury (Cr 400umol/L), with an associated rise in serum kappa FLCs to 1040mg/L (lambda FLC 19mg/l), but stable IgM paraprotein (10g/L).

Renal biopsy demonstrated severe cast nephropathy.

Bone marrow biopsy revealed a markedly increased plasma cell infiltrate, without a B-lymphoid infiltrate. The plasma cell immunophenotype was non-aberrant, cytogenetics were normal and next-generation sequencing identified both MYD88 L265P and CXCR4 mutations, consistent with WM (rather than IgM myeloma).

Treatment with high-dose cyclophosphamide (2g/m²) and dexamethasone, followed by bortezomib/cyclophosphamide/dexamethasone, was initiated achieving a VGPR (IgM <1g/L, kappa FLC 49mg/L) and stabilisation of renal function (Cr 200-300umol/L). Repeat bone marrow assessment revealed no B-lymphoid, and only minor (<10%) plasma cell, infiltrate.

Conclusion

Whist rarely described in the literature, WM patients have the potential to undergo "light-chain escape" and develop associated renal complications. Monitoring of serum FLCs may identify patients at risk of such events.

P074. A retrospective analysis of Burkitt Lymphoma in Western Australia from 2000 - 2017

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Background

Burkitt lymphoma is a rare form of B-lymphocyte non-Hodgkin lymphoma. The WHO classification recognises three clinical variants of the disease – endemic, sporadic and immunodeficiency-associated Burkitt lymphoma. They share the characteristic dysregulation of the c-myc oncogene.

Aim

This is a retrospective analysis to assess the incidence, pathology, type of treatment and overall survival of patients who were diagnosed and treated with any form of Burkitt lymphoma in public hospitals in Western Australia between 2000 and 2017.

Method

Information on Burkitt lymphoma patients was obtained using linked data systems of the Western Australian Health Department. 83 patients were identified. 10 patients were excluded due to lack of date of diagnosis, leaving 73 patients for analysis

Results

73 patients were included in the final database. Of these, 50 were males and 23 females: age range 20 to 83 years. 67 patients were diagnosed with sporadic Burkitt lymphoma, with 6 having HIV-related Burkitt lymphoma. No cases of endemic Burkitt lymphoma were identified. Using Ann Arbor staging, 63% had stage 3 or higher disease at diagnosis. Multiple chemotherapy regimes were used, most commonly, R-HyperCVAD, R-CODOXM, R-CHOP, DA EPOCH-R and R-IVAC. Complete response rates varied with each treatment, from 100% in patients treated with DA EPOCH-R to 28.6% treated with R-CHOP alone. 24 patients died by the time of data collection, giving an overall survival rate of 67% at 6 years following treatment.

Conclusion

The standard of care for Burkitt lymphoma has still to be defined with enrollment into a clinical trial the preferred option. Otherwise treatment with intensive short duration chemotherapy remains the best option. Our results are consistent with the international literature giving a 60 to 80% overall 5 year survival.

P075. Phenotypic classification and outcome in Diffuse Large B Cell Lymphoma

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Aim

To classify diffuse Large B cell Lymphoma (DLBCL) based on molecular abnormality using standard diagnostic laboratory techniques; fluorescence in situ hybridisation (FISH) and immunohistochemistry (IHC), and to assess outcomes based on classification and treatment.

Method

A retrospective outcome study identified DLBCL and B cell lymphoma unclassifiable (BCLU) from two tertiary centres in Queensland between January 2010 and December 2016. We collected diagnostic and prognostic information in addition to molecular classification, clinical features, treatment and survival outcomes.

Results

293 patients with DLBCL (n=277) and BCLU (n=16) were identified where biological abnormality was detected by FISH and/or IHC. Median age was 68 years (21.8-92.8). Hans algorithm identified 119 (40.6%) germinal centre B-cell (GCB) DLBCL and 127 (43.3%) Non-GCB DLBCL, 47 (16.1%) un-classified. Progression free survival (PFS) based on Hans classification was equivalent (3 year PFS GCB 70.9%, NGCB 65.1% p = 0.3797). 24 cases of double hit (DH) or triple hit (TH) based on MYC translocation and Bcl2 or/and Bcl6 by FISH were identified. 16 (67%) were de novo DLBCL and 16 (67%) were GCB. DH cases had higher IPI, more advanced stage and increased extranodal sites. 12 (50%) were treated with R-CHOP based regimens, 6 (25%) with DA-R-EPOCH and 6 (25%) with R-HyperCVAD. 3 year PFS is 48.1%, 50% and 83.3% respectively. 15 Double Expresser (DE) phenotypes of MYC and Bcl2 over-expression by IHC were identified. 3 year PFS is not statistically different to DH (DE 78% vs DH 57.4%), however longer follow-up is required due to the recent introduction of MYC IHC.

Conclusion

Classification by the Hans algorithm did not impact survival outcomes. Considering DH cases there is not currently a significant change in outcome based on treatment choice, however follow-up is short and we will continue to follow this cohort.

P076. CSF flow cytometry and cytopathology are complementary in assessing CNS involvement in haematological malignancy

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Aim: Central nervous system (CNS) involvement with lymphoma or leukaemia has significant treatment and prognostic implications; correct diagnosis is essential. We aimed to analyse cerebrospinal fluid (CSF) flow cytometry and paired cytopathology data to determine the relative utility of these testing methodologies.

Method: 371 CSF flow cytometry and 287 CSF cytopathology samples from 166 adult patients (pts) at a single tertiary hospital were reviewed. Flow cytometry samples had count and viability assessment, and limited or extended disease-specific panel on 10-colour Navios flow cytometer. Cytopathology smears were prepared using Shandon Cytospin 4 and Romanowsky stain.

Results: 97 pts had a haematologic malignancy and ≥ 1 paired cytopathology and flow cytometry samples. Disease groups in individual patients: 54 B-cell lymphoproliferative disorders, 37 acute leukaemia, 4 myeloma, 2 blastic plasmacytoid dendritic cell neoplasm (BPDCN).

5% of the samples were diagnostic, 32% staging, and 63% restaging during treatment.

239 paired samples of haematological malignancy reviewed (Table 1).

		Cytopathology				Total
		Negative	Inconclusive	Suspicious	Positive	
Flow Cytometry	Negative	118	25	0	2	145
	Inconclusive	37	14	0	1	52
	Suspicious	1	2	0	0	3
	Positive	13	5	0	21	39
	Total	170	46	0	24	239

Table 1.

Two results showed positive cytopathology with negative flow cytometry, both in restaging samples during treatment in a patient with mantle cell lymphoma with CNS involvement.

One sample of cytopathology was positive when flow cytometry was inconclusive due to blood contamination. This was a restaging test in a patient with BPDCN with CNS involvement; no blastic population detected.

Flow cytometry results were inconclusive in 52 pts: 80% due to low cell recovery (0-58 cells), 10% from blood contamination, 6% uncertain diagnosis, 1 possible anaplastic large cell lymphoma difficult to categorise.

Three suspicious flow cytometry results noted: two suspicious populations and low cell recovery, one with monocytes of uncertain significance in acute monoblastic leukaemia.

Cytopathology missed 13/34 flow positive cases. Flow cytometry missed 2/24 cytopathology positive cases.

Conclusion

Paired cytopathology with flow cytometry in analysis of CSF adds value in assessing for CNS involvement in haematological malignancy. Flow cytometry appears more sensitive and should be performed for all patients

P077. Patient-specific immunoglobulin heavy chain (IGH) rearrangement detection in circulating tumour DNA in B-cell lymphoproliferative disorders correlates with conventional biomarkers

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Aim: Circulating tumour DNA (ctDNA) is a promising biomarker for solid organ and haematological malignancy for tracking disease activity. We aimed to determine the potential clinical utility of ctDNA across a range of B-cell malignancies by assessing patient-specific IGH rearrangement as a disease biomarker.

Method: ctDNA was extracted from plasma of patients treated at Peter MacCallum Cancer Centre. Patient-specific IGH rearrangements were determined by amplicon-based next-generation sequencing. Patient-specific oligonucleotide primers and probes were designed for droplet digital PCR assays. For each patient assay, sensitivity and specificity were determined and optimised by using CD19+ selected blood samples from healthy volunteers and serial dilution standard curves of either diagnostic sample or synthetic gBlock DNA.

Results: A range of B-cell lymphoproliferative disorders were included in the cohort including diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, myeloma, chronic lymphocytic leukaemia (CLL) and follicular lymphoma. The general sensitivity of patient-specific IGH assays in ctDNA was 10^{-3} - 10^{-4} . Patient-specific IGH sequence burden in ctDNA correlated with conventional quantitative markers of disease burden measurement including PET/CT (metabolic tumour volume [MTV]), peripheral blood lymphocytosis and bone marrow morphological/immunophenotypic burden. Figure 1 showed ctDNA burden from two illustrative cases: (i) a patient with double-hit DLBCL where ctDNA burden correlated with PET/CT MTV and (ii) a patient with CLL where ctDNA correlated with peripheral blood and bone marrow lymphocytosis.

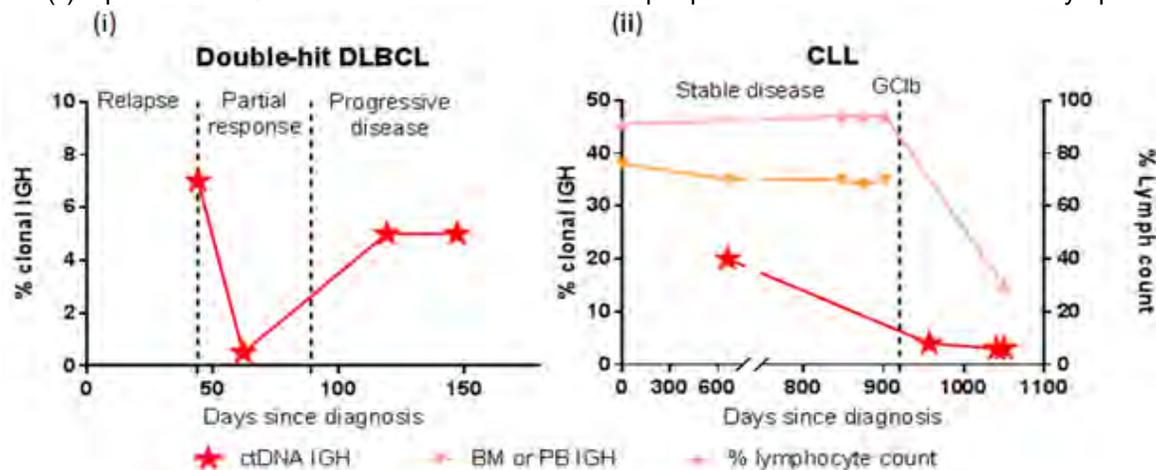


Figure 1. ctDNA dynamics reflect tumour burden in B cell disorders. Disease progression as observed on PET/CT scan were summarised on top of the graph. GClb = Obinutuzumab in combination with Chlorambucil therapy.

Conclusion: Our data demonstrates that detection of patient-specific IGH rearrangement in ctDNA is possible and that the burden of disease in ctDNA tracks with conventional markers of disease activity. ctDNA may therefore represent an alternative to conventional biomarkers for disease monitoring in B-cell lymphoproliferative disorders.

P078. A case of ALK negative anaplastic large cell CNS lymphoma on a background of spontaneously resolved ALK negative cutaneous lymphoma

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ALK negative anaplastic large cell lymphoma (ALK- ALCL) is a rare T cell non hodgkins lymphoma. Central nervous systems (CNS) involvement is very rare and best therapy for this is yet to be defined. ALK-negative ALCL presents at an older age (>65 years) and case series show very poor outcomes with 5 year overall survival rates <12.5%. ALCL frequently involves the lymph nodes and only a handful of case studies have reported CNS involvement.

A 67M presented with a three month history of worsening headaches, mild ataxia, unintentional weight loss, and personality changes. MRI revealed a small cerebellar lesion, a repeat MRI two months later showed a new large R frontal lobe lesion. This lesion was excised and the biopsy confirmed a diagnosis of ALK-negative ALCL, CD30+ with a Ki67 index 100%. A staging PET-CT and MRI spine showed FDG avid disease confined to the brain, without any leptomeningeal involvement. His bone marrow examination was normal. On clinical examination he had mild ataxia and there was no lymphadenopathy, organomegaly or skin lesions.

The patient had history two years prior of a L elbow skin lesion which was a primary cutaneous CD30+ and ALK-negative cutaneous lymphoma, without any systemic disease. The lesion spontaneously resolved, subsequently he was lost to follow up up till his most recent presentation.

Treatment options for isolated CNS disease are limited. Brentuximab vedotin has been trialed in cases of relapsed systemic ALK-negative ALCL however there's no evidence for CNS penetration. After discussion with the patient and his family he opted to proceed down a palliative pathway and have whole brain radiation therapy.

This clinical scenario is a unique presentation of a rare T cell lymphoma, which may either be primary CNS lymphoma or related to the previous cutaneous lesion. Which in both instances provides significant treatment challenges.

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P080. A novel case of primary bone lymphoma with concurrent plasma cell neoplasm: A clinical discussion and literature review

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A 72-year-old female presented with persistent right-sided chest pain. Bone scan revealed a lytic lesion of the sternum. She was diagnosed with DLBCL of non-germinal centre phenotype on core biopsy. Subsequent PET/CT revealed glucose avid lytic lesions of the sternum (maximum SUV 62.91), spine, ribs and clavicle without lymphadenopathy or other extranodal disease (stage IV) as well as diffusely increased bone marrow uptake. There was no evidence of DLBCL on bone marrow biopsy, however infiltration with >40% abnormal plasma cells (kappa light chain positive, normal karyotype, no cytogenetic abnormalities) was demonstrated. Renal function, haemoglobin and calcium were within normal range but she had an abnormal serum paraprotein of 19g/L (IgG kappa).

Synchronous diagnosis of DLBCL or Multiple Myeloma (MM) with any haematological malignancy is rare (<1%) and primary bone lymphoma accounts for <1% of DLBCL. Paraprotein production with lymphoma is infrequent (16%) but well described and is more commonly associated with non-GCB subtype DLBCL. The presence of a concurrent monoclonal plasma cell population has not been previously described. It is unclear from PET/CT staging alone whether any of the bony lesions are attributable to the plasma cell dyscrasia (and therefore constitutes myeloma) or whether they all represent disseminated lymphoma. A biopsy was not able to be obtained prior to commencing chemotherapy. Whilst DLBCL classically presents with a higher SUVmax (median around 20), SUVmax as low as 2 has also been described. Median SUVmax in MM is lower (<10), however a SUVmax of up to 22 has been reported and higher SUVmax appear to be associated with worse outcomes in both diseases.

This is a novel case of synchronous haematological malignancies that raises clinical dilemmas around diagnosis and management and will be used to explore the literature.

P081. The disappearing paraprotein: cryoglobulinaemia in Waldenstrom's macroglobulinaemia

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Cryoglobulins are immunoglobulins in the serum that precipitate below 37 °C. This may give rise to false negative results in paraprotein testing, a phenomenon that has clinical implications in both the diagnosis and monitoring of Waldenstrom's macroglobulinaemia.

A 62-year-old gentleman was referred for mild anaemia of 98g/L and a trace IgM kappa paraprotein. There were no constitutional symptoms, lymphadenopathy, organomegaly or symptoms of hyperviscosity. His blood film demonstrated marked rouleaux formation. Renal function, calcium and LDH readings were normal. Total protein was 85g/L and his protein electrophoresis showed trace IgM kappa paraprotein of < 1g/L. IgM levels, in contrast, were markedly elevated at 43.86g/L. Subsequent tests showed positivity for serum cryoglobulins and plasma cryofibrinogen. Incubation for 72 hours at 37 °C showed a total protein of 97g/L and an IgM kappa paraprotein of 26g/L. Repeated sampling prior to treatment showed fluctuating total protein levels. Imaging studies showed no organomegaly or lymphadenopathy. Bone marrow biopsy revealed significant infiltration with a CD5/10 negative B-cell non-Hodgkin lymphoma. This case illustrates the potential for false negative paraprotein results in patients with type 1 cryoglobulinaemia. As paraprotein levels are used for both diagnosis and as a marker of disease activity, it is imperative that accurate readings are obtained. Current laboratory procedures in dealing with trace IgM levels to ensure the detection of underlying cryoglobulins will detect most, but not all cases of cryoglobulinaemia, and a high index of suspicion is required when the results of multiple tests are discordant. In cases such as this, meticulous handling of samples is critical, and all care should be taken to keep the sample warm up until the point of testing.

P082. Invasive fungal infections in patients treated with a BTK inhibitor: A case series

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Introduction

Inhibitors of Bruton's tyrosine kinase (BTK), an essential kinase for antigen-stimulated B-cell receptor signalling, are increasingly used in chronic lymphocytic leukaemia and selected B-non-Hodgkin lymphomas. The agents are generally well-tolerated, however an increasing number of case reports of invasive fungal infections (IFI) occurring in the context of BTKi therapy highlights the importance of phase IV surveillance. We describe two patients who developed IFI during treatment with a BTKi.

Case presentations

Patient 1, a 51-year-old male, presented with left eye *Scedosporium apiospermum* complex reactivation one month after commencing zanubrutinib for relapsed Walderström's Macroglobulinaemia. He was managed with intra-ocular and oral voriconazole, and vitrectomy, while zanubrutinib was continued. One month later, progressive *scedosporiosis* was found with vertebral discitis/osteomyelitis, pneumatosis intestinalis, and multiple abscesses (epidural, prostatic, and intracranial). He commenced miltefosine, terbinafine, and voriconazole therapy and zanubrutinib was withheld for one month. Due to progressive infection, zanubrutinib was permanently ceased and he underwent experimental T-cell therapy with no response. He was palliated and passed away one month later.

Patient 2, a 79-year-old man with newly diagnosed diffuse large B cell lymphoma, developed *Cryptococcus neoformans* pleuropulmonary infection while receiving ibrutinib and R-miniCHOP. Following cycle 2, he developed a left-sided pleural effusion and pulmonary nodules. The pleural fluid and serum cryptococcal antigen tests were positive. He commenced fluconazole 400mg daily for 12 months and ibrutinib was ceased. Chemotherapy was continued and the patient remains in remission 6 months later.

Conclusion

Inhibition of BTK alone is not anticipated to be associated with IFI however BTKi drugs have variable specificity for BTK. In the context of increasing reports of IFI during all BTKi therapy including the two reports in our institution are of concern and systematic reporting of cases is essential to determine whether a true association exists.

P083. A national pathology review committee for the Lymphoma and Related Diseases Registry

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Background

The Australian Lymphoma and Related Diseases Registry (LaRDR) is a national registry capturing diagnoses, treatment and clinical outcomes. It aims to support evidence-based management, reduce variation in care and improve outcomes.

Aims

Establish a LaRDR pathology review committee for quality assurance purposes, since lymphoma diagnosis is both complex and dynamic.

Methods

A national pathology review committee has been established to oversee diagnostic aspects of registry cases and advise on data collection and interpretation. LaRDR cases will have their pathology reports de-identified and reviewed by committee members periodically (not in 'real time'). Diagnosis via histopathology will be reviewed by committee pathologists and committee haematologists will review bone marrow involvement. On queried results, local Directors of pathology departments will be contacted to recommend local review. A further randomly selected 2-5% cases will have diagnostic material independently reviewed by committee members with issue of an identifiable report. Follow-up will be documented. Practical considerations include timeframes, logistics and management of review findings.

Results

To date, 900 cases of lymphoma have been registered on the LaRDR, consisting of 33 separate sub-types, demonstrating the spectrum of lymphoma diagnoses. The national pathology committee consists of anatomical pathologists and haematologists and will commence reviews shortly.

Discussion

Pathology review will provide quality assurance for the LaRDR, contribute to improved clinical care, and provide peer review and educational resources.

P084. Bing Neel Syndrome: Retrospective Australasian experience of a rare treatable complication of Waldenström Macroglobulinaemia

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Introduction and Aims

Bing Neel syndrome (BNS) is a rare complication of Waldenström Macroglobulinaemia (WM) characterised by infiltration of the CNS by malignant cells. It has diverse presentation and can be difficult to recognise. We present the Australasian experience of this rare treatable entity.

Methods

Retrospective data was extracted after obtaining consent from patients or next of kin. Ten patients were included from 9 sites in Australasia.

Results

Seven of the 10 patients were males with overall mean age of 63.5 yrs (range: 49-78); 4 patients were < 60 years. Four patients did not have a prior diagnosis of WM; 6 patients were diagnosed ~ 11 years post diagnosis of WM (range: 3 -26 yrs.). Most had low level WM at diagnosis of BNS with IgM and/or PP levels between 3 - 70 g/L; 6 had levels < 10 g/L.

Symptoms at presentation of BNS varied from headache, ptosis/ophthalmoplegia, memory loss, subacute hemiplegia, cognitive defects, hearing loss, and sensory or motor neuropathy.

Brain +/- spine MRI was done in all cases with 5 showing leptomeningeal or orbital infiltration, 3 had focal signs/masses, 1 had cortical atrophy, and 2 were normal. CSF analysis was abnormal in all cases on cytology, flow cytometry or molecular studies (MYD88 L265P+ in n=3).

Treatment of BNS included systemic chemoimmunotherapy (n=3), CNS penetrating intravenous agents (n=4), Ibrutinib (n=3), intrathecal chemotherapy (n=3), and radiotherapy (n=1) with > 1 modality being given in some patients.

Response data was available in 7 patients with ORR in 5 (1 CR, 4 PR) and PD/SD in 2. Two of the 10 patients died at an average follow up of 2 years.

Conclusion

BNS can be diagnosed with MRI brain/spine and/or CSF analysis investigations and can be treated with a number of regimens including Ibrutinib, which crosses the blood brain barrier.

P085. Infusional chemotherapy during daily haemodialysis in a patient with newly diagnosed Burkitt lymphoma

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Background: The effect of haemodialysis on a medication is rarely evaluated more than once¹. Early published recommendations are likely to underestimate dosing and dosing is usually recommended after dialysis to maximise duration of action¹. R-DA-EPOCH is an infusional chemotherapy regimen given continuously over 96 hours² to maximise the pharmacological effect of cell-cycle specific cytotoxics. Therapeutic drug monitoring and pharmacodynamic parameters are generally not available for cytotoxics making it difficult to ascertain if dose adjustment for haemodialysis is appropriate. There is one case of infusional chemotherapy during haemodialysis described in abstract form in the literature³.

Aim: To report on the successful use of R-DA-EPOCH during haemodialysis. Clinical details: A 63-year-old female presented with newly diagnosed Burkitt lymphoma and anuric acute kidney impairment due to tumour lysis syndrome. R-DA-EPOCH chemotherapy was commenced. Four consecutive days of haemodialysis were required from day one to four. We conducted a review of the Renal Drug Handbook⁴, University College London Hospitals dosage adjustment for cytotoxics in renal impairment guide⁵ and the Amgen dialysis of drugs handbook⁶ and consulted a National Institutes of Health pharmacotherapy expert.

Rituximab, doxorubicin and vincristine were dosed at 100%. Etoposide phosphate was dosed at 50% and made in a 50mL sodium chloride bag. Cyclophosphamide is dialysed thus was dosed at 100% with dialysis repeated a day after to clear it. Prednisolone is unlikely to be dialysed. Renal function improved by day six and haemodialysis was no longer required after this. Filgrastim support was given as per protocol.

Outcomes: Per protocol, twice weekly blood counts were measured, and neutrophil nadir targets were met without significant myelotoxicity. This indicated that our dosing during haemodialysis was both adequate and safe. The only chemotherapy related complications were steroid induced paranoia and hyperglycaemia.

Conclusion: Infusional chemotherapy was safely administered to an anuric patient on haemodialysis with the desired level of effect.

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P086. Thrombotic Thrombocytopenic Purpura associated with Hodgkin Lymphoma and Non Hodgkin Lymphoma

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Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare haematological disease characterized by thrombotic microangiopathy in the setting of decreased ADAMTS13 enzyme activity. Presenting as a constellation of clinical and laboratory findings, it can be classified as primary, or secondary from autoimmune conditions, or malignancy. We present the first case of TTP secondary to Hodgkin lymphoma and low grade B cell lymphoma.

Case report

A 77 year old female presented to the emergency department following 4 weeks of increased fatigue, weight loss, and pruritic rash. Imaging revealed mesenteric and retroperitoneal lymphadenopathy. Biopsy revealed mixed pathology, with both a classical Hodgkin lymphoma infiltrate, as well as background low grade B cell lymphoma. Further blood tests revealed raised LDH, microangiopathic haemolytic anaemia, and low ADAMTS13. Rituximab, ABVD, and plasma exchange were commenced, which lead to the normalization of platelets and recovery of ADAMTS13 levels.

Discussion

TTP is characterized by a thrombotic microangiopathy in the setting of ADAMTS13 deficiency. It can be primary, in association with autoimmune conditions, and in disseminated malignancy. Hodgkin lymphoma is associated with autoimmune conditions, including hepatitis, and other autoimmune haematological conditions. TTP has previously been described in only a handful of cases of Hodgkin lymphoma, which have responded to chemotherapy and plasma exchange. Treatment with both lymphoma based therapy and plasma exchange resulted in a remission and a durable response. The patient experienced prolonged cytopenias following chemotherapy. It is difficult to determine if that was due to primary cytotoxic effect, or residual effect from the underlying TTP.

Conclusion

This case gives further insight into the paraneoplastic effects of Hodgkin lymphoma. It also prompts whether malignancy screening is appropriate for patients with newly diagnosed TTP. Further studies are required to address the management for a rare presentation.

P087. High dose methotrexate toxicities and the use of glucarpidase

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Introduction: We conducted a retrospective audit on toxicities attributable to high dose methotrexate (HD MTX) in an adult population undergoing treatment of a haematological malignancy. An additional objective of the study was to assess adherence to published guidelines¹ on the use of glucarpidase for delayed methotrexate clearance.

Method: Patients who received HD MTX between 1/1/2013 to 31/12/2017 were identified using the chemotherapy pharmacy database. Adult patients who received a dose of methotrexate $\geq 1\text{g/m}^2$ were included. Combination chemotherapy regimens were excluded. Delayed methotrexate clearance was defined as a serum methotrexate level $> 0.05\mu\text{mol/L}$ more than four days post completion of the methotrexate infusion. Toxicities were graded according to the CTCAEv5. A literature review was performed to identify guidelines for the use of glucarpidase.^{1,2,3}

*Length of stay (ie. duration of inpatient admission)

	No. of Patients	No. of cycles of HD MTX	Average Age (years)	No. of days to clear MTX	Average LOS* (days)	No. of cycles with delayed MTX clearance
ALL	36	62	60.3 (25 – 83)	4.2	6.8	11
3g/m2	30	51	57.7	4.6	7.3	11
< 3g/m2	6	11	71.7	3	5.3	0

All patients had normal renal function (serum CrCl $>60\text{ml/min}$) prior to methotrexate. All patients received adequate hydration, urinary alkalinisation and leucovorin as per guidelines.⁴ Review of medication histories found that two (3.2%) patients received medications known to interfere with methotrexate clearance.⁵

	No. of cycles complicated by toxicity (%)
Acute kidney Injury (\square Grade 3)	10 (16.1%)
Anaemia (\square Grade 3)	6 (9.6%)
Neutropenia (\square Grade 3)	7 (11.2%)
Neutropenic Sepsis	3 (4.8%)
Mucositis (\square Grade 3)	7 (11.2%)
Acute Liver Injury (\square Grade 3)	2 (3.2%)
Admission to Intensive Care	2 (3.2%)
Death	0 (0%)

Toxicities were attributable to delayed methotrexate clearance in all patients. The average length of stay for patients with delayed methotrexate clearance was 15.6 days. The incidence of methotrexate-related toxicities was similar to those reported in the literature.⁶ One of the 11 patients with delayed methotrexate clearance received glucarpidase. A retrospective review found that 5 of these 11 patients met criteria for glucarpidase based on recently published guidelines.¹

Conclusion: Despite optimal supportive care, toxicity attributable to delayed methotrexate clearance remains a significant cause of morbidity for patients with haematological malignancies. Glucarpidase is an under-utilised treatment. Local guidelines on the criteria for glucarpidase are required as well as studies to assess the longer term clinical impact of its use in this patient population.

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P088. Functional and survival outcomes of central nervous system lymphoma treated in Gold Coast University Hospital

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Aim

Patients with central nervous system (CNS) lymphoma often experience disease and treatment related cognitive and physical decline. This study aimed to evaluate how patients diagnosed with CNS lymphoma at the Gold Coast University Hospital were treated and obtain data on functional and survival outcomes.

Method

Electronic medical records for patients diagnosed and treated for CNS lymphoma between 2010 and 2017 were examined. Data was collected on demographics, treatment protocols used, treatment completion rates, premorbid and post treatment function and abode, time to relapse and time to death.

Results

Twenty-one patients were identified including one patient requiring salvage treatment for relapse. The induction protocol MPV +/- rituximab was used in 19 cases, MATRix in 1 case and high dose methotrexate alone and cytarabine + rituximab in 1 case each. Cytarabine +/- rituximab was used for consolidation in 13 cases, whole brain radiotherapy in 1 case, carmustine/thiotepa with autologous stem cell rescue in 1 case and no consolidation in 7 cases. 19 patients were living independently and prior to diagnosis compared to 13 after treatment. 19 patients were living at home prior to diagnosis with only 15 still at home after treatment. 6 patients were working or studying prior to diagnosis with only 3 still doing so after treatment. At a median follow up duration of 16 months (range 1-60 months), 6 cases (28.6%) had relapsed or were refractory with a median time to relapse of 7 months. Time to death was only available in one case (14 months) with 10 patients lost to follow up.

Conclusion

Survival outcomes are similar to published data. A considerable proportion of patients however suffered significant functional decline affecting their ability to live independently or continue with work or study. This is of particular concern for those who fall below age thresholds for access to funding and care.

P089. WhiMSICAL (Waldenström's Macroglobulinemia Study Involving CArt-wheel): A validation of patient-reported data against the Lymphoma and Related Diseases Registry

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Aim: Waldenström's macroglobulinemia (WM) is a rare lymphoma with an indolent but progressive trajectory⁽¹⁾. Its disease landscape and treatment paradigm is evolving. Patient-reported outcomes are under-utilised in understanding WM's real-world impact. The WhiMSICAL is a collaboration between CART-Wheel.org, a rare cancer database managed by BioGrid Australia, and international WM communities⁽²⁾. It empowers patients to upload clinical data and outcomes. We conducted a validation study to determine its robustness.

Method: WhiMSICAL participants provide consent online at www.cart-wheel.org and enter their data. For those treated at LaRDR (Lymphoma and Related Diseases Registry) Australian sites, self-entered data were paired with registry records retrospectively completed by investigators. Diagnosis date, haemoglobin and IgM and 1st line therapy were used for validation.

Results: As of June 2018, 303 participants from 14 countries have enrolled in WhiMSICAL, mostly from USA (45%) and Australia (23%). Median age was 68y (43-86) and 61% were male. Median age at diagnosis was 60y (41-83), median IgM 2750mg/dL (IQR 1530-3907mg/dL, n=101) and median haemoglobin 11.1g/dL (IQR 9.4-12.7g/dL, n=106). The most common symptom at diagnosis was fatigue, which is associated with lower Hb (10.1g, IQR 8.8-12.1g/dL). Using the Impact of Event Scale (no stress=0, maximal=24) for symptoms of PTSD, 11.8% of respondents (30/254) scored ≥ 13 (PPV 94% for PTSD).⁽³⁾

21 participants were treated at LaRDR sites allowing validation. Among them data completion rate was 74% (78/105 data-fields) in WhiMSICAL and 90% (95/105) in LaRDR. There was a high degree of concordance, with diagnosis date, first treatment date and agents being 78-86% concordant. Diagnosis IgM and haemoglobin had 63% (n=8) and 90% (n=10) concordance, respectively.

Conclusion: The WhiMSICAL represents an innovative and robust platform to generate patient-reported outcomes, particularly symptoms and quality of life. With ongoing recruitment and validation, it has potential to deepen understanding of real-world challenges faced by WM patients.

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P090. Case Study - Bendamustine induced CMV retinitis with permanent vision loss

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Aim

To highlight the serious, yet poorly recognised complication of CMV retinitis with Bendamustine treatment.

Introduction

Cytomegalovirus (CMV) infections are commonly seen in immunocompromised patients, including those undergoing chemotherapy for lymphoma. Bendamustine has been known to cause reactivation of CMV in up to 10-20% of patients treated, leading to pulmonary, neurological, gastrointestinal and cardiovascular complications from active infection. However, Bendamustine induced CMV retinitis resulting in permanent vision loss is a rare but serious complication of treatment.

Result

A 63 year old female with newly diagnosed with Follicular Lymphoma in late 2016, had completed 6 cycles of Bendamustine-Rituximab in January 2017. In May 2017 she developed acute impairment of vision in the left eye.

On examination her visual acuity was 6/9 right eye and 6/60 left eye. Her vision loss was not associated with any pain or trauma to the eye. An Ophthalmologist review noted several foci of resolving retinitis in both eyes, associated with occlusive retinal arteritis and a trace of vitritis consistent with CMV infection.

She was subsequently commenced on Valganciclovir 900mg BD. Her CMV viral load gradually decreased over the following 6 months from 1.56×10^4 to 5.46×10^1 IU/mL, however her significant visual impairment of the left eye persisted.

Conclusion

Caution and vigilance is required when Bendamustine is used for Follicular Lymphoma and other haematological disorders. Monitoring for CMV reactivation with a view to prompt treatment is imperative. Discussion needs to be made on the need for monitoring of CMV PCR and the role of CMV prophylaxis with Bendamustine treatment.

Unfortunately in this case, the patient developed long term visual loss as a result of CMV retinitis despite CMV treatment and a diminishing viral load to the lower limits of detection.

P091. Large and small vessel vasculitis complicating myelodysplastic syndrome

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Introduction

While vasculitis in the context of the myelodysplastic syndrome is a recognised entity, the concurrent development of large and small vessel vasculitis has not been previously reported.

Case report

We present a case of aortitis, ophthalmic vasculitis and leukocytoclastic vasculitis in a 62 year old man with newly diagnosed high risk myelodysplastic syndrome (refractory anaemia with excess blasts) with complex karyotype, shortly after commencement of azacitidine.

Our patient was found to have aortitis on CT during workup for persistent febrile neutropenia. He was commenced on high dose prednisolone after infectious aetiology was excluded. Despite this, within several days he had also developed several erythematous skin lesions found on skin biopsy to be consistent with leukocytoclastic vasculitis. These eventually responded to steroid therapy. One month later during an admission for febrile neutropenia, he developed retinal vasculitis. He was treated successfully with addition of colchicine and escalation of steroid dose. Several months later, his vasculitides have resolved and his MDS has responded to azacitidine therapy.

Conclusion

The myelodysplastic syndrome may be associated with a wide variety of autoimmune phenomena including small, medium and large vessel vasculitis, which may present uncharacteristically. Atypical febrile illness and otherwise unexplained symptoms in patients with myelodysplastic syndrome should prompt consideration of autoimmune pathology.

P092. MDS rates following treatment for metastatic Neuroendocrine Tumour

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Aim

Here we present three cases of MDS we have observed following treatment of patients with metastatic Neuroendocrine Tumour (NET). These cases were identified after *Peptide Receptor Radionuclide Therapy* (PRRT) and sensitising chemotherapy.

Cases

Case 1

A 77yo man developed MDS four years following PRRT plus Capcitabine sensitization for metastatic NET. BMAT confirmed trilineage dysplasia and a complex karyotype. The total cumulative Lu177 dose received was 39.7 GBq.

Case 2

A 76yo man developed high risk MDS with complex cytogenetics 12 years following first exposure to cytotoxic therapy for metastatic NET. The patient received Carboplatin and Etoposide in 2005, with PRRT administered in 2011, 2013 and 2017. The total cumulative dose of Lu177 was 61.7 GBq and and Y-90 was 4.2 GBq. One 5-FU infusion was administered as sensitizing chemotherapy.

Case 3

A 73yo lady presented with a persistent normocytic anaemia 2 years following PRRT for metastatic NET. Trilineage dysplasia on BMAT confirmed MDS with a normal karyotype. She underwent multiple cycles of PRRT with sensitising Cacitabine and infusional 5-FU. The total cumulative dose of Lu177 was 47.4 GBq.

Conclusion

Therapy related myeloid neoplasms have been described as a long term complication of PRRT therapy for metastatic NET with estimates ranging from 1-15%^{1,2}. In our cohort, all cases received relatively high cumulative radiation doses of 40GBq- up to over 60GBq. The latency from initial chemoradiotherapy to MDS diagnosis was 2-12 years. Identification of these cases has prompted a more comprehensive retrospective audit of MDS rates in patients treated for metastatic NET in Tasmania to determine prevalence and examine risk factors.

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P093. The efficacy and costs of azacitidine treatment in myelodysplastic syndromes in an Australian tertiary centre: a matched cohort study

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Background

Azacitidine is an expensive and complex treatment for a subgroup of higher-risk myelodysplastic syndrome (MDS) patients. Previous clinical trials have shown an improved overall survival (OS) compared to best supportive care (BSC).

Aim

This study aims to investigate the efficacy and cost of azacitidine treatment in a large tertiary centre compared to a retrospective international prognostic scoring system (IPSS)-matched cohort treated with BSC prior to the availability of azacitidine.

Method

Between 2010 and 2017, 24 patients received azacitidine. This group was compared with an IPSS-matched control cohort of 21 patients from 2006 to 2010. Hospital admissions, outpatient clinic appointments and transfusion requirements were analysed.

Result

There was no significant difference in age, gender, MDS subtype or IPSS scores between groups. A median of 5 cycles (range 1-25) of azacitidine were given per patient. Bone marrow responses to azacitidine were: CR 0, PR 3, SD 10, 6 not evaluated and 5 transformed to acute leukaemia whilst on therapy. 7 patients achieved red cell transfusion independence at 56 days. There was no significant improvement in median OS in the azacitidine group compared to BSC (1.1 year vs 0.6 year; $P=0.27$). The median cost of azacitidine therapy alone was \$21,849 (range \$2,544-\$134,487). Patients treated with azacitidine had more MDS-related admissions (median (interquartile range) 2 (0.75-5) vs 0 (0-3); $P=0.035$), more clinic appointments (24.5 (13-42) vs 8 (1-13); $P<0.001$), more platelet transfusions (5 units (1-23) vs 1(0-5); $P=0.029$), but similar red cell transfusions (18.7 units (0-24) vs 5.5(0-17) $P=0.19$).

Conclusion

There was no significant improvement in OS but more costs incurred with MDS-related admissions, clinic appointments and platelet transfusions for patients treated with azacitidine compared to BSC. The considerable cost of AZA management may not result in a significant survival advantage in real world clinical practice.

P094. Myeloproliferative Neoplasm in A Secondary Level Hospital of Malaysia: A Cross-sectional Study

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Introduction

Polycythaemia vera (PV), essential thrombocythaemia (ET), and primary myelofibrosis (PMF) are three classical chronic myeloproliferative neoplasms (MPNs) which are BCR-ABL fusion gene-negative. The discovery of molecular markers has improved the understanding on the pathogenesis of this group of stem cell-derived clonal disorders. Despite that, limited published epidemiology data is available on these disorders, especially in Malaysia. Thus, this study aimed to determine the prevalence, clinical characteristics, and outcome of MPNs in a secondary level hospital.

Methods

An observational study was conducted in a district hospital to include patients with diagnosis of MPNs from 2011 till 2016. Demographic data, risk factors, clinical characteristics, complications, treatment, and outcome were analysed.

Results

35 patients were recruited with the median age of 61±16years old and equal gender distribution. The median time from presentation to diagnosis was 6±17weeks. ET accounted for the majority of the patients(43%), while PV and PMF accounted for 40% and 17% respectively. Majority of the patients(54%) were symptomatic upon presentation, which included headache and cerebrovascular accident. All the patients with PV were JAK-2 positive, as compared to ET(67%) and PMF(83%). Venesection was the main cytoreduction modality in PV (85.7%), while hydroxyurea accounted for 80% in ET. The median follow-up was 113 weeks(IQR = 200) with 3 patients developed thrombotic events, while 2 patients (1 each from PV and ET) progressed to myelofibrosis. One patient developed acute leukaemia(AL) and succumbed to death. Haematological profiles during follow-up compared to baseline were significant for PV with regards to haematocrit(p=0.005) and platelet for ET(p = 0.011) and PMF(p=0.028).

Conclusion

The discovery and application of molecular studies has resulted in early diagnosis of BCR-ABL1 negative MPNs. This has resulted in early initiation of treatment, hence, a reduction in thrombotic events. However, 9% of our patients eventually progressed to myelofibrosis and AL, and this remains a challenge yet to be addressed

P096. Aiming for treatment free remission in Chronic myeloid leukaemia

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Background

With the success of tyrosine kinase inhibitors (TKI), many patients with chronic myeloid leukaemia (CML) are able to achieve deep durable molecular control of their disease. A new goal in the management of CML is achieving treatment free remission where patients can maintain control of the condition off treatment. Many studies have examined outcomes after treatment cessation with no consensus on selection criteria of suitable patients. Duration of treatment with TKI and duration of deep molecular response prior to treatment cessation are emerging as predictive variables.

Objectives

In this study, we examine our real-world experience with outcomes of attempts at TKI discontinuation. We also examine the influence of potential prognostic variables.

Patients/Methods

Literature search was performed to identify potential predictive factors. A retrospective review of medical records for patients who have attempted TKI cessation was performed. Statistical analysis was performed to examine outcomes. The primary end-point of this study was the probability of molecular relapse-free survival at 12 months follow-up (Treatment-free remission, TFR).

Results

Thirty-five patients attempted treatment cessation. The probability of treatment free remission was 51% at 12 months. No significant associations were noted between Sokal risk score or time taken to achieve complete molecular remission and the probability of treatment free remission. Duration of TKI therapy was longer in patients maintaining TFR however results were not statistically significant.

Conclusions

Overall, our patient group had comparable outcomes to that reported in clinical trials. Low patient numbers prevented any conclusions to be drawn regarding associations between various prognostic predictors and rate of molecular relapse free remission.

P097. Ruxolitinib induced leukemoid reaction presenting as Sweets Syndrome: A Case Report

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Background

Ruxolitinib is a JAK2/JAK1 inhibitor used for primary myelofibrosis (MF) and has shown benefit in reducing MF symptoms, prolonging overall survival and reducing splenomegaly (1). Ruxolitinib can cause anaemia, leucopenia and thrombocytopenia through JAK inhibition in the bone marrow (1).

Case Synopsis

A 60-year-old presented with facial and limb skin lesions 3months after starting ruxolitinib 10mg twice a day. The patient had been treated for MF with ruxolitinib after developing pancytopenia with hydroxyurea. The patient had shown MF symptomatic improvement and a reduction in massive splenomegaly. The white cell count was 31.2mmol/L and the skin lesion after a biopsy and negative culture revealed a diagnosis of Sweets syndrome. Bone marrow did not show any leukaemic transformation and there was no evidence of systemic infection.

Discussion

We postulate that a reduction in splenomegaly secondary to ruxolitinib treatment lead to a decrease in splenic white cell sequestration, subsequent leucocytosis and neutrophilic dermatosis. Concurrent use of cytoreductive agent may be considered for uncontrolled leucocytosis.

Conclusion

In patients with massive splenomegaly, ruxolitinib splenic volume reduction may lead to a paradoxical leukemoid reaction that may presents as Sweets syndrome.

References

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P098. The need for a QAP program for amyloid biopsies: Experience at the Victorian and Tasmanian Amyloidosis Service (VTAS)

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Introduction

Amyloidosis is a heterogeneous group of diseases characterised by tissue deposition of misfolded proteins as amyloid fibrils. Congo red positivity on biopsies with apple-green birefringence is the gold standard of diagnosing amyloid, however, this can be difficult and subtle. Immunohistochemistry (IHC) is mandatory to accurately determine amyloid type and treatments. Background staining can make interpretation difficult. Transthyretin (TTR) IHC is essential for cardiac, bladder and bone marrow biopsies, AA for renal, and kappa/lambda for all histology. VTAS has fortnightly multidisciplinary meetings, with histology reviews. We audited our experience of histology reviews to determine the frequency and type of IHC performed externally, and whether our reviews altered diagnosis and management.

Methods

We performed a retrospective audit of all biopsies assessed at VTAS meetings 2015-2017.

Results

189 biopsies from 149 patients were reviewed, 88% (n=171) from external laboratories.

Amyloid was present in 85% (n=146) of external biopsies, 78% (n=133) had amyloid reported by the original laboratory (false negative rate 9%). In 2 cases, amyloid was reported by the original laboratory but not confirmed on review (false positive rate 1%). Sub-classification of amyloid was attempted externally in 50% (n=66); but of these, IHC was incomplete in 50% (n=33). Thus, only 25% had full amyloid IHC workup.

We attempted sub-classification on 83 of these biopsies. 41% (n=34) had diagnostic immunoprofiles: 59% (n=20) AL, 32% (n=11) TTR and 9% AA (n=3). Biopsies unable to be typed underwent mass spectrometry. In 32% (n=21), interpretation of amyloid type was altered on review.

Conclusion

The false negative rate of 9%, incomplete IHC in 75% and change in interpretation in 32% highlights the need for greater education and expert review of amyloid biopsies. Laboratories without full IHC panels should be considered referring histology to an Australian Amyloidosis Network service for review. This study highlights the need for a QAP program for amyloid histology.

P099. Case Report: Toxic shock syndrome in a patient with multiple myeloma

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Background

Toxic shock syndrome (TSS) is a rare, life-threatening disorder resulting in multi-organ dysfunction. This case presentation details the diagnosis and management of TSS in a patient with multiple myeloma (MM) previously managed with autologous stem cell transplantation (ASCT).

Case Presentation

A 62 year old female, 8 months post ASCT for multiple myeloma presented with fever, conscious collapse and 1 day history of diarrhoea and vomiting. Rapid deterioration occurred within 24hrs including the development of disseminated intravascular coagulopathy (DIC) (platelet count 4×10^9 , INR 3.8, APTT 51s, D.Dimer 17.8mg/L), acute kidney injury (AKI) (creatinine $297 \mu\text{mol/L}$) and refractory hypotension necessitating transfer to the intensive care unit for inotropic support and escalation of antibiotics. Septic screening did not yield any microbial source. Within 1 week an erythematous rash developed across her face and torso with significant swelling of her hands and feet which progressed to extensive desquamation to the level of the dermis to approximately 50-60% of her total body surface area including face, torso, limbs and mucosal surfaces. A clinical diagnosis of TSS was made and managed with broad spectrum antibiotics with burns wound management until resolution of symptoms.

Discussion

Toxic shock syndrome is a rare, acute life-threatening condition with an incidence of 0.07 per 100,000 people. It is predominately a clinical diagnosis consisting of fever, rash, desquamation and hypotension followed by multi-organ impairment including gastrointestinal, muscular, renal, hepatic, haematological abnormalities and neurological disturbance. On screening for risk factors for TSS, an acquired IgA deficiency post ASCT was identified with IgA reported at $<0.07\text{g/L}$.

Conclusion

This case highlights a rare presentation of TSS in a patient with MM with an acquired immunodeficiency post ASCT. Prompt recognition of the disorder is critical for timely introduction of appropriate antibiotics and management with supportive care of other organ complications.

P100. Pattern of immune system reconstitution after allogeneic stem cell transplant (alloSCT) for multiple myeloma (MM) using the EuroFlow-MM assay

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Introduction

The 8-colour EuroFlow-MM multiparametric flow cytometry (MFC) assay is used for minimal residual disease (MRD) testing in MM, however identification and quantification of B-cell subsets (precursor B-cells, naïve B-cells and memory B-cells), T-cell and NK-cell populations¹ is also possible.

Aims: to use the EuroFlow-MM assay to describe the pattern of immune cell reconstitution after alloSCT for MM and assess the impact of these populations on transplant outcomes.

Method

Single centre retrospective audit of all MM patients with sequential EuroFlow-MM assessments post non-myeloablative alloSCT, following introduction of the assay into routine post alloSCT care (11/2014). EuroFlow MRD assessments were undertaken at 3, 6, 9, 12, 18m then yearly post-alloSCT. Clinical data collected: demographics, MRD status, survival (relapse/death), CD3 chimerism and acute graft versus host disease (aGvHD). Statistical analysis was performed in Excel.

Results

30/35 patients who had undergone NMA alloSCT for MM (11/2014 to 11/2016) and had EuroFlow-MM data at 3 months post-alloSCT were included. Median age: 58 years.

There was no significant change in the absolute number or relative proportions of B, T or NK cell populations over time post-alloSCT (3, 6 and 9m).

At 3 months post-alloSCT, patients with the highest proportion of T-cells (upper quartile) when compared with those with the lowest proportion (lower quartile) had superior CD3 chimerism at 3m (99.0% vs 79%, p=0.004) and increased incidence of aGvHD (87% vs 37%, p=0.02). However, there was no association with achievement of MRD negativity (67% vs 37%, p=0.175), relapse (37% vs 67%, p=0.175) or death (25% vs 37.5%, p=0.30).

Conclusion

The EuroFlow-MM assay may have additional utility aside from MRD, providing additional information about the non-MM/immune cell compartment, and in patients post alloSCT, may potentially identify those with poor engraftment as well as those with a higher risk of GVHD

These findings provide rationale for further studies.

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P101. Efficacy of Bortezomib, Cyclophosphamide and Dexamethasone in Cardiac AL Amyloidosis

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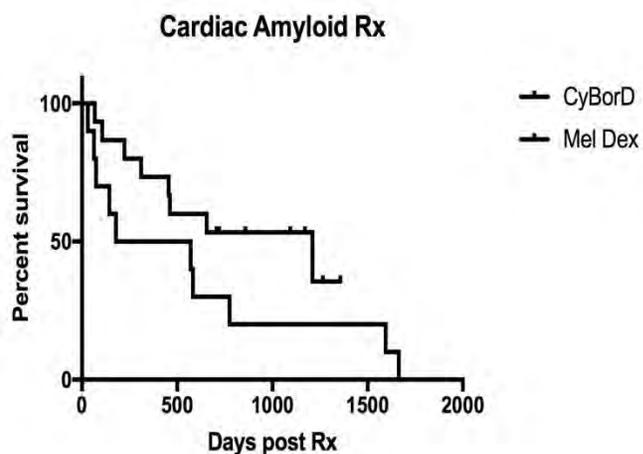
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Aim: To review the disease free and overall survival of patients with cardiac AL amyloidosis treated with bortezomib, cyclophosphamide, and dexamethasone (CyBorD) when compared to the melphalan and dexamethasone (MDex) regime. Secondary objective include the haematological response to CyBorD

Methods: A retrospective single centre study with patient data collected from St. Vincent's Public Hospital and the Kinghorn Cancer Centre. Diagnosis of AL Amyloidosis was confirmed by myocardial biopsy with haematological and cardiac staging confirmed on blood tests. 41 patients were identified between 1997 and 2017 with 16 being excluded as did not receive chemotherapy.

Results: A total of 15 patients received CyBorD (median age 61, 46% male) and 10 patients MDex chemotherapy (median age 63yrs, 60% males) . The median survival for the CyBorD group was 710 days (range: 67-1265 days) compared to 567 (range: 31-1664 days) for Mdex (as per below KM curve). 8/15 (53.3%) patients in the CyBorD group had a very good partial response (VGPR) compared to 2/10 (20%) in the Mdex during the first 12 months post chemotherapy. In terms of cardiac stage the CyBorD group had worse cardiac involvement with 6 patients having stage IV disease and no patients in Mdex meeting this criteria.

Conclusion Cardiac AL Almyoid Patients who received CyBorD compared to Mdex appear to have improved survival and more patients achieved a VGPR.



P102. Efficacy of frontline CyBorD chemotherapy in elderly transplant ineligible myeloma patients: retrospective single centre review

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Introduction

CyBorD is a well-established induction treatment for patients with newly diagnosed multiple myeloma who are transplant eligible. The purpose of this study is to review the efficacy of such treatment strategy in the elderly population.

Methods

Consecutive patients aged 70 or above, with newly diagnosed multiple myeloma, who received at least one cycle of CyBorD between 1 January 2012 and 31 August 2017 were included. Patients who received any prior anti-myeloma treatment or autologous stem cell transplantation were excluded.

Results

A total of 68 patients were included in the study. The median age was 78.7 (range 70.7 – 93.0), and 55.9% of the patients were male. The median Charlson Co-morbidity Index was 4 (range 2 – 9), and the median eGFR was 51ml/min. The median number of cycles of bortezomib-based chemotherapy given was 5 (range 1 – 9). Thirty-nine (57%) patients achieved at least a VGPR, and 14 (21%) achieved a partial response. The overall response rate was 78%. The median event-free survival (calculated from date of diagnosis to either change of treatment due to suboptimal response, toxicity, disease progression or death by any cause) was 18.4 months (18.5 months for <80 vs 17.9 months for ≥80, $p = 0.084$), and the median progression-free survival was 19.5 months (21.6 months for <80 vs 18.4 months for ≥80, $p = 0.067$). Median duration of response for those who achieved at least PR was 21.6 months, and the median overall survival was 42.8 months (57.6 months for <80 vs 30.2 months for ≥80, $p = 0.018$).

Conclusion

Our real-world data demonstrates a respectable long-term outcome for elderly transplant ineligible patients treated with CyBorD despite the age and frailty of this cohort.

P103. Preference alignment in the treatment of multiple myeloma in Australia – patient, carer, physician and nurse preference study

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Aim

Multiple Myeloma (MM) is a cancer of plasma cells. In Australia, approximately 1700 people are diagnosed with MM each year (equivalent to 4 people every day). This paper outlines a study designed to examine MM patient preferences for treatment and compare to treatment preferences of other groups involved in treatment decision making; including carers of patients (often family members), as well as physicians and nurses who treat patients with MM.

Method

Data were collected using discrete choice experiments (DCEs) through an online survey. The DCEs presented participants with a traditional treatment choice experiment (e.g., treatment A vs treatment B), focusing on the clinical benefits of treatments and the associated risks. The attributes and levels of the attributes were selected based on previous research, literature review and expert opinion. The DCE data were modelled using a Latent Class Model (LCM) and Mixed Multinomial Logit Model (MMNL).

Results

Both the LCM and MMNL revealed significant heterogeneity in preferences for treatment attributes. In particular, overall survival, remission period and annual out of pocket cost were the attributes with the most variation. In comparison to patients, carers were less cost sensitive and concerned more with quality of life (remission period). Physicians and nurses were generally more concerned with overall survival and more cost sensitive than patients.

Conclusion

This study demonstrated that not all MM patients valued the same treatment attributes equally. Further, not all groups involved in MM treatment decision making had preference alignment on all treatment attributes. This has important implications for healthcare policy decisions and shared decision making. Results from this study could be used to guide decisions around the value of new MM medicines.

P104. Background rate of venous thromboembolism in patients undergoing treatment for Multiple Myeloma

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Introduction: Malignancy increases a persons risk for thrombotic complications. Studies have shown that VTE occurs in as many as 10% of patients with a cancer diagnosis¹ with higher rates seen in myeloma.

Aim: The aim of this audit was to determine the incidence of VTE in our patient cohort undergoing treatment for Multiple Myeloma. Secondary aims included; determining what anticoagulation was used to treat VTE and VTE recurrence.

Methods: Data was collected on patients undergoing treatment for myeloma between Jan 1st 2017-Dec 31st 2017. Patients receiving Bortezomib, Thalalidomide, Lenalidomide, Pomalidomide, Carfilizomib, Daratumumab were included.

Results: 88 patients were included. Ages from 39-90 (mean 68). VTE occurred in 11/88 (12.5%), 4/11 female (36%).

PE was the most common event 64% (7 patients), 27% (3 patients) had a DVT and 1 patient (9%) had a co-existing DVT/PE.

Most common circumstance of VTE was on treatment with Lenalidomide/Dexamethasone and aspirin (fig 1).

Of these patients: 5 were treated with a NOAC, 5 Warfarin and 1 patient LMWH.

5 patients remained on anticoagulation for duration of treatment. Of these patients; 4 remain on a NOAC with 1 patient on Warfarin.

Indications for ceasing anticoagulation include: at patient's behest (1), ITP (1), bleeding complications (1), treatment duration of 6months (1), unknown (2).

2 patients had recurrence of VTE. The first while on subtherapeutic Rivaroxaban (dose reduced at patient's request). The second patient had ceased anticoagulation at the time of his 2nd event.

Conclusion: VTE events occurred at a rate of 12.5% in keeping with literature. 45% of our patients with VTE were treated with NOACs. The recent Edoxaban for Cancer Assoc Thrombosis trial demonstrated equivalence between edoxaban and dalteparin for the end point of VTE recurrence or major bleeding². Our patient cohort seems to provide real world data supporting these findings. Further RCT are required.

References:

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P105. Myeloma in Queensland: a retrospective review of the impact of treatment era, socioeconomic status (SES) and residence on survival

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Aim: Multiple Myeloma over the past 30 years has had a rapidly changing treatment landscape. This study examines predictors of relative survival (RS) in Queensland.

Method: This is a retrospective population-based study of all Queensland patients with MM diagnosed from 1982 to 2014 with data extracted from the Queensland cancer database OAsys. Three treatment eras were defined: 1: 1982-1995, chemotherapy alone (n=1432); 2: 1996-2007, introduction of autologous transplantation (n=2400); 3: 2008-2014, introduction of novel agents (n=2099).

Result: 6025 patients were identified: 43% females; median age at diagnosis 70yrs. In multivariate analysis (Table 1), there was a significant improvement in survival across all 3 treatment eras: 5-yr RS 30% vs 43% vs 54% (P<0.001). Affluent and middle SES conferred a survival benefit over disadvantaged SES, as did living in an urban area over rural. Gender did not impact RS but increasing age was associated with worse RS.

Improvement in survival across eras was seen in all age groups. The median OS of those <60yrs and 60-69yrs increased from 3.76 to >8.95-yrs and 2.67 to 7.22-yrs by era 3, respectively. Those 70-79-yrs and >80-yrs increased median OS from 1.89 to 3.89-yrs and 0.67 to 1.56-yrs, respectively.

Table 1. Multivariate analysis of Relative Survival		HR [95% CI]	p-value	5yr RS
Era	1982-1995	-	-	30%
	1996-2007	0.62 [0.57-0.68]	<0.001	43%
	2008-2014	0.46 [0.41-0.51]	<0.001	54%
Residence	Urban	0.85 [0.78-0.92]	<0.001	45%
	Rural	-	-	40%
SES	Affluent	-	-	45%
	Middle	1.04 [0.93-1.17]	0.476	44%
	Disadvantaged	1.23 [1.07-1.40]	0.004	39%
Age group	<60	-	-	60%
	60-69	1.32 [1.17-1.49]	<0.001	52%
	70-79	2.17 [1.94-2.43]	<0.001	35%
	80+	3.91 [3.47-4.40]	<0.001	21%

Conclusion: The relative survival of both younger and older patients with myeloma has significantly improved over treatment eras. Survival is worse among the economically disadvantaged and those living in rural communities.

P106. Global coagulation assays in patients with multiple myeloma and monoclonal gammopathy of unknown significance

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Aim: To evaluate the utility of global coagulation assays (GCA) in assessing the clotting profiles of patients with multiple myeloma (MM) and monoclonal gammopathy of unknown significance (MGUS) in comparison to normal controls.

Method: Blood samples from patients were sent for routine laboratory tests and GCA testing. The GCA examined were (i) thromboelastography using TEG®, (ii) thrombin generation via calibrated automated thrombogram (CAT) and (iii) fibrin generation via the overall haemostatic potential (OHP) assay. Citrated whole blood was used for TEG® whilst platelet poor plasma was used for CAT and OHP. Results from these studies were then compared to previously collected normal controls (n=96). Statistical analysis was performed using IBM SPSS, version 23.0.

Results: Thirty-two patients (MM n=14, MGUS n=18) were recruited. Compared to normal controls, the study group demonstrated significantly higher factor VIII, von Willebrand factor antigen, von Willebrand factor activity and D-Dimer levels (p<0.001). Study patients showed hypercoagulable TEG® results with significantly increased maximum amplitude (68.9 mm vs 57.9 mm, p<0.001) and reduced clot lysis (0.0% vs 0.6%, p<0.001). Thrombin generation parameters including endogenous thrombin potential, velocity index and thrombin peak were also elevated. The overall coagulation potential and overall haemostatic potential parameters were increased in our study patients (p<0.01) with otherwise preserved overall fibrinolytic potential. Interestingly, there were no significant differences across assays when comparing MM to MGUS patients. Paraprotein levels and subtypes did not correlate with differences in GCA parameters.

Conclusion: Our findings suggest that GCA can be used to differentiate the haemostatic profile of MM and MGUS patients from normal controls. These patients demonstrated a significant hypercoagulable state made evident by thromboelastography, increased thrombin and increased fibrin generation. Future studies are required to correlate these findings with the clinical risk of thrombosis.

Table 1: Comparison of investigation results between study patients and normal controls

	Normal Controls (n = 96)	MM & MGUS (n = 32)	p-value
Factor VIII (%)	101.0	157.0	<0.001
von Willebrand factor antigen (%)	102.0	157.0	<0.001
von Willebrand factor activity (%)	102.0	148.0	<0.001
D-dimer (ng/mL)	190.0	540.0	<0.001
Thromboelastography (TEG®)			
R-time (min)	6.9	4.7	<0.001
a-angle (°)	58.0	62.5	0.055
Maximum amplitude (mm)	57.9	68.9	<0.001
Lysis 30 (%)	0.6	0.0	<0.001
Calibrated automated thrombogram			
Lag time (min)	3.1	3.1	0.826
Velocity index (nM/min)	65.0	88.5	0.009
Endogenous thrombin potential (nM.min)	1347.6	1459.2	0.035
Thrombin peak (nM)	222.6	263.8	0.002
Overall haemostatic potential assay			
Overall coagulation potential (%)	59.7	67.1	0.005
Overall haemostatic potential (%)	27.5	32.2	0.002
Overall fibrinolytic potential (%)	52.2	47.6	0.170

P107. Physician survey sheds light on the use of minimal residual disease (MRD) testing in patients with multiple myeloma (MM)

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Background

Clinical studies have shown the correlation between MRD negative status and progression-free and overall survival; in 2016, the International Myeloma Working Group (IMWG) published guidance for the use of MRD testing in clinical practice. This survey study sought to explore the use of MRD testing in MM practice one-year post-guidance release.

Methods

Oncologists and haematologists/oncologists from the United States who concurrently managed ≥ 3 MM patients were recruited to participate in a 20-minute online survey. Descriptive analyses of survey responses were conducted for the total sample and stratified based on physicians' self-reported characteristics (practice setting, MM patients treated annually, and percent that received MRD testing).

Results

200 physicians completed the survey from September-November 2017. The majority were primarily affiliated with a community centre/hospital (n=125, 63%), treated a high volume of MM patients annually (>30) (n=116, 58%), and used MRD testing on $\geq 1\%$ of patients (n=159, 80%). Overall, 31% of MM patients currently receive MRD testing; this was similar in both academic and community settings (33% and 30%, respectively). The top reasons endorsed by non-MRD testers (n=41) for lack of testing were that results would not change their treatment approach (n=25, 61%), uncertainty on how to apply results (n=23, 56%), and lack of data/guidelines supporting its use (n=22, 54%). The majority of physicians (n=117, 59%) reported being somewhat familiar with MRD testing in MM. 31% of physicians (n=82) were not aware of IMWG guidelines, while out of those who were (n=118), 62% (n=73) reported some familiarity. Guidelines on MRD use to assess complete response was most top of mind (n=46, 39%).

Conclusions

Despite most physicians (80%) having experience with MRD testing in MM practice, uncertainty around the value of testing and lack of familiarity with guidelines persist, underlining opportunities to expand the knowledge of MRD testing in MM.

P108. Significant rates of MGUS are seen in TTR amyloidosis: potential for the wrong diagnosis

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Aim

Bone scintigraphy has significantly simplified diagnosis of TTR. Up to 5% of men >75 years with LV hypertrophy (LVH) have TTR, yet incidence in Australia and uptake of novel treatments seems low. We audited our experience at the Victorian and Tasmanian Amyloidosis Service.

Methods

52 patients (51 male, 1 female) were diagnosed with wild-type TTR from September 2014 to January 2018. Cardiac biopsy confirmed TTR in 18, biopsies from other sites in 8. All had suggestive echocardiograms, 48 underwent bone scintigraphy, all demonstrating cardiac uptake - Perugini score 3, 2, and 1 seen in 22, 24 and 2 respectively. Genetic screening in 9 patients confirmed wild-type (non-hereditary) disease. Thirty-seven (71%) had carpal tunnel syndrome (CTS), 8(15%) had co-existing plasma cell dyscrasiae.

Results

Using Gillmore staging (NTproBNP and eGFR): 24 (46%) were Stage I, 20 (38%) Stage II, 8 (15%) Stage III. Treatment to slow disease progression included: diflunisal in 19 patients (median 7 months; range 1-26), doxycycline in 16 (median 8; range 1-20) and epigallocatechin gallate (EGCG; green tea extract) in 26 (median 8; range 1-28). Discontinuation rates from toxicity were: diflunisal 37%, doxycycline 19%, EGCG 19%.

At 12 months median follow-up (range 1-41), 8 (15%) patients died: five Stage II, three Stage III.

Conclusion

Our data confirms bone scintigraphy reliably detects TTR. There is marked male bias for wild-type TTR. Despite short follow-up, Gillmore staging predicted prognosis and TTR treatments are reasonably tolerated. In men >75 with LVH and CTS, bone scintigraphy should be performed and if positive, consider TTR treatment. Frequency of co-existing MGUS in this population highlights the importance of immunohistochemistry in order to accurately define the amyloid subtype.

P109. Time for tea? A retrospective, single-center study of epigallocatechin-3-gallate (EGCG; green tea extract) in wild-type transthyretin amyloid cardiomyopathy

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Introduction

There is a paucity of treatments for wild-type (non-hereditary) transthyretin amyloid cardiomyopathy (TTR-AC). EGCG, the most abundant catechin in green tea, has been shown *in-vitro* to inhibit amyloid fibrillogenesis by binding native unfolded precursor polypeptides and preventing conversion into toxic intermediates. Two observational studies have reported clinical activity of EGCG in TTR-AC (Kristen *et al*, 2012, Siepen *et al*, 2015)

Methods

We performed a single-centre, retrospective observational study of TTR-AC patients treated with EGCG 450 to 600mg daily at the Victorian and Tasmanian Amyloidosis Service from September 2014 to May 2018. Data was collected on tolerability and efficacy including serial cardiac biomarkers (Troponin T and NT-proBNP) and echocardiograms. Decreasing/increasing NTproBNP concentrations was defined as change of >30%.

Results

26 patients were identified, all male, with Gillmore Stage I disease in 10 (38%), Stage II in 14 (54%); and Stage III in 2 (8%). Eleven (42%) patients had co-existent MGUS and 22 (85%) had history of carpal tunnel syndrome. Median follow-up post-commencement of EGCG was 11 months (range 1-29) with three patients lost to follow-up. 19 patients had EGCG for ≥6 months. Four (21%), 11 (58%) and 4 (21%) had decreasing, stable and increasing NTproBNP levels respectively. Follow-up echocardiograms were available for six patients, none demonstrating progressive disease. Three of 23 patients (13%) discontinued EGCG at median 6m (range 2-15) due to dysrhythmia, insomnia, gastrointestinal symptoms or liver toxicity, all potential but not definitive toxicities. One died from disease progression whilst on EGCG.

Conclusion

This is one of the largest reported case series of TTR-AC treated with EGCG. Co-incidental MGUS and carpal tunnel syndrome are common. Within limitations of a small retrospective cohort, we conclude that EGCG is associated with cardiac biomarker stabilisation and is largely well tolerated. Prospective studies in TTR-AC and AL amyloidosis are needed.

P110. KRAS-mutated myeloma cells' adaptation to glutamine-deprived conditions is linked to autophagy and macropinocytosis

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Aim

Sustained cancer cell growth requires up-regulation of nutrient acquisition mechanisms. Novel approaches can identify "tumour fuel", the way it is obtained and then altered for cellular usage. We investigated the contribution of macropinocytosis and autophagy as the cellular mechanisms involved in protein uptake and degradation, respectively, to myeloma cells growth and survival.

Method

Macropinosomes were visualized using confocal microscopy in KRAS-mutated and WT human myeloma cells utilising TMR-dextran and 5-[N-ethyl-N-isopropyl] amiloride (EIPA) as a marker and specific inhibitor of macropinocytosis, respectively. Degradation of internalized albumin and its co-localization with TMR-dextran were evaluated. Cell sensitivity to glutamine deprivation was examined with an ATP-based viability test. To evaluate the possible role of macropinocytosis and autophagy under glutamine-deprived conditions, the effect of albumin supplementation on cell growth and viability was studied in the presence or absence of EIPA or chloroquine. The intracellular concentration of glutamine was directly measured after albumin supplementation.

Result

KRAS-mutated KMS28-PE, KMS18 and MM1S cells showed heightened EIPA-sensitive macropinocytosis compared to WT-KRAS KMS34, KMS12-BM and TK1 cells. Macropinocytosis led to internalization and subsequent degradation of albumin. The viability of WT-KRAS cells was reduced in sub-physiological concentrations of glutamine when compared with KRAS-mutated cells that remained viable and even continued to slowly proliferate over 7 days. Glutamine rescued the compromised growth of KRAS-mutated cells at low concentrations of albumin, which was abrogated by EIPA or chloroquine ($p < 0.05$). KRAS-mutated cells demonstrated an EIPA-sensitive increase in intracellular concentration of glutamine following albumin supplementation ($p < 0.05$) abrogated by chloroquine. In WT cells, however, intracellular glutamine level remained unchanged.

Conclusion

Autophagy and macropinocytosis maintain cellular growth and survival in the context of nutrient deprivation by provision of glutamine, and potentially other amino acids, in RAS-mutated myeloma. These data suggest that novel anti-cancer strategies interrupting these cellular mechanisms may represent a promising therapeutic approach to myeloma.

P111. Health-related quality of life (EQ-5D-5L) at diagnosis in patients with multiple myeloma in the Myeloma and Related Diseases Registry

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Aim: Multiple myeloma (MM) is an incurable disease associated with high disease burden and health-related quality of life (HRQOL) assessment can help to optimise patient care.

Method: HRQOL was assessed using the EQ-5D-5L questionnaire at diagnosis in MM patients in the MRDR (Jan 2013 - Apr 2018). Stata version 15.1 was used.

Results: 413 patients on the MRDR had completed all 5 EQ5D domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and the EQ VAS score (self-rated health status from the worst [0] to the best [100] health imaginable). Median age was 67y (60-74) and 65% were male. Characteristics did not differ substantially between patients who completed the EQ5D (n=413) and those who did not (n=848).

In self-care (washing or dressing), 69% of pts reported no problems at diagnosis, while only 22% were pain-free. Problems with mobility were reported in 55%, anxiety/depression in 56%, and problems with usual activities in 68% of patients at diagnosis.

41% of patients reported moderate to extreme problems in usual activities and 39% in pain/discomfort. With increasing age, more patients had problems with mobility, self-care and usual activities ($p \leq 0.009$), and a lower EQ VAS score ($p = 0.04$). As disease stage (ISS) increased, limitations in mobility and usual activities were more frequent ($p \leq 0.01$), and EQ VAS score reduced (0.005). Problems in all 5 health domains were more frequent in patients with ECOG ≥ 2 and EQ VAS score was lower (53 ± 21 v 74 ± 18) compared to ECOG < 2 ($p < 0.001$).

Problems with mobility, usual activities, and EQ VAS score were associated with a higher risk for early mortality (12m post diagnosis, $p < 0.05$) in univariate analyses.

Conclusion: Pain/discomfort was the most frequently reported health issue in MM, and self-care related problems the least, compared to the other health domains. Also, more health problems were reported with increasing age, ECOG ≥ 2 and increasing disease stage (ISS).

P113. Retrospective survival review of patients with multiple myeloma in Western Australia public hospitals over the recent 10 years period

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Background

In Western Australia (WA), multiple myeloma is mainly managed by tertiary public hospitals located in Perth and private practices despite the massive land area of the western state.

Aim

To estimate overall and R-ISS staging specific survival time for patients with multiple myeloma in WA public healthcare.

Method

Patients diagnosed between 2008 to 2017 and managed in the 4 tertiary hospitals were included (n=569). Staging information was extracted retrospectively from the laboratory information system (LIS) and the cytogenetic database within PathWest. Patient demographics, complications requiring admission, mortality and follow-up data were extracted using the Cobra auditing software and clinical manager (iCM). Private patients (n=434) that were diagnosed and/or followed-up in the private sector were excluded.

Patients are staged with the revised international staging system (R-ISS) established by Palumbo et al with biomarkers including initial serum albumin, beta-2-microglobulin, lactate dehydrogenase levels and specific cytogenetic abnormalities. Survival was analysed with Kaplan-Meier curves and Logrank test.

Result

Median age at diagnosis was 67 years old (range 29 to 98), with 56% above 65 year olds. 56% were males, 44% were females.

Overall median survival was 46 months (95%CI:41,52). 1-year, 3-years and 5-years survival rates were 80%, 56% and 30% respectively. Median survival by R-ISS staging was 78(95%CI:58,95) months for stage I, 48 (95%CI:41,60) months for stage II, and 33 (95%CI:27,37) months for stage III. (p<0.0001)

No statistically significant difference in survival time between patients from metropolitan and non-metropolitan areas was detected (47 months 95%CI:43,54 and 42 months 95%CI: 33,54 respectively, p=0.2).

Conclusion

This retrospective study provides real life survival data that is risk stratified by the R-ISS, in an Australian-based population and public practice environment. Mortality outcomes of rural/remote patients were not significantly compromised, giving credit to the support network for travel, accommodation and Telehealth.

Reference:

Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. *Journal of Clinical Oncology*. 2015;33(26):2863-2869. doi:10.1200/JCO.2015.61.2267.

P114. Role of BNP in predicting cardiovascular adverse effects associated with the proteasome inhibitor carfilzomib in multiple myeloma

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Aim

Despite the reproducible incidence of carfilzomib-associated cardiovascular adverse events (CVAEs) in the treatment of multiple myeloma, the clinical course and underlying mechanisms have not been well described, and the utility of brain natriuretic peptide (BNP) remains incompletely characterised. This study aimed to determine the clinical nature of carfilzomib-associated CVAEs, the pattern of BNP changes during carfilzomib therapy, and investigate BNP's usefulness as a predictive biomarker for CVAEs.

Method

In this single-centre retrospective review of 76 patients who received at least one cycle of carfilzomib, patients had serial BNPs performed during each week of carfilzomib infusion of every cycle. The incidence of grade ≥ 3 CVAEs was characterised using summary statistics. The association between persistently elevated BNPs and increased incidence of CVAEs was tested using Student's t-test.

Results

The overall incidence of grade ≥ 3 CVAEs was 46.1%. Treatment-emergent grade ≥ 3 hypertension, dyspnoea and cardiac failure were reported in 27.6%, 23.7% and 13.2% of patients respectively. Of the 62 patients who had serial BNPs, 54 (87.1%) had elevated levels (BNP >100 ng/L). There was a significant increase in the incidence of grade ≥ 3 CVAEs in patients whose mid-cycle BNPs were elevated in $\geq 50\%$ of measurements during the first 4 cycles of carfilzomib compared to those who did not (65.5% vs. 25.0%, $p=0.0084$). In patients with dyspnoea, persistently elevated mid-cycle BNPs trended towards an increased incidence of pulmonary hypertension as detected on transthoracic echocardiogram (21.7% vs. 7.9%, $p=0.0543$).

Conclusion

The incidence of grade ≥ 3 CVAEs reported in this real-world single-centre setting was higher than reported in clinical trials. Serial mid-cycle BNPs performed during the first 4 cycles of carfilzomib may be a useful biomarker for identifying patients at risk of CVAEs. Persistently elevated BNP appeared to be predictive for pulmonary hypertension and this relationship supports endothelial dysfunction caused by carfilzomib both systemically and within the pulmonary vasculature.

P116. Loss of CD38 expression in relapsed multiple myeloma following daratumumab therapy

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Daratumumab is a humanised monoclonal antibody targeting CD38, an antigen variably, but frequently highly expressed on the surface of plasma cells. We present the case of a heavily pre-treated multiple myeloma (MM) patient, with CD38+ plasma cells which became CD38– concomitant with refractoriness to daratumumab.

Case report

A 62-year-old male was diagnosed in 2011 with IgG kappa MM. His initial paraprotein was 44g/L, with sheets of cytogenetically normal plasma cells infiltrating the marrow. He had received six lines of therapy prior to daratumumab treatment, with variable responses. Prior to commencing daratumumab, a bone marrow biopsy demonstrated cytogenetic evolution with hyperdiploidy, gain of 1q and monosomy 7. Flow cytometry demonstrated a monoclonal plasma cell population that was CD38+, CD138+, CD56+ and CD19–.

He initially responded to daratumumab, but relapsed after four cycles with multiple extra-medullary plasmacytomas. Marrow biopsy at relapse showed 70% plasma cells, with a clonal population that showed dim to no CD38 expression by flow cytometry (Figure 1), but had an otherwise similar immunophenotype to the pre-therapy clone.

Discussion

CD38– MM after daratumumab is uncommon, with only one other case described in the literature. The mechanism whereby CD38 expression may be lost remains unclear. It has been postulated that daratumumab may induce downregulation of CD38 by epigenetic mechanisms or result in the positive selection and expansion of small pre-existing CD38– clones.

Awareness of the potential for myeloma cells to lose CD38 expression is important for accurate assessment of disease response, especially after anti-CD38 therapy. An improved understanding of the mechanism(s) underlying both primary and acquired resistance to daratumumab will help guide future strategies to optimise its use in treating MM.

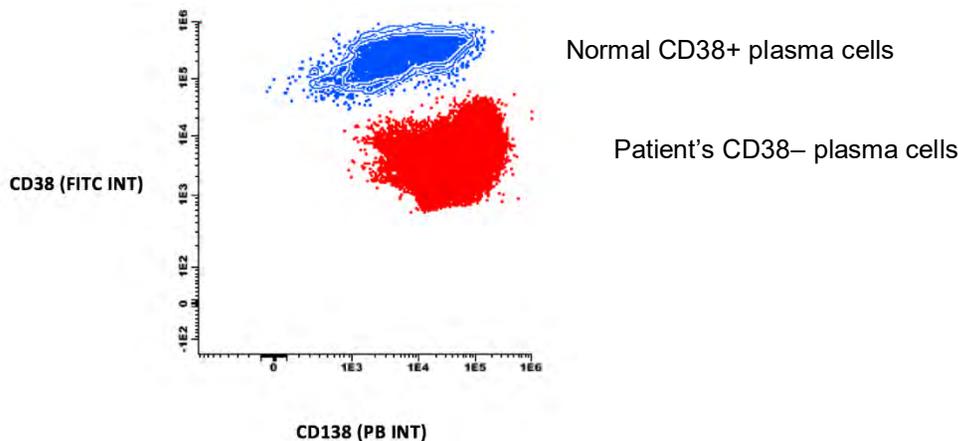


Fig 1. Patient's CD38– clonal plasma cells (red) compared to normal CD38+ plasma cells (blue)

P117. Atypical plasma cell infiltrate in renal cell carcinoma

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Plasma cell infiltrates can be seen in inflammatory and malignant processes. We report an unusual case where an inflammatory plasma cell infiltrate mimicked renal plasma cell dyscrasia by demonstrating light chain restriction and low level paraproteinaemia.

This case features a 62 year old female who underwent right total nephrectomy for the management of renal cell carcinoma. Histopathology of the renal specimen showed a clear cell renal cell carcinoma with dense plasma cell infiltrate. Immunohistochemistry (IHC) suggested lambda light chain restriction (lambda:kappa ratio 7:1) but multiplex polymerase chain reaction (PCR) of the immunoglobulin heavy locus (IGH) gene rearrangement studies was oligoclonal. She initially had a detectable IgG lambda paraprotein of 2g/L, but no excess of plasma cells on bone marrow biopsy and no other biochemical and radiological features of multiple myeloma. The paraprotein resolved post operatively and she remains under surveillance.

Plasma cell infiltration in a single extramedullary organ can be due to either primary clonal proliferation, such as plasma cell myeloma and plasmacytoma, or a reactive response to malignancies or infections. Clonality can be demonstrated via IHC light chain restriction or PCR gene rearrangement studies. One should also take into account the clinical scenario, as well as results from other investigations such as bone marrow examination, radiological imaging and serum and urine electrophoresis/ light chains studies, to rule out systemic myeloma. Serial monitoring is also recommended.

P118. Resistance to nutrient deprivation via metabolic re-programming as mechanism of 'metastasis' promotion in multiple myeloma

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Aim

Multiple Myeloma (MM) is a disease of the intra-medullary (IM) compartment but with progression can survive in nutrient deprived extramedullary (EM) sites. Autophagy, mediates the degradation and re-cycling of intra-cellular proteins and may promote tumor resistance to metabolic stressors, including nutrient deprivation. Using the MM cell lines TK1 and TK2, contemporaneously propagated from bone marrow (IM) and peripheral blood (EM), respectively, of a MM patient we investigated the role of autophagy in resistance to glutamine (Gln) deprivation.

Methods & Results

TK2 but not TK1 exhibited up-regulated autophagy under both basal and Gln deprived conditions with higher LC3BII/I turnover on immunoblotting and autophagic vacuole formation on electron microscopy following chloroquine (CQ) exposure. Under conditions of Gln deprivation, TK2 was able to proliferate until day 14, whereas TK1 stopped proliferating at day 3. This proliferative advantage under Gln deprivation was abrogated by autophagy inhibitors (CQ or 3-MA) as determined by both viable cell enumeration ($p=0.008$ at day 7, inhibitor vs no inhibitor) and Ki67 expression ($p=0.0017$) only in TK2. Modulation of Gln concentration demonstrated an inverse correlation with the viability of TK1 but not TK2 – TK1 cell death increased from 36% at Gln 8mM to 56% at Gln 0mM, irrespective of autophagy inhibition. In contrast, while Gln deprivation had no significant effect on the viability of TK2, under Gln deprivation CQ exposure induced a 2-fold increase cell death. Finally, Gln deprivation induced the expression of glutamine synthetase (GS) only in TK2 and GS inhibition induced cell death in TK2 but not TK1 (32.56% vs 2.5% increase, respectively) demonstrating that Gln synthesis is a potential additional mechanism enabling TK2 to overcome Gln deprivation.

Conclusion

Metabolic reprogramming mitigating against nutrient deprivation may promote a more 'metastatic' phenotype in advanced MM.

P119. Diagnostic dilemma: two CD138-positive malignancies with overlapping morphology in the same patient

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Introduction

CD138 immunostaining is useful to identify and quantitate plasma cells in biopsy specimens, however CD138 may be positive in other malignancies. We report a case of a patient with multiple myeloma (MM) and concurrent CD138-positive plasmacytoid carcinoma.

Case Description

RM (69yo man) was initially diagnosed with smouldering IgG K MM in 10/2016, but demonstrated biochemical progression (paraprotein 23 to 27g/L, kappa:lambda ratio >100, 60% plasma cells on bone marrow trephine) and was commenced on bortezomib, cyclophosphamide, dexamethasone in 2/2017. RM had a suboptimal response to induction (<PR), and began carfilzomib, thalidomide and dexamethasone as part of a clinical trial. After 4 cycles (12/2017), although the paraprotein responded (17g/L to trace), the bone marrow trephine demonstrated 20% CD138-positive cells. Over the next 3 months, RM developed progressive, refractory hypocalcaemia, and in 3/2018, spontaneous bilateral subdural haematomas and disseminated intravascular coagulation. On repeat bone marrow biopsy, trephine imprints demonstrated 78% abnormal plasmacytoid cells (Figure 1). >90% of cells in the trephine were CD138-positive, but were dyscohesive, which is unusual in MM (Figure 2). Further immunohistochemistry revealed the CD138-positive cells were positive for EMA, CKAE1/3, CK7 and CK20, and negative for CD45, S100 and PSA.

In view of the unusual clinical and pathological features, an alternate malignancy was considered. Whilst epithelial stains can be positive in MM, the constellation of findings was most consistent with a plasmacytoid carcinoma of unknown primary (PET scan did not identify a primary site). RM subsequently developed haematuria with abnormal plasmacytoid cells identified on urine cytology in keeping with plasmacytoid variant of urothelial carcinoma^{1,2}.

Discussion

Plasmacytoid carcinoma is rare but recognised, and most commonly originates from urothelium. We present a patient who developed plasmacytoid carcinoma whilst his MM was responding to therapy. This case highlights the challenges of reliance on CD138 staining to identify plasma cells.

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P120. Anaemia with Carfilzomib use – could haemolysis be responsible?

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Introduction

Carfilzomib, an irreversible inhibitor of the [20S proteasome](#), causes grade 3 anaemia and thrombocytopenia in approximately 30% of patients. The mechanism has not been fully elucidated, though rare case reports have described thrombotic microangiopathy (TMA) associated with proteasome inhibitor use. Here, we postulate that carfilzomib may cause non-immune hemolysis.

Methods

19 patients receiving active treatment with carfilzomib at our institution were identified and screened for haemolysis between April and June 2018. The majority of patients (16/19) were on one of two clinical trials – CANDOR or MM17. The 3 patients on carfilzomib but not on clinical trials, were not included in this analysis as they did not have complete data. The baseline characteristics of the 16 patients are presented below. No patients were of South East Asian descent.

Median Age	Median lines of therapy	ISS Stage at diagnosis (median)	High risk CG or FISH	<PR to Bortezomib induction
61	1	2	3/16 (19%)	7 (44%)

Table 1 – Baseline characteristics of carfilzomib patients

Results

Pt.	Age and Sex	Days on K as of 1/6/2018	Hb Pre K	Nadir Hb	Platelet count at Hb nadir	Platelet nadir	Haptoglobin (0.30-2.00g/L)	LDH Peak (120-250)	Reticulocyte % (0.40-2.20%)	Renal impairment	G6PD Screen	Peak mcv	Fragmentation on film?
1	67F	248	102	71	154	97	0.13	719	7.28%	No	normal	114	No
2	69M	144	112	82	48	48	<0.08	441	7.50%	Yes, acute on chronic	Deficient	108	No (oxidative changes)
3	54F	191	122	110	258	81	<0.08	410	N/A	No	normal	96	No
4	70M	240	132	114	Increase	Increase	<0.08	422	3.92%	No	normal	102	No
5	62M	233	100	70	182	66	<0.08	364	5.03%	No	Normal	105	No
6	70F	127	129	98	90	64	<0.08	410	6.71%	No	Normal	119	No
7	61F	46	127	108	Increase	Increase	0.09	244	3.53%	No	Normal	106	No

Table 2 – Carfilzomib patients with evidence of hemolysis

7/16 patients had biochemical evidence of haemolysis (Table 2). In all cases, this was temporally related to the carfilzomib and improved during the non-dosing week or if treatment was interrupted. No patient required complete cessation of carfilzomib. Renal impairment and red blood cell fragmentation on blood film evaluation were not a feature; only 1 patient had a mild deterioration in renal function. Additionally, though thrombocytopenia was often present, it was mild and did not correlate clearly with the anaemia. One patient had an underlying predisposition to haemolysis (G6PD deficiency) unmasked by carfilzomib – he was hitherto undiagnosed and had tolerated bortezomib and Bactrim before without issue. The DAT was negative in all patients.

Conclusion

Haemolysis, in the absence of TMA, may contribute to the anaemia seen with carfilzomib use. The mechanism is unknown and should be explored – we speculate that it may be related to irreversible proteasome inhibition in red blood cells possibly resulting in increased membrane fragility.

P121. Daratumumab in the immunology lab

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Aim

In the United States, Daratumumab has recently been approved as a first line treatment for Plasma Cell Myeloma (PCM) in patients who are ineligible for an autologous stem cell transplant (ASCT). As of October 2017 in Australia, daratumumab has been approved by the Therapeutic Goods Administration for pre-treated MM. Since daratumumab's approval, we in private pathology are encountering more patients receiving this monoclonal antibody (MoAb) therapy. We will present PCM case studies showing the presence of daratumumab and how it can be identified in the immunology laboratory. We will also discuss the use of appropriate commenting for daratumumab and other MoAb therapies.

Method

Flow cytometry and serum protein electrophoresis were used to identify the presence of daratumumab. Serum protein electrophoresis (SPE) is routinely performed at SNP via capillary zone electrophoresis (CZE). We have a largely automated method using the Sebia CAPILLARYS 3 TERA (CAP 3). Immunofixation (IMF) is also semi-automated and performed with the Sebia HYDRASYS 2 SCAN FOCUSING. At SNP, we can also perform Isoelectric focusing (IEF) with this system.

Flow cytometry was performed on a FACSCanto II flow cytometer. We have a four tube myeloma panel. Two plasma cell markers (CD38 and CD138) allow for detection of plasma cells in patients receiving daratumumab without implementing a multi-epitope CD38 clone.

We have also created comments to apply to SPE reports where appropriate.

Results

The presence of daratumumab can be inferred in a routine immunology laboratory. The challenge lies in discriminating between daratumumab and monoclonal protein as complete remission (CR) is defined by the International Myeloma Working Group (IMWG) as the serum and urine being negative for monoclonal protein.

Conclusion

Importantly, the frequency of PCM patients being treated with MoAb therapies is increasing and interpretation of SPE results has important clinical implication for patient management.

P122. Pilot study of ⁶⁸Ga-Pentixafor PET for the detection of myeloma bone disease

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Aim: Preliminary studies of positron emission tomography (PET) using [⁶⁸Ga]-Pentixafor, a novel radiolabelled CXCR4 ligand, show favourable imaging characteristics in humans with multiple myeloma ^{1,2}. Our aim was to assess the diagnostic performance of this tracer in a cohort of newly diagnosed myeloma patients using whole-body magnetic resonance imaging (WB-MRI) as the gold standard.

Method: This is a prospective, single-centre pilot study of patients with untreated multiple myeloma. Simultaneous WB-MRI (T1, T2 STIR) and [⁶⁸Ga]-Pentixafor PET were performed using the Siemens Biograph mMR with image interpretation by two separate assessors. Focal lesions >5mm on MRI, or displaying SUVmax > 2.5 on PET, were tallied and expressed as ordered categorical variables. The primary outcome was test accuracy. Secondary outcomes included correlation with ISS stage, serum LDH and cytogenetic risk group.

Results: Eight patients have been recruited since March 2017, with median age 69.5 years. Baseline characteristics were well-balanced for ISS stage and cytogenetic risk (see Table). [⁶⁸Ga]-Pentixafor identified focal bone lesions in 5/8 patients compared with 8/8 using WB-MRI, giving a sensitivity of 62.5%. Mean SUV max for the positive PET scans was 15.4. No extramedullary lesions were detected. The three discordant cases had low-risk clinical features with few and/or small lesions on WB-MRI. The most avid PET study occurred in a patient with heavy bone marrow disease and adverse cytogenetics (17p deletion). There was good tracer uptake at pathological fracture sites and favourable lesion-to-background characteristics.

Conclusion: [⁶⁸Ga]-Pentixafor PET identifies bone disease in a majority of cases but underestimates lesion count compared with WB-MRI. Whilst sensitivity was inadequate for use as a diagnostic test, PET showed concordance with WB-MRI for all major findings, including pathological fractures. Lesion pickup rate and SUVmax appeared higher in patients with high-risk clinical features. These preliminary findings provide hypothesis-generating data for future staging and theranostic applications of this molecule.

Patient	ISS	FISH findings	Focal lesions		SUVmax
			MRI	PET	
1	1	+1q21, del13q	6-20	0	-
2	2	+1q21, del13q, t(4;14)	>20	1-5	9.1*
3	2	+1q21	1-5	0	-
4	3	normal	1-5	1-5	8.3
5	NA	+1q21, del17p	>20	>20	30.2
6	1	normal	6-20	1-5	30.9*
7	1	normal	1-5	0	-
8	2	normal	6-20	1-5	12.4*

*pathological fracture site

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P123. Bortezomib use and its outcomes for the treatment of multiple myeloma

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Introduction

While the use of bortezomib-based treatment for the initial therapy of elderly patients with multiple myeloma in Australia was based on the VISTA trial, such results may not be applicable to the overall population. We evaluated the feasibility of bortezomib in a 'real world' setting, its outcomes, and limitations compared to the VISTA and GIMEMA trials.

Methods

We evaluated bortezomib-based treatment in three Queensland public hospitals. Data was collected retrospectively from medical records including baseline demographics and disease characteristics, chemotherapy schedule, and response. The primary outcomes were overall survival and progression free survival (PFS). We performed multivariable Cox regression analyses using Stata 14.

Results

We identified 74 patients. Compared to VISTA/GIMEMA data, our cohort was older (75 vs 71/72 years), had higher incidence of severe renal impairment (GFR <30%; 35% vs. 6%/9%), and had higher incidence of ISS stage 3 disease (64% vs. 35%/31%). Dosing intensity was less in our cohort compared to VISTA data and the median cumulative dose was less (29.6±19 vs. 36.6±20 mg/m²). 53% discontinued treatment early due to toxicity (30%, 16% with peripheral neuropathy), suboptimal response or disease progression (15%) or early death (8%). Overall response rates were similar (81% vs. 74%), whilst complete remission was less (13% vs. 33%). Median OS was 40.7 months compared to 56.4 and 60.6 months in the VISTA and GIMEMA cohorts, respectively. Median PFS was 17.7 months and the 2 year PFS was 33% (95%CI, 22%, 45%), also lower than trial cohorts.

Conclusion

Bortezomib-based regimens as published in clinical trials are not deliverable to most elderly patients in the real world setting and, while response rates were similar, survival outcomes were worse. These data suggest that we need trials with minimal exclusion criteria that specifically include elderly people.

P125. Anti-CD38 monoclonal antibody induced hypothyroidism

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Introduction

Daratumumab, the anti-CD38 monoclonal antibody, is a highly efficacious treatment in patients with relapsed and refractory myeloma. We report a case of severe hypothyroidism due to daratumumab, an adverse effect that has not been reported in the literature to date.

Case Report

A 71-year-old man with multiply relapsed kappa light chain myeloma was commenced on fourth line treatment with intravenous daratumumab. A weekly 16mg/kg dose was administered for four weeks. The patient developed somnolence and cold-intolerance after commencing daratumumab. Examination revealed a mild bradycardia (55bpm) and generalised cutaneous myxoedema. There was no palpable goitre or thyroid tenderness.

Thyroid function tests demonstrated a TSH of 42.9 uU/mL (0.35-4.94), free T4 < 6 pmol/L (9-19) and free T3 < 1.6 pmol/L (2.6-5.7), consistent with severe hypothyroidism. Twenty-four hours later the patient's TSH had risen to 62.9 uU/mL, suggestive of an acute, dynamic process. The patient's TFTs prior to commencing daratumumab were normal. Thyroid antibodies commonly associated with autoimmune thyroid disease were not detected. Anterior pituitary hormones and cortisol levels were normal. A thyroid ultrasound showed no abnormality.

This patient's presentation was most consistent with drug-induced thyroid disease. His symptoms improved with thyroxine. Daratumumab was continued as there were limited alternative treatment options for this patient's refractory myeloma.

Discussion

CD38 is a transmembrane glycoprotein that is expressed on many cell types and highly expressed on plasma cells. CD38 is expressed in the fibrous septa of the human thyroid. Furthermore, naturally circulating anti-CD38 autoantibodies are a known autoimmune marker in chronic autoimmune thyroiditis and Graves' disease. Thus it is feasible, that daratumumab can potentially cause drug-induced immune-mediated thyroid dysfunction.

As this treatment becomes more widely available, it is expected that other off-target adverse effects of anti-CD38 antibodies may become apparent.

P126. Innovation in autologous stem cell transplants for myeloma - redesigning the service delivery model

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Aim

To improve service delivery, outcomes, and experience, by redesigning current autologous stem cell transplant service delivery model for myeloma.

Method

A working group consisting of clinical haematology and management lead, as well as expert haematology nurse, worked collaboratively with key multidisciplinary stakeholders to redesign the service delivery model.

This group analysed key safety points, to determine changes to the current clinical pathway. It was identified key resources including a clinical guideline, care plan, assessment tool, patient resource, and medical alert form, all needed creating. The expert haematology nurse is responsible for the development of these new documents. Evaluation identifiers will include clinical data, as well as data collection on adverse events and quality of life. Following research, the CTCAE will be used to collect data on transplant specific toxicity, and the reputable EORCT-QLQC30+MY20 will be utilised to collect data on patient quality of life. This service model will be piloted on 6 participants, over a 6 month period.

Result

As a result of collaboration between experts, a clinical guideline, care plan, assessment tool, patient resource, and medical alert form, were developed. The development drew links with existing, as well as purposely amended, hospital policies. The patient resource included new patient self-assessment forms, and information that encourages increased consumer engagement. The preparation to start using the redesigned pathway required training and planning with nursing staff, and lead to increased knowledge and scope of practice in multiple clinical areas.

Conclusion

This redesign has shown that through research of best practice, and collaboration between key stakeholders, service delivery models can be innovated. Improvements can be gained in clinical delivery and utilisation of resources, as well as collection of valuable data to guide future treatment. Advanced care is also possible by increasing clinical knowledge and scope of practice of existing nursing staff.

P128. A rare case of relapsed multiple myeloma with intracranial and cutaneous plasmacytomas

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Introduction

Multiple myeloma (MM) is a disorder characterised by a clonal proliferation of plasma cells. Although MM is usually confined to the bone marrow, it can also occur in other tissues. These lesions are known as extra-medullary plasmacytomas (EMP).

Case

We present the case of a 64-year-old lady who developed an intracranial and multiple cutaneous EMPs following autologous stem cell transplant for MM. The patient was initially diagnosed with IgA kappa MM following the discovery of multiple skeletal plasmacytomas. At diagnosis she was Durie-Salmon stage 3. She was treated with cyclophosphamide, thalidomide and dexamethasone. Her treatment was complicated by a widespread cutaneous reaction to the thalidomide so she was subsequently given cyclophosphamide, bortezomib and dexamethasone. This was followed by a high dose melphalan autologous stem cell transplant achieving a stringent CR. Unfortunately, 2 months following her transplant she developed multiple large cutaneous plasmacytomas and an extra-axial intracranial lesion. Bone marrow biopsy performed at the time of relapse showed an infiltrate of approximately 15% plasma cells. She was treated with carfilzomib and dexamethasone with radiotherapy to the intracranial lesion and the bulky skin lesions. This treatment resulted in short term improvement of the EMPs. Shortly after her initial improvement she developed progressive disease with further cutaneous lesions and plasma cell leukaemia.

Discussion

In a large study of 1003 patients Varettoni et al reported extramedullary disease in 7% at diagnosis and 6% throughout follow up ¹. Intracranial EMPs are very rare. Dural involvement without a contiguous bone lesions are an even rarer scenario. Unfortunately even in the era of novel agents, EMPs portend a poor prognosis^{1,2}. Due to its rarity there are no guidelines on how to treat such patients. Given the hypersensitivity reaction to thalidomide in this case, our treatment options were limited to regimens not containing immunomodulatory drugs.

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P129. Outcomes of myeloma patients in regional Queensland Health service

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Aim

Studies have shown that patients with cancer living in regional Australia have a poorer outcome than their metropolitan counterparts. Due to the tyranny of distance, this impacts on access and choice of therapy. Current 5 year survival rates for multiple myeloma is about 50%. To date, there are no studies assessing outcomes for patients with multiple myeloma in regional Australia. We perform a retrospective study looking at survival outcomes for myeloma patients in the Darling Downs Hospital and Health Service. Toowoomba Hospital is the major regional hospital servicing an area over 90,000km² and is situated 120km away from Brisbane.

Method

Data was collected via the chemotherapy prescribing software (CHARM) from the period of 2010 to 2017. Patients receiving myeloma-based therapy for amyloidosis were excluded. Patient baseline characteristics (including staging, cytogenetics and ECOG), choice of initial therapy, eligibility for stem cell transplant, best response to treatment, lines of treatment, and outcomes were assessed. Outcome was assessed by overall survival, rurality of patients (with rurality defined as >100km from treatment centre), choice of injectable versus oral therapy, and number receiving bortezomib-based therapy as first line.

Result

54 patients were included in the retrospective study. There was no significant survival differences between those living 'locally' in Toowoomba versus those in more rural areas. 36 patients received bortezomib-based therapy as initial therapy, 18 received oral therapy. 22 patients received an autologous stem cell transplant. 16 patients achieved Complete Response (including 8 stringent CR) and 10 Very Good Partial Response.

Conclusion

Survival for patients with myeloma is not necessarily impacted by distance. With an evolving treatment landscape, this will continue to improve. Further assessment at the Darling Downs Hospital and Health Service will be made on how to better deliver therapies to patients who live a significant distance away from Toowoomba Hospital.

P130. Primary refractory myeloma - A tail of two clones

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We report a case of JC, a 57 year old female, diagnosed with stage II multiple myeloma. At diagnosis, her IgG kappa was 59g/L, kappa light chain 460mg/L and lambda light chain 8mg/L. Bone marrow biopsy showed 40% plasma cells with normal cytogenetics. MRI demonstrated multiple lytic lesions in the thoracic spine, L5 and right T11 rib.

She was commenced on Bortezomib-Cyclophosphamide-Dexamethasone (VCD) achieving a partial response at the commencement of her fourth cycle. She presents one week into the fourth cycle with increasing back pain. PET/CT shows no new FDG avid lesions.

However, she re-presents one week later with acute lower limb weakness and urinary retention. Urgent MRI reveals new large left paraspinal lesion infiltrating the spinal canal at T9-T12. Urgent decompressive laminectomy was successfully performed with neurological recovery. Histology confirms plasmacytoma with kappa restriction. Cytogenetics showed gain 1q21, trisomy 4, trisomy 14, trisomy 13 and deletion 17q. Repeat bone marrow biopsy showed plasmacytosis <5% and no cytogenetic abnormalities.

Ten fractions of radiotherapy was given, but the patient redeveloped neurology due to extension of the plasmacytoma to T6-T12. Treatment with Carfilzomib-Thalidomide-Dexamethasone (KTD) was commenced following the development of a new lesion at T2-T5 two weeks later. Interval scans showed regression of the thoracic lesions. However, the patient developed new upper limb neurology three weeks later due to new C6-T1 lesion. Repeat radiotherapy and high dose dexamethasone was given. Treatment was escalated to DR-PACE in which a complete metabolic response by PET was achieved following two cycles.

Clonal evolution is well documented throughout the course of myeloma. However, patients with two distinct clonal populations, in particular early in diagnosis, is very rare. Further investigation is required to better understand the biology of plasmacytomas given the extremely aggressive behaviour in this case and its resistance to standard myeloma therapies.

P131. Antenatal haemoglobinopathy screening – improving specificity and cost effectiveness

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Aim

An efficient antenatal haemoglobinopathy screening program is key to providing timely genetic advice to expectant parents to facilitate prenatal diagnosis. There is great variation in screening programs across Australia, and developing the optimal and most cost effective approach is vital particularly with the increasing ethnic diversity of the Australian population.

Method

An audit of haemoglobinopathy screening results performed at NSWHP Haematology Randwick was conducted between 1st Jan 2015 and 31st Dec 2017. This included HPLC, HbEPG, red cell indices and iron studies.

Results

A total of 1628 females and 729 male partners were screened. 133 (8.2%) women had a haemoglobin variant detected including alpha thalassaemia trait (29%), beta thalassaemia trait (28%) and haemoglobin E trait (24%). 75% had concomitant iron studies. In a further 13% alpha thalassaemia trait or borderline HbA2 was unable to be excluded.

Of the 729 couples screened, 626 partners (86%) were screened simultaneously while 103 (14%) were screened sequentially. There was an average 22.1 +/- 20.61 days of delay between screening of the female and male in those screened sequentially. 218 (35%) of those male partners who underwent simultaneous screening did not require screening based on the female's risk.

On average, women were 16 weeks of gestation when screened. 62 couples were recommended to undergo further genetic testing, 40 were tested in our laboratory and 3 were considered high risk. One underwent amniocentesis, while the other two couples declined.

Conclusion

Our variant trait detection rate of 8% is consistent with the worldwide carrier frequency of 7%. 13-43% required further assessment with either partner screening or molecular testing. Greater access to definitive diagnostic methods and greater understanding of community expectations are required. Improvements can be made to our current screening algorithm to reduce costs while maintaining the ability to identify those at highest risk of affected children.

P132. External quality assurance in malarial parasite density counts

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Introduction

Density counts by microscopic visualisation of malarial parasites on thick and/or thin blood smears, provide information on the severity of infection. The Royal College of Pathologists of Australasia Quality Assurance Programs (RCPAQAP) conducts a biannual malarial parasite external quality assurance program, using digital images of peripheral blood films. Results from the 2014-2017 program (8 samples) were analysed to assess how participants perform counts at varying densities.

Method

Participants received digital images of *Plasmodium falciparum* infection and were asked to perform density counts using either the thick or the thin film image and report methods used. Medians and coefficients of variation (CV) at varying parasite densities were used to assess trends.

Results

Median density counts ranged from 9300 parasites/ μ L – 171000 parasites/ μ L. At lower parasite densities CVs were lower in thick films compared to thin films (27.3% and 49.9% respectively). Conversely, at higher parasite densities CVs were lower in thin films compared to thick films (22.3% and 36.8% respectively). The majority of participants counted 100 white blood cells (WBC) to estimate parasite density on thick films and used a miller ocular square on thin films. For thin films, miller ocular square CVs (17.7% - 43.8%) were lower than those of counting fields of 200 Red blood cells (CVs 25.1% - 56.9%).

Conclusion

The suitability of film type was directly related to parasite density; thick films at lower densities and thin films at higher densities. This reflects the World Health Organisation (WHO) SOP that stipulates thin films should be used when parasite load is $>80\,000$ parasites/ μ L. However, the number of participants that used thick or thin films, and the number of WBC counted on thick films were not correlated to parasite density as would be expected. Additionally, when thin films were used, use of a miller ocular square consistently improved accuracy.

P133. Case Report: An unusual presentation of extramedullary haematopoiesis in a patient with transfusion dependant B-thalassaemia intermedia

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Background

Extramedullary haematopoiesis (EMH) is a known complication in patients with severe phenotypes of thalassaemia. This case presentation of extramedullary haematopoiesis in the unusual location of the inner ear ossicles was identified on detection of conductive hearing loss during annual audiometry screening.

Case Presentation

An 11 year old male with a rare, severe form of β -thalassaemia intermedia (β^+/β^0 , $\alpha\alpha/\alpha\alpha\alpha\alpha$) with transfusion dependence since age 4 months was diagnosed with unilateral conductive hearing loss on annual audiometry screening as part of deferasirox therapy. Imaging demonstrated a mass in the left middle ear cavity with resorption of the incus, stapes and erosion of the malleus. Bone marrow hyperplasia involving the skull vault, skull base and cervical vertebral bodies was noted. Biopsies from a tympanomastoid exploration confirmed the mass to be EMH. Haemoglobin nadir values prior to transfusions ranged from 70-80 at the time of development of EMH. Subsequently his transfusion program was modified aiming for a pre-transfusion nadir of 95-100. The radiological findings are currently stable.

Discussion

Managing patients with β -thalassaemia intermedia remains challenging due to the heterogeneous nature and lack of standardised clinical guidelines. The approach to management remains individualised and is often balanced between risks of under-treating and the potential complications of regular transfusions i.e. iron overload. There is a need to consider the role of the pre-transfusion haemoglobin nadir and its relationship with the development of thalassaemia related complications such as EMH. Screening is a valuable tool to assist with the detection of potentially reversible complications that may otherwise be asymptomatic.

Conclusion

This case highlights a rare presentation of extramedullary haematopoiesis identified through routine audiometry in a patient with transfusion dependent β -thalassaemia intermedia. It emphasises the importance of screening for extramedullary haematopoiesis in patients who do not routinely meet a pre-transfusion haemoglobin nadir of 95.

P134. Complication rates of central venous access devices in patients with inherited bleeding disorders: the Australian experience

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Aim: To evaluate current practice and complications associated with central venous access devices in Australian patients with inherited bleeding disorders. For certain patients with inherited bleeding disorders the replacement therapy necessitates the insertion of a central venous device (CVAD) to allow rapid and repeatable access. Whilst there are advantages to central devices, there are accompanying risks associated with CVADs. The most commonly reported in the literature is infectious, with a rate that varies from 0.0578 infections/1000 catheter days (1) to 0.57 infections/1000 catheter days (2).

Method: Multi-centre retrospective data analysis of patients registered on the Australian Bleeding Disorders Registry, in collaboration with national haemophilia treatment centres (HTC). The data includes any patient with an inherited bleeding disorder with a central venous access device registered from January 1997- February 2018. A central venous access device refers to line inserted into a large central vessel and includes external lines (Broviac, Hickman, PICC) as well as implantable devices (Port-A-Cath). Complications evaluated include infectious and non-infectious (thrombotic and device malfunction).

Results: 258 patients were identified on the registry with central venous access device. In the preliminary assessment of the data there were 80 patients with complete data to assess complication rates. Further data is sought from local HTCs for 148 patients, and 30 patients have been excluded due to incomplete data. The 80 patients with complete data showed 117 CVADs in total, with 139836 catheter days. The complication rates of these devices showed an infectious complication rate of 0.50/1000 catheter days, a thrombotic rate of 0.007/1000 days and a malfunction rate of 0.19/1000 catheter days.

Conclusion: This data demonstrates a multi-centre retrospective data of complication rates of central venous access devices in Australian patients. The rates of complications in Australian patients is similar to other multi-centre studies published internationally and provides an Australian benchmark.

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P135. Dermatopathic lymphadenitis – an uncommon cause of progressive lymphadenopathy

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Background

Dermatopathic lymphadenitis (DL) is an uncommon cause of paracortical hyperplasia often associated with chronic exfoliative or eczematoid skin disease. We present a case of a man with progressive lymphadenopathy and an extensive rash.

Case presentation

A 58 year-old man with a history of psoriasis presented with 2-3 weeks of axillary lymphadenopathy and fevers. Full blood examination (FBE) only showed mild eosinophilia. Lactate dehydrogenase (LDH) was borderline at 257U/L. Computer tomography (CT) scan of his chest/abdomen/pelvis showed bilateral axillary lymph node enlargement. A core only showed reactive changes with no malignancy. A repeat CT scan after 3 months of observation showed progressive cervical and axillary lymphadenopathy. In the interim, the patient had developed a new suberythrodermic rash with scaly and non-scaly patches and plaques on sun-exposed and covered sites. An excisional axillary lymph node biopsy showed preserved follicular architecture with nodular paracortical expansion by aggregates of histiocytes with occasional cytoplasmic pigment and scattered eosinophils. No abnormal lymphoid population was detected on flow cytometry. Punch biopsy of the skin lesions showed subacute spongiotic dermatitis with overlying parakeratosis. There was no significant epidermotropism. A perivascular inflammatory infiltrate of lymphocytes with scattered eosinophils was seen in the superficial dermis. T-cell receptor (TCR) gene rearrangement analysis returned a polyclonal result. The patient was given a clinical diagnosis of eczema and treated with topical corticosteroid and ultraviolet light therapy.

Conclusion

Lymph node enlargement is a problem commonly referred to haematology for further investigation. Cases associated with cutaneous disorders require consideration of cutaneous T cell lymphomas (CTCLs). Adequate core and skin biopsies may both be required for proper diagnosis. This case illustrates DL secondary to benign skin pathology. However, skin biopsy in this situation may have limited specificity and longitudinal monitoring is important to ensure response to treatment and exclude future development of CTCL.

P136. Retrospective analysis of the causes of hypereosinophilia

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Aim

To describe the causes of moderate to severe hypereosinophilia (HE) in our hospital cohort.
To study the association between severity of eosinophilia and end organ involvement.

Methods

Retrospective analysis was undertaken on subjects with HE $\geq 3.0 \times 10^9/L$ presented to our institution between 2013-2017. Data on age, sex, etiology, haematology investigations and outcome were collected from the computerized hospital records.

Results

Of the 615 subjects identified with eosinophilia, 186 had an eosinophil count of $\geq 3.0 \times 10^9/L$ (mean age 56.6 years). Ninety six (51.6%) were male and 90 (48.4%) were female, with a mean peak eosinophil count of $6.4 \times 10^9/L$ and $4.3 \times 10^9/L$, respectively. Unknown etiology was the most common cause of HE (n=54, 29%). Other causes were infection/inflammation (n=46, 24.7%), malignancy (n=46, 24.7%), immune (n=26, 13.9%), medication (n=9, 4.8%), and hypereosinophilic syndrome, HES (n=5, 2.7%). The highest peak eosinophilia count ($78 \times 10^9/L$) was seen in one HES case. Peak eosinophilic level for a reactive cause was noted as high as $30 \times 10^9/L$. All patients with HES were treated with prednisolone, and 3 had successful treatment response. End organ involvement was observed in immune related HE and HES, with a mean peak eosinophil level of $8 \times 10^9/L$ and $44.1 \times 10^9/L$ respectively.

Conclusion

The most cases of moderate to severe HE had unknown etiology. HES was relatively rare. Reactive HE could show marked eosinophilia as high as $30 \times 10^9/L$. End organ involvement was observed in HES and immune related HE. All patients with undiagnosed HE should be re-evaluated regularly for the first one to two years to monitor eosinophil count, assessing resolution or progression as well as continuing to monitor for end organ effects.

P137. Analysis of checkpoint marker expression on immune cells using a 12-color flow cytometry assay

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Aim

Antibodies that block ligation of immune checkpoint receptors, such as the programmed cell-death protein 1 (PD-1), have demonstrated a durable antitumor response with acceptable toxicity in some patients with advanced melanoma. The clinical impact of immune checkpoint blockade may be increased by careful assessment of checkpoint receptor expression patterns in patients. Here, we demonstrate the potential of a comprehensive 12-color flow cytometry immune checkpoint pane.

Method

Expression of the immune checkpoint markers CD134 (OX40), CD273 (PD-L2), CD274 (PD-L1), CD279 (PD-1), CD152 (CTLA-4), CD366 (TIM-3), and CD223 (LAG-3) was analyzed on CD4+ and CD8+ T cells as well as NK cells using a 12-color antibody panel and the BD FACSLyric flow cytometer. PBMCs from healthy donors were cultured *ex vivo* with or without stimulation and immune checkpoint receptor expression was measured.

Result

Following *ex vivo* stimulation, PBMCs exhibited robust increases in immune checkpoint marker expression levels that followed specific patterns depending on the cell type. The expression pattern for CD4+ and CD8+ T cells was similar but not identical while the expression pattern for NK cells was distinct from T cells.

Conclusion

With the recent burst of reports in immuno-oncology research targeting checkpoint markers for therapy, a comprehensive analysis of checkpoint expression patterns in immune cells may further advance this emerging field. We show that the use of an optimized checkpoint marker panel system enables users to acquire results with a high degree of informational content.

P138. Relapse of HIV related acquired Thrombotic Thrombocytopenia Purpura (TTP), now primary refractory requiring Rituximab therapy

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Introduction

Thrombotic thrombocytopenic purpura (TTP) is an uncommon, life threatening microangiopathic haemolytic process and can be associated with advanced HIV infection and very low CD4 counts. It is a haematologic emergency with an untreated mortality approaching 90%.

Case report

We describe a 34 year old lady who was first diagnosed with TTP in late 2017 (ADAMTS level <1%, Inhibitor level 5.8 BU) and responded rapidly to daily plasma exchange and prednisone. She was found to have advanced HIV with a viral load of 258,160 RNA copies/ml and CD4 count of $0.18 \times 10^9/L$. She was commenced onto highly active anti-retroviral therapy (HAART) resulting in a rapid response (undetectable viral load in May).

However, the patient then self-ceased her HAART and within a month represented with morphological film features of TTP and associated renal impairment. Her HIV viral load on representation had increased to 150,493 RNA copies/ml.

She commenced plasma exchange and despite 7 daily exchanges, there was minimal improvement in her platelet count (<20). She was also commenced on new combination HAART (abacavir, dolutegravir, lamivudine). Re-initiation of prednisone had a marginal improvement in platelet counts (~20-30).

On day 17 of plasma exchange she was witnessed having a spontaneous tonic clonic seizure. MRI Brain was unremarkable and the seizure was attributed to primary refractory TTP. ADAMTS level was <1% and inhibitor level was 8.9BU. The decision was made to commence anti-CD20 therapy for primary refractory disease ($375\text{mg}/\text{m}^2 \times 4$ doses).

Conclusion

HIV related aTTP is an uncommon complication of advanced HIV and confers an increased mortality and morbidity. Management requires rapid control of both conditions. Immunosuppression can assist with achieving complete remissions and case reports have suggested at 100% response rate with the addition of Rituximab. Therefore, this treatment should be considered in primary refractory cases.

P139. A Case of Successful Intrauterine Transfusion for Hydrops Fetalis due to Maternal Parovirus B19 Infection

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Aim

We present a recent case of maternal parvovirus infection presenting with hydrops fetalis, successfully reversed with intrauterine transfusion therapy. A literature review is conducted to support the evidence-based practice of the Feto-Maternal Unit of our hospital.

Method

We analysed the maternal Parvovirus B19 referrals to the Feto-Maternal Unit of Liverpool Hospital in the last two years. We describe an illustrative case that demonstrated challenges with intrauterine transfusions and lesser known complications of fetal tachycardia and cerebellar stroke. A literature search was conducted and 64 articles were identified for this literature review.

Result

A 34-year-old healthy woman was referred to our Feto-Maternal Unit when her routine morphology scan showed fetal ascites. Maternal parvovirus B19 serology was positive for IgG and IgM. Middle cerebral artery peak systolic velocity indicated moderate-severe fetal anaemia. Initial intraperitoneal transfusion was performed due to difficulty with cord access. However, close serial monitoring showed ongoing severe anaemia. Second intravascular intrauterine transfusion was successful with eventual resolution of hydrops. This case was complicated by fetal tachycardia for which maternal digoxin was given with good effect, and fetal cerebellar stroke. Despite an arduous pregnancy, a healthy baby boy was born at term.

Our literature review found that pregnant mothers with parvovirus infection should be referred to a Feto-Maternal Unit; although most do not experience adverse events. Intravascular intrauterine transfusions are the standard of care, but intraperitoneal transfusions have an important role when fetal vascular access is difficult. Fetal cardiovascular stress and cerebrovascular events are rare complications from anaemia that warrant further research.

Conclusion

The literature review supported the management of our patient with Parvovirus B19 infection in pregnancy complicated by hydrops fetalis. A very favourable outcome was achieved with close monitoring and intrauterine transfusions. Long term outcomes, however, are yet to be seen with this baby.

P141. Haematologic abnormalities in natalizumab treated patients - more common than we think?

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Natalizumab is a recombinant, humanised monoclonal antibody directed towards the alpha 4 subunit of integrin molecules expressed on all leukocytes except neutrophils, used in the treatment of Multiple Sclerosis (MS). Alpha 4 integrins have multiple receptors including vascular cell adhesion molecule-1, which allow leucocyte adhesion, attachment and migration across activated vascular endothelium; in MS this potentially mediates their mechanism in inflammatory lesions in the CNS.

The alpha 4 integrin also interacts with fibronectin and is involved in preventing their release into the peripheral circulation. Blockade of this may result in the recognised effect of Natalizumab in increasing the number of circulating stem cells. However, much of the current literature describes these effects as potentially useful adjuncts to stem cell mobilisation or demonstration of effective therapy rather than an under-recognised cause for abnormal blood film morphology and cell counts.

All patients currently receiving Natalizumab at our institution were assessed; of these, 32 patients had a full blood exam (FBE) result available within 12 months. 69% (22/32), had a lymphocyte count above the normal range ($3.5 \times 10^9/L$), ranging from 3.6 - $12.9 \times 10^9/L$. Of the 10 patients who had a normal lymphocyte count, 3 had elevated eosinophils, and 2 had abnormal blood films reported with reactive lymphocytes. Only 15% (5/32) patients had a normal FBE.

There are previously published case series describing findings of nucleated red blood cells and myeloid precursors due to natalizumab. There is less information available describing just how common abnormal FBE parameters are in this cohort of patients; and these findings are often poorly described in drug information, and may not be well recognised by laboratory scientists and haematologists. In the absence of adequate clinical information alerting the haematologist to the potential use of Natalizumab, these features may result in unnecessary anxiety, bone marrow examination or flow cytometry.

P142. Single dose ferric carboxymaltose 1g in iron deficiency with or without anaemia

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Aim

Intravenous (IV) ferric carboxymaltose (FC) is a safe and efficacious formulation for treatment of iron deficiency. Dosing based on the Simplified method often requires >1g, however this requires split dosing at least a week apart. Multi-day dosing increases day unit workload, risk of side effects, and is inconvenient to patients. We aim to measure red cell parameters and iron studies 1 week after a single dose of 1g.

Method

Patients referred to our day unit for IV FC with confirmed iron deficiency within 2 months were included in our data. Dosing was based on the Simplified formula. If more than 1g was calculated, a second dose was given 1 week later. Tests for FBP, iron studies and phosphate were collected prior to infusion. Repeat tests were collected prior to a second dose when required. Paired t-test was used to compare pre- and post-infusion parameters.

Result

110 patients received IV FC, 84% were female with mean haemoglobin (Hb) 110, mean Hb for males was 112 and overall mean MCV was 82. Most patients were anaemic (60%), of these 48% were microcytic compared 14% of patients with normal Hb.

56 patients received >1g of FC with results available prior to second dose. MCV increased significantly (mean increase 1.6fL). Hb significantly increased in anaemic patients (mean increase 3.5g/L). Mean ferritin and transferrin saturations significantly increased, and was above the lower limit of normal in all patients. Phosphate significantly decreased and hypophosphatemia developed in 43% of patients.

Conclusion

A dose of FC 1g results in early haematopoietic response, rapid correction of iron studies and may be adequate for most patients. We recommend single dose FC 1g and reassessment after 4-6 weeks in patients with iron deficiency.

P143. Alpha thalassaemia syndromes: From phenotype to genotype

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Alpha thalassaemia, an autosomal recessive condition, is due to impaired or absent production of alpha globin chains which results in excess beta globin chains. Haemoglobins with excess beta globin chains form unstable soluble homotetramers that precipitate within the cell resulting in HbH inclusions. In the majority of cases, alpha thalassaemia is due to deletional mutations in the alpha globin locus of chromosome 16. Infrequently it can be due to large deletions of chromosome 16 or mutations in the *ATRX* gene on chromosome X.

We present the case of a twelve year old male with an undiagnosed syndrome characterised by intellectual disability, dysmorphic features, progressive limb spasticities, visual impairment, and hypothyroidism. The treating clinician suspected alpha-thalassaemia mental retardation syndrome (ATRXMRS) and requested haemoglobin electrophoretogram (HbEPG) given that in 70-0% of cases HbH inclusions are demonstrated often specifically after incubation of fresh blood smears with 1% brilliant cresyl blue. HbH prep demonstrated numerous HbH bodies with haemoglobin of 117g/L (MCV 73.65fL), minor red cell changes on the film, with no haemoglobin Barts detected on HPLC. The detection of numerous HbH inclusions was inconsistent with the red cell indices, which were more consistent with an alpha thalassaemia trait. This discrepancy was pivotal in directing investigations for the causative mutation. Sequencing of the *ATRX* gene revealed a novel c.741C>A (p.Asn247Lys) variant. This is considered likely pathogenic given deleterious *in silico* predictions, positional conservatory properties and variants that lie downstream of this variant are determined to be pathogenic. Sequencing of the alpha1 globin (*HBA1*) and alpha2 globin (*HBA2*) gene did not demonstrate any mutations. This case highlights the importance of considering alternative, less common causes of alpha thalassaemia anomalies such as ATRXMR.

We will discuss the evolution of the case in a vignette, the pathophysiology, differential and diagnostic approach for alpha thalassaemia like syndromes.

P144. Paroxysmal cold haemaglobinuria with florid peripheral erythrophagocytosis

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Introduction

Paroxysmal cold Haemoglobinuria (PCH) is a rare haemolytic anaemia where biphasic haemolysis is triggered by the Donath-Landsteiner antibody. This antibody is a cold reacting IgG antibody that shows cross reactivity with the P-antigen on red blood cells and red blood cell precursors. It affects mostly young children post viral stimulus such as Parvovirus or Mycoplasma who present with symptoms of brisk intravascular haemolysis including haematuria.

Case Review

The first case is a three year old who presented with “port stained” urine and a history of upper respiratory tract infection. Urinalysis was positive for blood and protein; however microscopy showed an absence of red blood cells. Routine blood film analysis by lab scientists identified florid peripheral granulocytic erythrophagocytosis. DAT was strongly positive for C3d and cold agglutinin screen was negative. Donath-Landsteiner testing was done by a referral lab and was negative.

The second case is a five year old female presenting with “frank blood in urine post treatment for acute left otitis media”. Blood film evaluation triggered by high MCHC revealed occasional erythrophagocytosis. DAT was 1+ IgG and 3+Cd3. Urine analysis was positive for bilirubin on dipstick but reported as <10 red blood cells on microscopy. Again, the Donath-Landsteiner send away test was negative.

Discussion

Positive confirmation is by the detection of bi-phasic haemolysis however low sensitivity occurs due to consumption of the antibody and complement during haemolysis. The test also requires strict collection conditions which can be compromised during referral of the specimen. Although the Donath-Landsteiner test was negative in both these cases, the florid peripheral erythrophagocytosis, particularly in the first case, has been used as evidence to conclude that haemolysis in both cases was due to PCH.

P145. Pancytopenia in an infant with Pearson Syndrome

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Background

Pearson syndrome is a rare genetic disorder resulting in sideroblastic anaemia, vacuolation of the haematological cell lines in the bone marrow, metabolic acidosis and pancreatic dysfunction. It is usually caused by deletions in the mitochondrial DNA.

Case Report

We present a case of a 3-days old female neonate, born via emergency caesarean section at 36 weeks due to intrauterine growth restriction, with severe macrocytic anaemia. Patient received a blood transfusion prior to transfer to Monash Medical Centre, and on arrival was diagnosed with necrotising enterocolitis. Pre-operative blood tests revealed metabolic acidosis, elevated plasma amino acids and lactate, neutropenia, thrombocytopenia and coagulopathy. Blood product support was given intra-operatively; platelets, packed red blood cells, cryoprecipitate and fresh frozen plasma were all required. Remaining colon was removed on day 5 of life due to infarct and bowel obstruction. FBE analysis over the following days showed persisting anaemia, neutropenia, thrombocytopenia and coagulopathy with blood product support being required every 24-48 hours.

Pearson syndrome was diagnosed on day 15 of life via ultra rapid exome sequencing (72 hour TAT) as part of the Acute Care Flagship Study of the Australian Genomics Health Alliance. A large deletion in the mitochondrial genome consistent with Pearson Syndrome was detected. Patient will receive ongoing medical support as required.

Conclusion

Clinicians and laboratory staff should consider mitochondrial genetic testing in the context of acidosis, raised lactate and bone marrow failure in an infant, to confirm a suspected diagnosis of Pearson syndrome.

P147. Retrospective validation of CareStart Malaria HRP2/pLDH (PF/PAN) Combo rapid diagnostic test

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Introduction

Malaria diagnosis and species confirmation is necessary following the introduction of newer, more expensive antimalarial treatments with prompt diagnosis necessary before treatment is started. Confirmation by microscopy remains the gold standard, however training and maintaining competency is becoming increasingly difficult for laboratories around Australia, particularly when malaria is not endemic. Malaria rapid diagnostic tests (RDT) are a rapid, cost effective option for laboratories when prompt diagnosis is required and microscopy experience is limited.

Method

We performed a retrospective validation of the CareStart Malaria HRP2/pLDH (Pf/PAN) Combo rapid diagnostic test compared to diagnosis performed by thick and thin film examination in our laboratory from January 2016 to March 2018.

Results

A total of 529 malaria diagnostic screens were performed during this time, with 493 being negative for malaria and 36 confirmed positive malaria cases by microscopy. Malaria RDT was performed in 422 cases. The positive cases were *Plasmodium falciparum* (n=20), *Plasmodium vivax* (n=3), *Plasmodium ovale* (n=1) and a mixed infection (n=1). The CareStart RDT successfully detected all negative cases of malaria compared to microscopy. For the *P. falciparum* cases, the RDT successfully confirmed HRP2/pLDH positivity in all cases. For the *P. vivax* and *P. ovale* cases the CareStart RDT successfully confirmed PAN positivity in all cases. The one mixed infection was *P. falciparum* and *P. vivax* and the RDT detected this as PHRP2/pLDH and PAN positive.

Conclusion

Quality Malaria RDT's and microscopy are recognised by the World Health Organisation (WHO) as both having a role in malaria diagnosis depending on the clinical situation. The CareStart Malaria HRP2/pLDH (PF/PAN) Combo is a suitable malaria RDT for use in laboratories where malaria diagnosis and species confirmation by microscopy is not available in an adequate time frame to start malaria treatment.

P148. Association between iron deficiency and thrombocytosis in a tropical North Queensland population

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This study aimed to determine the association between iron deficiency and thrombocytosis.

Iron deficiency has long been considered a differential diagnosis for patients presenting with thrombocytosis. However, in recent times there have been differing results in the literature which has brought this association into question.

A retrospective review was conducted of all serum ferritin results from January 2016 - June 2018 using data from an electronic results database.

This review included all patients from Cairns Hospital with iron studies and full blood count ordered on the same sample during the study period. Both inpatient and outpatient blood samples were included with a total of 14,956 samples over the study period. Of these 121 samples were excluded due to missing data, and a further 642 patients were excluded due to serum ferritin > 1000µg/L.

There was no linear relationship between serum ferritin and platelet count ($R^2 = 0.006$). Patients with thrombocytosis (Platelets > 400×10^9) had significantly higher mean serum ferritin levels, and C-reactive protein levels compared to patients without thrombocytosis (ferritin 198µg/L vs 166µg/L, $p < 0.001$; CRP 59.5mg/L vs 30mg/L, $p < 0.001$). Iron deficiency (ferritin < 30µg/L) was seen in 28.2% (237/840) of patients with thrombocytosis, compared with 32.1% (4286/13353) in the group without thrombocytosis.

The current study did not show any positive association between serum ferritin level and thrombocytosis. This may be related to the underlying patient population with higher levels of inflammation, as evidenced by the significantly higher CRP levels in those patients with thrombocytosis, and reflect the role of ferritin as an acute phase reactant.

Given the ongoing uncertainty in the literature further studies are required to enhance the understanding of the relationship between serum ferritin and thrombocytosis.

P149. Atypical presentation of multiply relapsed Thrombotic Thrombocytopenic Purpura: Stroke without initial laboratory evidence of TTP

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Introduction

Thrombotic Thrombocytopenic Purpura is caused by severely reduced activity of the von Willebrand factor-cleaving protease ADAMTS13 (typically < 10%) and is considered a medical emergency with high fatality rate unless urgent treatment is instituted. It is a rare disorder with incidence of 3 cases per one million per adult year and the hallmark features are Microangiopathic Haemolytic Anaemia and Thrombocytopenia.

Case

We report a case of a patient with relapsed refractory TTP with (ADAMTS13 Activity persistently < 1% for many years) who after receiving this diagnosis nearly four decades ago was treated with several different modalities including steroids, splenectomy, regular cryosupernatant infusions every 2 -3 weeks and Rituximab. On this occasion he was admitted with an acute ischemic stroke manifesting as dysphasia and left sided weakness without any evidence of MAHA and thrombocytopenia at presentation but went on to develop a relapse of his TTP over the next 48 hours. Once identified, urgent treatment with therapeutic plasma exchange was commenced and this led to rapid improvement in dysphasia as well as complete resolution of thrombocytopenia while more gradual recovery of hemiplegia occurred over the course of next few weeks. However, with tapering of plasma exchange the laboratory abnormalities suggestive of TTP returned and subsequently Rituximab was required for remission induction.

Conclusion

Atypical clinical presentation of TTP although rarely seen, can potentially lead to delay in initiation of appropriate treatment. Clinicians should remain vigilant for such atypical presentations particularly in patients with a known history of TTP.

P150. A retrospective study examining bleeding event severity on anticoagulation therapy related to distance from a major regional centre

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Aim

The risk of major bleeding in patients on anticoagulation therapy commonly used in Australia is approximately 2-3% per year (Eikelboom 2016). The aim of this retrospective study conducted at Lismore Base Hospital was to assess the relationship between severity of bleeding event presentations on anticoagulation and geographical distance from Lismore Base Hospital. We hypothesised that patients living greater than 10km from a major regional centre would potentially suffer increased severity of bleeding events.

Method

752 patients over 18 years old that presented to Lismore Base Emergency Department between January and July 2017 with a non-surgical major or clinically-relevant minor bleeding event were identified from the Clinical Information Department at Lismore Base Hospital from the assigned discharge diagnosis. Exclusion criteria included patients under the age of 18 years old, inherited or acquired bleeding disorders, surgical bleeds, and patients not on anticoagulation therapy. Once exclusion criteria was applied, 50 patients were included in the analysis. Data was reviewed by investigators and the International Society on Thrombosis and Haemostasis bleeding scale was applied to score the severity of the bleeding event. Results were stratified by distance from Lismore Base Hospital.

Results

There was not a statistically significant difference in major bleeds by distance, with a rate of bleeding in the group that lived greater than 10km away of 38%, compared with 21% for those that lived within 10km (P value 0.33).

Conclusion

Whilst not statistically significant, this small retrospective study indicates a trend towards increased severity of bleeding events in patients on anticoagulation who live greater than 10km from a major regional centre. This warrants further review into contributory factors, especially considering Australia's large regional and rural population.

P151. Analysis of critical value reporting in haematology – experience of a small laboratory in Malaysia

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Background

The policy of critical value reporting has become part of the requirement for an accredited laboratory. This practice has contributed to the clinical efficiency, patient safety and operational effectiveness of a healthcare centre. We aim to evaluate the implementation of laboratory critical value in our centre for the improvement of our reporting policies.

Methods

This is a cross sectional study done on critical value in haematology tests in UiTM Medical Specialist Centre, Sungai Buloh, Selangor Malaysia, from January 2017 until December 2017. A retrospective analysis was performed by retrieving previous records on critical value reporting and callbacks made by our staff on haematology critical value list i.e. HGB, PLT, PT, INR, APTT and presence of abnormal cells in the blood film.

Results

Out of 19,957 haematological results reported, about 0.5% (105) were critical value results. The most common critical value results were prolonged APTT of >80 seconds (30%), followed by raised INR of >5.0 (23%), low HGB of <6 gm/dL (17%) and prolonged PT of >38 seconds (10%). The critical callbacks were attended by nurses (91%), doctor/physician (4%) and medical assistant (3%). The average time from the critical value available upon test completion to the time when the critical value was notified to the patient's health caregiver was 32 minutes (± 115 minutes) and the median time of 14.5 minutes. We identified a few issues that warrant further investigations/attentions such as; callbacks that were made for non-critical values, failure to document person who received the calls, delay in reporting critical value (>100 minutes) and questionable critical values that could occur due to pre-analytical errors.

Conclusion

As there were some pitfalls in the critical value reporting, the laboratory need to be more efficient in identifying and informing critical values to the health caregivers. This is important to ensure all the critical results are notified at timely manner so that appropriate management can be justified.

P152. Monitoring an External Quality Assurance Performance for Haematology Analyser – Does the report type matter?

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Introduction

Participation in the inter laboratory assessment programme is an on-going exercise for an accredited laboratory. An informative statistical report is one of the key factors for the selection of an assessment programme. The aim of this study is to assess and document the external quality assessment (EQA) performance report for our two haematology analysers, Siemens Advia 2120i, through participation in the RCPAQAP.

Method

External quality assessment reports for both analysers were evaluated from 2013 to 2017. Common blood parameters i.e. WBC, RBC, HGB, HCT and PLT were included in this assessment. Interim and end-of-batch reports were selected for this review. The overall performance for each parameter was expressed as percentage of concordant versus discordant results.

Results and Discussions

For the interim reports (Figure 1), the laboratory secured 97% and 99% of concordance for WBC and RBC and 100% concordant results for HGB, HCT and PLT. On the contrary, the end-of-batch (Figure 2) reports showed 100% concordance only for HCT and PLT but 95% concordance for RBC and 75% each for WBC and HGB. The agreement between interim and end-of-batch performance report were consistent for WBC, RBC, HCT and PLT unlike HGB that showed disagreement for end-of-batch reports. An interim report is confined to values within acceptable limits of the within run but a cumulative end-of-batch report may pick imprecision, inaccuracy or total systematic errors (bias) for between run of that particular batch. Single unacceptable result for interim report could be a trigger for recognizing an error and reviewing historical batch data for end-of-batch report may help in assisting the troubleshooting process and identifying the root cause.

Conclusion

Each EQA programme provides different type of reports throughout the cycles. These reports contain information that need to be interpreted carefully before effective corrective and/or preventive actions can be employed. Regular review is warranted for the delivery of quality diagnostic services.

P153. What happens when an alpha male meets an alpha female?

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Aims

To describe a complex antenatal alpha thalassaemia parental workup where 5 alpha globin gene mutations were identified.

To highlight that a considered sequential multimodal approach (with knowledge of test limitations) is required to accurately diagnose alpha globin gene variants.

Method

An antenatal patient was referred for follow up and investigation of anaemia. Routine haematology, haemoglobin electrophoresis, iron studies and molecular testing were performed on the patient and subsequently on her partner. Molecular testing included GAP PCR for common deletions, HBA MLPA, HBB MLPA, PCR for the alpha gene triplication and alpha globin gene sequencing. Parental test results were reviewed and fetal risk assessment was performed. Confirmatory testing was performed on the baby postnatally.

Results

The maternal Hb was low (87g/L), with an MCV of 82fL and an MCH of 26.5pg. Testing revealed that the mother was iron deficient and by reflexed investigations also a carrier of 2 abnormal alpha globin alleles (α -3.7/aaa-3.7). Her partner was microcytic (MCV 77fL, MCH 25.1pg) and on Hb EPP, 3 variant haemoglobin peaks were identified. Subsequent alpha globin gene sequencing identified that the father was a carrier of 2 alpha globin variants (Hb Q India and Hb Brugg) plus an alpha thalassaemia (c.60delG) point mutation. With this knowledge, the risk to the fetus was calculated to be low and pre-natal diagnosis deemed unnecessary. Postnatal follow up of the baby demonstrated inheritance of 3 of the identified parental alpha globin mutations.

Conclusions

This case of multiple alpha-globin gene mutations detected in routine antenatal screening highlights the value of integrating haematologic and molecular testing and the need for a considered, sequential approach to investigation of haemoglobin disorders. It also validates our approach of progressing to thalassaemia testing in pregnant patients regardless of their iron status as thalassaemia and iron deficiency frequently co-exist.

P155. A possible Deferasirox-induced severe adverse reaction in a young adult with Beta Thalassaemia Major

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This case report details a unique case of acute, reversible liver toxicity and hyperammonaemia in a 19-year-old female with Beta Thalassaemia Major on chronic transfusion protocol and iron chelation. In the days prior to admission she was commenced on the oral iron chelating agent, Deferasirox. There is substantial literature documenting Deferasirox-induced renal injury, including Fanconi syndrome, but less documentation of hepatic toxicity and hyperammonaemia outside of the paediatric population. Despite rigorous biochemical and radiological testing a unifying diagnosis was not reached, however the patient required Critical Care Support for over a month and showed slow neurological improvement during this time. To the best of our knowledge this is a unique case in the adult population, that highlights possible serious adverse affect of Deferasirox.

P156. Practice patterns of pharmacological thromboprophylaxis following bariatric surgery in Australia and New Zealand

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Aim

To investigate the practice patterns of bariatric clinicians in Australia and New Zealand regarding pharmacological thromboprophylaxis following bariatric surgery.

Methods

We conducted a cross-sectional online survey consisting of 21 questions to investigate doctors' approaches to venous thromboembolism (VTE) pharmacological prophylaxis following bariatric surgery (choice of agent, dose, duration of treatment, risk-adjustment). It was distributed via the Australian & New Zealand Metabolic and Obesity Surgical Society to their members. Descriptive statistics were derived from the survey responses.

Result

A total of 20 bariatric surgeons and 1 bariatric medical practitioner completed the survey. 24%, 52%, and 100% of these clinicians used pre-operative, intra-operative, and post-operative thromboprophylaxis, respectively. Post-operatively, enoxaparin was the most common choice (57%), followed by unfractionated-heparin (UFH; 38%). The commonest dose and frequencies were: 40 mg daily for enoxaparin, and 5000 IU twice-daily for UFH. Most clinicians gave thromboprophylaxis until discharge (90%). The main risk factors for VTE considered by respondents were history of VTE (81%) and obesity (52%). 38% of respondents altered their thromboprophylaxis protocol based on the patient's body mass index, and 71% changed protocol if they deemed a patient high-risk for VTE. No clinicians measured Anti-factor Xa levels or screened for VTE in asymptomatic patients following bariatric surgery. 76% of clinicians utilised one or more thromboprophylaxis guidelines, and 67% agreed that there is a need for more specific guidelines for bariatric surgery.

Conclusion

In Australia and New Zealand, there is marked variability in bariatric clinicians' thromboprophylaxis protocols following bariatric surgery, particularly with the decision to use pre-operative and intra-operative dosing, and approaches to risk-adjustment. Specific guidelines in this area are warranted.

P157. Evaluation of a Cloud-Based Differential and Abnormal White Cell Morphology Tool

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Aim

Evaluation of cloud-based digital morphology tool including ease of use, remote access, differential count and white cell blood morphology assessment on blood films.

Background

Blood film evaluation continues to be a challenge for both G laboratories and B laboratories with main challenges being maintaining training and competency and access of regional and remote laboratories to fast and adequate review of blood films. The technology we evaluated is scanner agnostic and cloud based built on artificial intelligence and deep learning. It has been developed by Techcyte.

Method

In the first stage of the study 20 quality assurance slides were scanned into a .svs format using an Aperio scanner. The slides were uploaded to the cloud-based application and differential count was obtained. Each differential was compared with the median result and acceptable range on the quality assurance report. All slides were independently reviewed by at least 2 morphologists. Another 180 slides are currently being reviewed.

Results

Evaluation showed the Techcyte cloud-based tool is easy to use, allows remote access with approximately 20 minutes to upload and evaluate the blood film. Differential count performed showed acceptable concordance for neutrophils, lymphocyte and monocytes. Ongoing evaluation of 180 blood film with abnormal white cell morphology will be presented at the meeting.

Conclusion

Deep learning, artificial intelligence and improvement in internet services allows easy access to blood films for remote review and reduction of intensive morphology training requirements on laboratories. This is likely to help in faster diagnosis of various haematological diseases.

P158. A Single Centre Retrospective Review of Autologous Haematopoietic Progenitor Cell Mobilisation and Collection in AL Amyloidosis

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Aim

To review nursing management of immunoglobulin light chain (AL) Amyloidosis patients undergoing autologous haematopoietic progenitor cell (HPC) mobilisation and collection procedures, to seek to improve patient outcomes and delivery of care.

Method

A retrospective review of medical records of AL Amyloidosis patients from January 2016 to December 2017 (inclusive) who had HPC collection.

Results

Twelve patients underwent HPC mobilisation and collection. Of these, 9 patients had AL Amyloidosis - 5 with cardiac involvement, 2 patients had Cardiac Amyloidosis and one patient Myeloma and AL Amyloidosis with cardiac involvement.

Mobilisation approaches used were GCSF alone 10 (66%) GCSF and Plerixafor 2 (13%) Cyclophosphamide and GCSF 3 (20%). Three patients required a second mobilisation attempt to proceed to collection.

All patients had successful HPC collections (range 2-4 CD34⁺x10⁶/kg), over 1 – 3 days, using Com.Tec and Optia continuous flow cell separators. Venous access was obtained peripherally in 11 patients. Five patients with cardiac amyloidosis/involvement had elective IV calcium infusion and continuous ECG monitoring during collection. Adverse events were reported during collection procedures (see chart below).

Conclusion

AL Amyloidosis is a rare haematological disorder. Autologous HPC transplant has improved outcomes and overall survival for people with AL Amyloidosis, however there is an increased rate of morbidity and mortality during HPC mobilisation and collection (Yeh et.al, 2018. Comenzo & Gertz, 2002) compared with other diseases. This review has demonstrated that successful HPC mobilisation and collection can be achieved with minor, manageable adverse events. A thorough patient history and nursing management plan ensures the best outcome for AL Amyloidosis patients. Patient monitoring during mobilisation and nursing written reports were identified as areas for improvement.

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P159. Evaluation of activation and homing markers on regulatory T cells using a 12-color flow cytometry assay

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Aim

Deeper understanding of regulatory T cell (Treg) biology and heterogeneity in terms of phenotype, function and distribution is critical for the successful development of therapeutic and diagnostic applications. Several reports have identified markers correlating with different biological functions of Treg subsets, but the interplay between these markers as it relates to regulation of Treg biology and function remains largely unknown. In order to characterize Treg subsets in greater depth, we developed an 8 + 4 color modular flow cytometry assay exploring Treg activation and homing.

Method

An 8-color backbone panel was developed using antibodies against CD3, CD4, CD25, CD127, FoxP3, CD45RA, CD15s and CD161 for the detection of Treg subsets in fresh PBMCs from healthy donors. Two supplementary 4-color drop-in panels for activation or homing enabled deep phenotypic characterization of Treg subsets.

Result

The 8-color backbone panel enabled clear identification of CD3+CD4+CD127 low/neg CD25+FoxP3+ Treg cells, further categorized as CD45RA+ (naïve) and CD45RA- (activated) subsets. The inclusion of CD15s and CD161 in the backbone panel enabled identification of functionally suppressive effector and/or pro-inflammatory cytokine-secreting Tregs within the heterogeneous CD45RA- population. Supplementation to the backbone panel with a 4-color drop-in activation panel (PI16, CD147, CD39 and HLA-DR) enabled examination of the interplay between multiple activation markers in a single tube, and identification of a subset of Tregs co-expressing high levels of CD15s, HLA-DR, CD147, PI16 and FoxP3. Similarly, supplementation to the backbone panel with a 4-color drop-in homing panel (CCR4, CCR6, CXCR3, and CD31) enabled the identification of Treg subsets phenotypically similar to T-helper cell subsets. In addition, recent thymic emigrants were identified based on CD31 expression within the naïve Treg population.

Conclusion

Altogether, a modular 12-color flow cytometry assay presents a new approach to enable a deeper and more comprehensive analysis of different aspects of Treg biology in a simplified workflow.

P160. What is the best way to measure blood cell mean telomere length?

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Aim

Telomeres are a robust biological marker of cellular aging, with short blood cell telomere length considered a genetic risk factor for haematological disorders including myelodysplastic syndrome, AML, and CLL. Despite newer technologies, the measurement of mean telomere length by southern blotting remains the gold standard. In this study we aim to improve reliability of the method by comparing DNA extraction processes, digestion and amounts.

Method

Genomic DNA was extracted from whole blood using commercial kits (Qiagen) or from red cell lysed-white cell pellet by the salt-extraction method. DNA was digested overnight at 37°C using either a 2 (*RsaI*; *MspI*), or 6 (*HhaI*; *HinfI*; *MspI*; *HaeIII*; *RsaI*; *AluI*) restriction endonuclease combination (Promega). Amount of DNA (1.0, 1.5, 2.0 and 2.5 µg) in the digestion was also compared. Telomeres were detected with a DIG-labelled oligonucleotide probe, visualised by chemiluminescence and analysed with ImageQuant TL v8.1.0.0 software (GE Healthcare Life Sciences). Mean telomere length was calculated using the formula $\frac{\sum(MW_i \times NI_i)}{\sum NI_i}$. *Statistica* was used for all statistical analyses.

Results

Between blot variation was 6.5% (n=7). Samples digested with 2 endonucleases had a mean telomere length 12% longer than those digested with 6 endonucleases (n= 17; p=0.007). When comparing amount of DNA there was a significant difference in mean telomere length between samples extracted with the in-house salt-extraction method (p=0.03) but not DNA extracted using commercial kits (p=0.33).

Conclusion

Measurement of mean telomere length is more reliable and reproducible when using a commercial DNA extraction kit and digestion with the 6 restriction endonuclease combination. While the amount of DNA makes no difference under these conditions, a smaller volume is advisable for practical reasons. Telomere length analysis by southern blotting is a robust and consistent biomarker assay suitable for implementation in both clinical and research settings.

P161. Post-operative reactive thrombocytosis & the risk of venous thromboembolism in the setting of general surgery

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Aim

Surgery is a risk factor for venous thromboembolism (VTE). There is a paucity of data on how post-operative reactive thrombocytosis influences VTE risk in the setting of General Surgery. We aim to assess the rate of reactive thrombocytosis, defined as platelet count $\geq 450 \times 10^9/L$ amongst post-operative general surgery patients who develop a VTE.

Methods

This was a case control study undertaken at St. Vincent's Hospital Melbourne. Patients in the Colorectal, Hepatobiliary and Breast & Endocrine Surgery units who were diagnosed with a postoperative VTE between 2012 and 2018 were compared against a case matched control group. Patients receiving therapeutic anticoagulation, with myeloproliferative disorder or pre-operative platelet levels $\geq 450 \times 10^9/L$ were excluded. Post-operative platelet count prior to the VTE was recorded to observe the association between elevated platelet levels and VTE. The results were analysed using the Fisher's exact test, chi-squared test and logistic regression model.

Results

35 patients who developed an inpatient VTE following their procedure were chosen as the case group. Amongst the 35 cases, 24 patients underwent Hepatobiliary Surgery, 7 underwent Colorectal Surgery and 4 had breast or endocrine procedures. Of these patients 7 patients developed a post-operative reactive thrombocytosis prior to their VTE diagnosis (20 %, p-value = 0.18). Post-operative reactive thrombocytosis was not associated with an increased risk of VTE (odds ratio 2.45, P=0.25 95% CI 0.54 -11.19), after adjusting for other patient factors.

Conclusion

This study showed that post-operative reactive thrombocytosis did not significantly increase the risk of in-patient VTE following general surgery. Our study was limited by its small sample size. A multicentred study which includes a 90-day post-operative follow up would be better placed to determine the significance of reactive thrombocytosis as an independent risk factor for VTE.

P162. A family crisis - Pure red cell aplasia presenting in multiple family members

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Case report

Hereditary spherocytosis is an autosomal dominant inherited condition which due to defective red cell membrane proteins has reduced deformability and leads to decreased survival in the circulation¹. Red cell aplasia has been reported secondary to parvovirus B19 in those who have an acquired or hereditary haemolytic anaemia, and in particular patients with hereditary spherocytosis^{1,2,3}. One hypothesis of how an infection with parvovirus can lead to red cell aplasia is a temporary arrest of haematopoiesis as a direct infection of the erythroid precursors^{2,4}. Another theory is the occurrence of parvovirus-associated haemophagocytosis, resulting in a pancytopenia¹. This likely occurs in patients without chronic haemolysis, but because of their relatively long red cell survival and the self-limiting nature of the infection and aplasia, these episodes generally pass without symptoms⁵.

We will present a case report of a family with previously asymptomatic and undiagnosed hereditary spherocytosis that sequentially presented with red cell aplasia secondary to infection with parvovirus B19.

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P163. Haemoglobin SE disease: a rare or under reported entity

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Background

Haemoglobin (Hb) S and E are common haemoglobinopathies worldwide with distinct geographic areas of prevalence. Hb SE double heterozygous state is uncommonly reported.

Case report

A 25 year old, asymptomatic male with a family history of thalassemia/haemoglobinopathy underwent thalassemia screening. His parents migrated from Mauritius, were of mixed ethnic background (Portuguese, French, and Southeast Asian) but were not available for testing. Full blood examination showed Hb 127 g/L, MCV 74 fl, MCH 25 pg and RDW 14.8. HPLC (Biorad VII) showed HbA of 4%, elevated HbA₂ (31.2%) and HbF (4.8%). An additional abnormal Hb peak (58.6%) with a retention time of 4.32 mins was noted. Sickle solubility test was positive. Cellulose acetate gel electrophoresis (pH 8.6) and acid citrate agar (pH 6.2) showed bands consistent with HbS and HbE. DNA analysis (β globin sequencing) confirmed compound heterozygosity for HbE and HbS. No additional mutations were identified in the alpha globin genes. He has been advised about partner screening and haemolytic/ sickling complications.

Discussion

Common compound heterozygous beta globin gene mutations include Hb E- β thalassemia, Hb SC disease and Hb S- β thalassemia. The presentation of Hb SE disease can be variable with the majority being asymptomatic. Prevalence may be higher in countries with mixed migrant populations such as Australia. Partner screening is important because of the risk of more clinically significant haemoglobinopathies (such as Hb SS) in their children. Literature review suggests haematological parameters and levels of Hb S, E or F do not predict clinical severity. Presence of β -E dimers could interfere with Hb S polymerization in Hb SE double heterozygotes, explaining why these patients are asymptomatic with Hb S levels of nearly 60% (and Hb F <10%).

P164. ALK positive infantile histiocytosis: a rare cause of refractory thrombocytopenia

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Histiocytoses are a diverse group of rare, clinically heterogeneous disorders characterised by tissue infiltration of histiocytes, which may result in organ dysfunction and failure. Over 100 different subtypes of histiocytoses have been recognised, including rare case reports of ALK positive infantile histiocytosis. We report a case of histiocytosis in a neonate who presented with refractory thrombocytopenia, anaemia and intermittent neutropenia. Histiocytes were present in peripheral blood smears and bone marrow examination; ALK positivity was demonstrated by immunohistochemistry. Given the scarce reports of this condition, variable organ involvement, and different approaches to management in the rare cases described, we seek to expand the awareness of this entity by providing a report of our patient whose condition resolved without chemotherapy.

Bone marrow examination should be strongly considered in infants with severe or refractory unexplained cytopenias and ALK immunohistochemical staining should be performed in the work up of any atypical or abnormal histiocytic infiltrate. Without thorough and judicious work-up, there is a risk of delayed diagnosis, non-recognition, unwarranted investigation, and potentially, inappropriate management. Furthermore, the presence of histiocytes in peripheral blood smears of patients with this condition has not previously been reported and underscores the importance of routine careful evaluation of blood smears.

P165. Serum free light chain in chronic hepatitis C infection

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Introduction

Chronic hepatitis C (HCV) infection is associated with the development of benign and malignant lymphoproliferative disorders including mixed cryoglobulinaemia and B cell non-Hodgkin Lymphoma (NHL). HCV infection induces chronic stimulation of the adaptive immune response with dysregulation of B cell proliferation. Serum free light chain (FLC) is a known marker of prolonged immune stimulation and B cell proliferation. Past studies have only shown an association of raised FLC and chronic HCV in patients with an underlying lymphoproliferative disorder.

Case report

We present a case of a 79-year-old lady with chronic HCV, who presented with dysphagia and myalgia and was found to have a raised lambda FLC level (1467 mg/l), without any evidence of an underlying myelomatous or lymphoproliferative disorder. HCV eradication with direct-acting antiviral agents (DAA) resulted in resolution of all her symptoms and marked reduction of lambda FLC levels (104 mg/l), one year after HCV eradication.

Conclusion

This case study highlights the association between chronic HCV infection and raised FLC levels, which regresses slowly with HCV eradication. This suggests that raised FLC in hepatitis C is an inflammatory response to immune stimulation, which is slow to wane despite HCV eradication. Patients with chronic HCV who have a high serum FLC level may be at risk of developing a lymphoproliferative disorder. There is no current guideline for routine measurement of FLC but monitoring of FLC at diagnosis of HCV infection and after eradication may be beneficial in its role as a potential marker for patients at higher risk of developing lymphoproliferative disorders.

P166. Red cell exchange improves pregnancy outcomes in sickle cell disease – a local experience

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Aim

Pregnancy outcomes in women with Sickle Cell Disease (SCD) have traditionally been poor. Whilst this association has been well characterised in large international multi-centre audits, local data of pregnancy outcomes in sickle cell, particularly in patients receiving regular Red Cell Exchange (RCE), is lacking.

Method

We conducted a retrospective review of pregnancies within the SCD population managed at the Royal Melbourne Hospital between 2001 and 2018 to identify pregnancy outcomes.

Results

We identified 10 pregnancies amongst 5 patients with SCD (4 = HbSS, 1 = HbSC) managed during this time. Two patients were receiving regular RCE prior to pregnancy and continued throughout, with a further patient commenced on RCE at 27/40 as per local practice. Of the 3 women receiving regular RCE during pregnancy, all had live births (n=7); 1 via normal vaginal delivery (NVD) and 6 elective caesareans due to cephalopelvic disproportion. Six of these were at term, with one induced at 32/40 due to line sepsis as a complication of RCE. Two of these pregnancies were also complicated by gestational diabetes.

Two patients were not managed with regular RCE. The first declined treatment in both pregnancies, with pregnancy 1 complicated by intrauterine growth restriction (IUGR) and delivery via NVD at 37/40, and pregnancy 2 complicated by placental abruption and fetal death in utero (FDIU) at 22/40. Both pregnancies were also complicated by gestational thrombocytopenia. The second patient was on hydroxyurea at time of conception, initially continued during pregnancy due to a rare blood phenotype prohibitive of RCE, but ceased at 27/40 in the setting of IUGR. She commenced RCE at 30/40 but suffered placental abruption, sickle cell crisis, and FDIU at 34/40. No offspring had a Haemoglobinopathy of clinical significance.

Conclusion

RCE was well-tolerated and associated with apparent improved maternal and fetal outcomes in this small cohort of sickle cell patients.

P167. Let the lanterns lead the way

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Introduction

Parvovirus B19 is a single stranded DNA virus, which primarily replicates in human erythroid progenitor cells, and uses the erythrocyte P antigen as a cellular receptor for entry. It is commonly implicated in transient aplastic crises in haemolytic anaemia, but may also present as a chronic infection resulting in pure red cell aplasia. Serological testing is rapidly available, sensitive and diagnostic in most such cases and thus classic bone marrow findings are rarely seen in daily laboratory practice. We present here two cases where a bone marrow was necessitated by clinical context and where parvovirus B19 infection was suspected after the classic morphological findings were noted on the aspirate.

Patients

Patient 1: A 28 year old female with stage IV Hodgkin lymphoma who had completed escalated BEACOPP chemotherapy three months prior presented with predominant profound anaemia with subsequent transfusion dependence and mild persistent neutropenia. A concern for relapsed Hodgkin lymphoma resulted in a bone marrow biopsy with the trephine demonstrating giant foamy proerythroblasts with nuclear inclusions.

Patient 2: A 72 year old female with known gastrointestinal stromal tumour had mild pancytopenia of unknown cause. The bone marrow aspirate demonstrated red cell aplasia. The trephine demonstrated numerous pronormoblasts with foamy nuclei, and condensed intranuclear inclusions. Subsequent parvovirus B19 immunohistochemistry showed strong nuclear staining of these cells.

Discussion

Findings in both cases were confirmed by parvovirus IgM and parvovirus PCR positivity. The images from these two cases clearly demonstrate the classic cytopathic effects of parvovirus B19 with the pathognomonic lantern cells on bone marrow aspirate and trephine. They serve as an example of a seldom encountered, but useful morphological feature for trainees and haematopathologists alike.

P169. Towards appropriate prescribing of intravenous iron in a regional setting

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Aim

To assess the appropriateness of intravenous iron prescribing in a regional setting and implement service improvement projects where deviations from best practice were identified.

Methods

Latrobe Regional Hospital (LRH) deliver all outpatient intravenous (IV) iron therapy through their chemotherapy day unit (CDU), providing an opportunity to study the total prescribing practices in a busy rural referral centre. Baseline data of all IV iron infusions was collected from September 2017 to January 2018 (PRE-phase 5 months). Appropriate diagnosis of iron deficiency and failure to trial oral supplements, were identified as key gaps in practice. From February to May 2018 (POST-phase 4 months), referrals were streamlined for Local medical officer's (LMO) into a single outpatient general medical clinic. Specialist Hospital Physician referrals were coordinated through an existing haematology clinical nurse consultant (CNC) led iron infusion service for high risk complex medical patients. An education program on optimal diagnosis and management of iron deficiency for all prescribers was delivered. Data was analysed according to three referral groups, Physician, LMO and Obstetrics and Gynaecology (O&G).

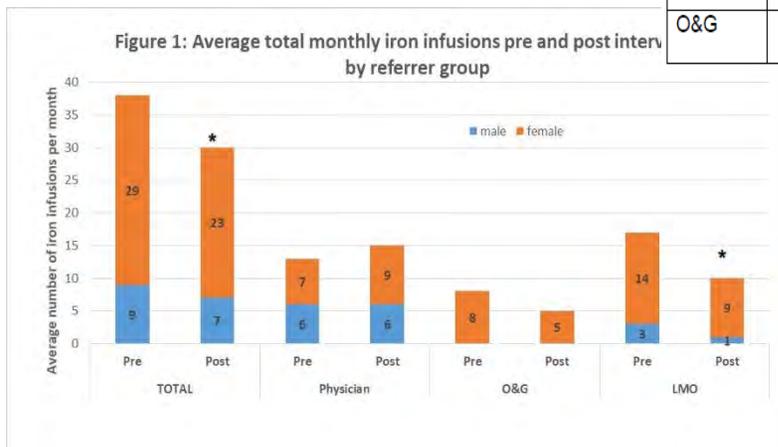
Results

Table one summarises the total 311 iron infusions delivered over the 9-month data collection period. The physician group referred an older population of both males and females. The LMO referral group were predominantly female.

Table one: Patient numbers and demographics between referral groups

Referrer	Total N	Female N (%)	Age Median (range) Years	
			Female	Male
Physician	126	74 (59)	66 (22-92)	77 (27-99)
LMO	123	103 (84)	51 (19-91)	73 (18-93)
O&G	62	62 (100)	25 (16-50)	

Figure one shows the average monthly iron infusions for the entire collection period (Total) and as per each referral group.



There was a significant reduction in average monthly iron infusion delivered from 38 to 30 ($p < 0.02$). Referrals from the LMO group reduced significantly from 17 to 10 ($p < 0.01$). Whilst referrals from the physician group increased and O&G group decreased, these were not significant.

The CNC coordination service, resulted in a reduction in red cell transfusions and acute hospital

admissions.

Conclusion

Rapid intravenous iron preparations have simplified the delivery of parenteral iron, however this may be at the expense of good prescribing practices. Provision of a safe and appropriate outpatient iron infusion service must be delivered with adherence to best practice guidelines.

P171. A case report of fetal haemoglobin induction with metformin and hydroxyurea in beta thalassaemia major

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Introduction

Pharmacological induction of fetal haemoglobin (HbF) has the potential to alleviate globin chain imbalance and ameliorate the clinical course of beta thalassaemia major. Metformin, a biguanide used widely in type 2 diabetes, has been reported to increase HbF levels. Whilst the precise mechanism of action is yet to be elucidated, a recent *in-vitro* study has shown that metformin increases HbF levels in haematopoietic stem and progenitor cells from normal human blood donors and patients with sickle cell disease, and that hydroxyurea and metformin combined induce HbF additively[1]. We describe a Jehovah's Witness patient with beta thalassaemia major treated with metformin in addition to hydroxyurea for HbF induction.

Case Report

A 69-year-old man with beta-thalassaemia major with co-inheritance of a single - α 3.7 gene deletion had not received a blood transfusion for more than 18 years due to his beliefs as a Jehovah's Witness. He had undergone a splenectomy, and developed multiple complications, including widespread extramedullary haematopoiesis requiring radiotherapy for spinal cord compression, mild hepatic iron loading requiring chelation therapy, high-output cardiac failure and severe pulmonary hypertension, osteoporosis, and hypogonadism.

He was commenced on hydroxyurea eleven years prior for extramedullary haematopoiesis with spinal cord compression. HbF was 98.1% on the maximum tolerated dose of hydroxyurea (14 mg/kg), before metformin 250 mg twice daily was added as a HbF inducer without adverse events. His haemoglobin progressively increased from 70 g/L to 91 g/L after 12 weeks, whilst HbF percentage remained stable.

Conclusion

This case shows that metformin in combination with hydroxyurea as a HbF inducer can lead to a progressive and significant increase in haemoglobin levels without adverse events in beta thalassaemia major. The potential of this approach requires further clinical evaluation; a pilot study is enrolling patients with haemoglobinopathies to determine the effectiveness of metformin as a HbF inducer[2].

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P172. Functional decline following allogeneic stem cell transplant may be improved with structured exercise

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Aim

To measure changes in physical function and health related quality of life in patients from pre- to 60-days post allogeneic stem-cell transplantation; to investigate the feasibility of an 8-week exercise program post-transplantation; and to measure changes in patient outcomes before and after the program.

Design

Prospective case series.

Method

43 patients undergoing allogeneic stem-cell transplantation were included. The intervention was an 8-week outpatient and home-based exercise and education program. Outcomes included exercise capacity (incremental shuttle walk test), self-reported physical activity and health-related quality of life measured pre-transplant, 60-days post-transplant (pre-intervention) and 100-days post-transplant (post-intervention).

Results

The consent rate was 93%. From baseline to 60-days post-transplantation there was significant decline in exercise capacity (mean difference 224 meters, 95%CI 153 to 295, $p < 0.0005$), self-efficacy for physical activity ($p = 0.001$) and quality of life ($p < 0.0005$). Ten participants did not commence the exercise program due to death, illness or cancellation of transplant. Following intervention, there was significant improvement in exercise capacity (mean difference 152 metres, 95%CI 76 to 227, $p = 0.001$) and quality of life ($p = 0.001$). No adverse events occurred.

Conclusion

Allogeneic stem-cell transplantation results in significant physical impairments and poor quality of life, which may be improved through structured exercise.

The high consent rate shows the willingness of patients to consider exercise in their recovery.

Not all patients were well enough to commence exercise at 60 days post-transplantation.

Commencing exercise pre-transplantation may improve this.

The addition of a structured exercise program to routine care post-transplant could be considered for transplant centres. Further research is required.

P173. Screening for distress - use of the distress thermometer and problem list

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Aim

Psychosocial care is a very prominent aspect for consideration in the treatment and management of adults with cancer. A diagnosis of cancer can have a significant impact upon many different aspects of a person's life. 'Distress' has subsequently been identified as the sixth vital sign for assessment in patients who have been diagnosed with cancer, both haematological and solid tumours. It is now a requirement for accreditation as an oncology facility in the USA to have an effective distress management program. Therefore, there is a need in Australian healthcare facilities to manage distress in adults with cancer, by screening for distress, identifying the associated problems to refer to appropriate services and implement necessary interventions. The National Comprehensive Cancer Network developed a screening tool called the "Distress Thermometer and Problem List" that can be utilised by healthcare professionals to detect distress, and identify the aetiology of the issues. The aim was to determine the validity and reliability of the tool.

Method

A systematic review (as a Masters of Nursing Project – unpublished) of the current literature was performed. Studies were included if they were conducted in Australia, pertaining to adults with cancer (any type of malignancy), both inpatient and outpatients

Result

A total of 1313 patients were included, 30% reported a clinically significant level of distress. There was a strong correlation between the level of distress and number of identified problems.

Conclusion

Screening for distress is an integral part of providing care to adults with cancer in Australia. The NCCN Distress Thermometer and Problem List is a valid and reliable tool that can detect distress levels and identify associated problems. The tool has been proven to be effective when administered by healthcare professionals to screen for distress in a population of adults with cancer in the Australian healthcare setting. The identification of issues can assist in providing information to the healthcare professionals as to what type of services the patient requires, and subsequently what referrals are needed.

P174. BloodSTAR – Australia’s Immunoglobulin Management System....and a world first!

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BloodSTAR (Blood System for Tracking Authorisations and Reviews) is an integrated online system developed to serve the needs of health providers and support Australia’s National Immunoglobulin (Ig) Governance Program. Introduced in 2016, and used by prescribers of Ig nationally, the system was developed by the National Blood Authority (NBA) on behalf of all Australian Governments and is the first of its kind in the world.

Ig is a precious biological product, and it offers a significant therapeutic benefit to people with haematological, neurological and immunological disease. However, due to the high cost of Ig and the demand for use in Australia, eligibility for access to Ig is achieved through strong governance arrangements. The objectives of the National Ig Governance Program include ensuring government-funded Ig products are directed to patients who are most likely to benefit based on reliable evidence, using the lowest effective dose, and where alternative therapies are limited.

Through BloodSTAR, prescribers are able to determine whether patients are eligible to receive government-funded Ig and seek authorisation for access. Clinicians and dispensers of Ig products utilise BloodSTAR and associated systems to manage infusions and dispensing practices to approved patients. The system replaces outdated paper based faxing processes which were previously used across Australia and streamlines the authorisation process. BloodSTAR also reduces variability and standardises prescribing practices, and increases efficiency and transparency while strengthening decision-making and improving data capture.

The system is now live in seven Australian states and territories with over 8,900 registered users. Rollout to NSW, the final state to go-live, is scheduled for 22 October 2018.

BloodSTAR’s design features support health providers to meet their Ig Governance obligations, and promote sustainability of Ig products well into the future. A major revision to the Criteria will also be released within BloodSTAR on 22 October 2018.

P175. The National Immunoglobulin Governance Program – partnering with clinicians to meet patient needs

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Treatments involving immunoglobulin (Ig) offer significant therapeutic benefit to people with haematological, neurological and immunological disease. However, Ig is a high cost product and the demand for use in Australia, per capita is amongst the highest globally.

Access to Ig in Australia is provided through specific governance arrangements. Where eligibility criteria are met, Ig is supplied at no direct cost to the patient. The cost instead, is met by all Australian governments via a process managed by the National Blood Authority (NBA).

In 2016-17, the cost of Ig exceeded \$532 million, representing 50% of the NBA's expenditure for the supply and management of blood products. To meet this demand, 44% of Ig issued in Australia was imported. While supply arrangements ensure Ig availability for those who need it, demand has been growing at an average 11% for at least the last eight years. Furthermore, variation in use has been observed between jurisdictions. Of greatest concern is an 11.9 fold variation observed across jurisdictions for Ig use in multiple myeloma.

The objective of the National Ig Governance Program is to improve governance, and ensure use and management of government funded Ig reflects appropriate clinical practice and represents efficient, effective and ethical expenditure of government funds, in accordance with relevant national safety and quality standards for health care.

The program measures include:

- developing policies and procedures for access to Ig
- establishing a national network of committees
- maintaining clinical access criteria
- implementing a national ordering and outcomes database
- developing a performance improvement program
- facilitating knowledge development

With the introduction of the National Ig Governance Program from 2014, the NBA is actively working to develop a robust framework to further improve the governance and management of Ig products in Australia.

P176. Development and Implementation of an algorithm to management mucositis in patients post autologous and allogeneic stem cell transplant

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Aim

Evidence from clinical practice has highlighted that the management of mucositis pain in patients undergoing stem cell transplantation for a haematological disease is frequently suboptimal. There is a paucity of evidence specific to the management of mucositis pain in the extant literature despite acknowledgement that in addition to causing significant pain, mucositis frequently impacts patient's nutrition and length of stay.

The aim of this study is to evaluate the efficacy of introducing an algorithm for the management of mucositis pain post autologous and allogeneic stem cell transplant on pain assessment, prescribing practices and patients pain outcomes.

Method

An assessment and treatment algorithm for mucositis has been developed using the literature and expert consensus from the anaesthetic and haematological units at Austin Health. The algorithm provides guidance for the assessment, prescription, and administration analgesics from the onset of mouth pain to the resolution of pain.

A longitudinal, multi-method design using patient survey and medical record audit will be used to evaluate the algorithm.

Result

The algorithm has been implemented into practice. The preliminary findings indicate improved:

- consistency in prescribing practices
- understanding of mucositis management by nursing staff in both the haematology and acute pain services teams
- processes for responding to patients' pain.

Conclusion

Four key improvements to the management of patients with mucositis are expected at the completion of this research:

- Reduction in unnecessary variation with prescribing practices within and across both acute pain services and haematology teams
- Improved pain assessment and completeness of documentation of pain assessments by nursing staff. This information is integral to the best management of patient symptoms
- Better understanding of the long term patient outcomes for patients who experience mucositis

Implementation of this algorithm for other patient cohorts that experience mucositis as a result of their treatment.

P177. Benefits of inpatient exercise classes

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Introduction

In my role as a Haematology Physiotherapist it was highlighted to me that the inpatient Haematology ward gym was not being utilised by patients. I began discussions with colleagues from Leukaemia and Blood Cancer New Zealand to create a group exercise class.

The aims of the classes were to increase patient use of the gym, increase activity levels, and provide a support network for patients and their families.

Method

The classes are advertised through posters and leaflets, as well as word of mouth through staff. Colleagues from Leukaemia and Blood Cancer New Zealand arrive on the ward prior to the classes to invite patients and their families to attend.

Classes run for an hour in total twice a week. Patients are educated on knowing their blood results and observations prior to attending. Exercises vary between resistance weights and theraband, cycling and group activities.

Results

An average of four patients attend each class per week. Physiotherapy treatment sessions usually last between 30-45 minutes. Therefore the classes approximately save me between 3 to 5 hours per week.

No data has been collated from the classes at present but conclusions can be drawn from experience.

Patients and their relatives frequently comment that they find it beneficial speaking to other patients and families in the ward going through similar experiences. Patients are distressed by losing muscle mass and find advice to combat this beneficial.

Conclusion

High participation rates are achieved on a regular basis in our ward exercise classes.

Running the classes prove to be cost effective compared to running one to one to Physiotherapy sessions and a greater number of patients partake in exercise on the ward. There also appear to be social and emotional benefits of the attending classes for patients and their families.

My future plan is to conduct research with the classes to gain potential data around exercise benefits in this patient population group.

P178. Impact of Bezlotoxumab in recurrent Clostridium Difficile Infection in MODIFY I/II participants with Haematologic Malignancy

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Aim: To evaluate the efficacy of bezlotoxumab in reducing recurrent CDI (rCDI) during the 12-week follow-up period in participants included in the Phase 3 MODIFY I/II trials who had a haematologic malignancy as a comorbid condition.

Methods: The modified intent-to-treat population from MODIFY I/II who received either bezlotoxumab or placebo was included in this *post-hoc* sub-analysis. The proportion of participants who achieved initial clinical cure (ICC), the incidence of rCDI, 30-day CDI-associated re-hospitalisation and mortality rate were assessed. Disease severity was assessed in participants who experienced rCDI during the follow-up period.

Results: In total, 107 participants were included in this sub-analysis: 53 participants in the bezlotoxumab group (56.6% female, median age 59 years) and 54 in the placebo group (38.9% female; median age 69 years). Almost all participants had ≥ 1 prespecified risk factor for rCDI (100% vs 96.3% in the bezlotoxumab and placebo groups, respectively), but a higher proportion of participants in the placebo group experienced ≥ 1 CDI episodes in the previous 6 months compared with the bezlotoxumab group (35.2% vs 15.1%). The proportion of participants treated with bezlotoxumab achieving ICC was higher than in the placebo group and the incidence of rCDI was lower in bezlotoxumab-treated participants compared with placebo (Table). Among participants who experienced rCDI, no bezlotoxumab-treated participants had severe CDI (Zar score ≥ 2) compared with 33.3% of those treated with placebo. A lower proportion of bezlotoxumab-treated participants had a CDI-associated re-hospitalisation compared with placebo (4.3% vs 11.6%). During the 12-week follow-up period, the mortality rate was 9.3% in participants receiving bezlotoxumab and 14.5% in participants receiving placebo.

Conclusions: Sub-analysis of the MODIFY I/II trials showed that bezlotoxumab reduced the rate of rCDI compared with placebo in participants with haematologic malignancy. However, due to the small number of participants included in this sub-analysis, further investigation is warranted to confirm these results.

	Bezlotoxumab % (n/N)	Placebo % (n/N)	Difference (95% CI)*
Proportion of participants that achieved ICC	81.1% (43/53)	66.7% (36/54)	14.5% (-2.3, 30.7)
Proportion of participants with rCDI	14.0% (6/43)	33.3% (12/36)	-19.4% (-38.1, -0.7)

*Based on Miettinen and Nurminen method

CI, confidence interval; ICC, initial clinical cure; n, number of participants in the subgroup analysis population meeting the criteria for endpoint; N, number of participants included within the subgroup; rCDI, recurrent *Clostridium difficile* infection

P179. Evidence for Adherence to Antifungal Guidelines in Haematology Patients

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Objective

To review the published literature assessing adherence rates to antifungal guidelines and reasons for non-adherence in the haematology/oncology setting.

Data sources

The databases Embase, Medline and PubMed (from data inception to March 2018) were searched using the terms haematology, oncology, antifungal, guidelines, adherence and stewardship limited to human subjects and published in English. This yielded, 123 hits. From this list, studies that were published in peer-reviewed journals were extracted, leaving 9 citations that met the final inclusion criteria.

Study Selection and Data Extraction

Nine studies were selected assessing adherence to consensus antifungal guidelines in the haematology/oncology setting. These included studies investigating the introduction of antifungal stewardship programs in tertiary hospitals.

Data Synthesis

Although the studies were heterogenous, most focused on appropriateness of antifungal therapy in the inpatient setting. Adherence to antifungal guidelines for optimal antifungal prophylaxis and treatment was suboptimal in most studies, with rates of inappropriate antifungal therapy ranging from 25 to 70% of fungal prescriptions.

Relevance to Patient Care and Clinical Practice

This review highlights that adherence rates for antifungal therapy to consensus guidelines are low in the haematology/oncology inpatient setting. This may affect infection rates impacting morbidity and mortality in this population.

Conclusion

This review has shown that adherence to established antifungal guidelines is suboptimal and opportunities such as antifungal stewardship exist to improve this. Adherence to antifungal guidelines in the outpatient haematology setting is unknown and should be evaluated in future studies.

P180. Strengthening Access Criteria for Immunoglobulin in Australia

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The National Blood Authority (NBA) is standardising and strengthening access criteria for immunoglobulin (Ig) funded by all Australian governments under the national blood arrangements and managed within the National Ig Governance Program.

Ig is a precious biological product, and it offers significant therapeutic benefit to people with haematological, neurological and immunological disease. However, due to the high cost and demand for use in Australia, eligibility for access to Ig is achieved through governance arrangements.

The *Criteria for the Clinical Use of Intravenous Ig in Australia* (the Criteria) describes the diagnosis and eligibility requirements to access government-funded Ig. It is based on evidence identified through systematic reviews of the literature and the opinions of clinical experts. The national Criteria was first published in 2007 and updated in 2012. On 22 October 2018, the NBA will release the third version (V3) of the Criteria, supported by a comprehensive communication strategy.

Developed by clinical working groups including practicing haematology, neurology, immunology and transplantation specialists and in collaboration with relevant clinical colleges and societies, V3 of the Criteria aims to more clearly articulate and standardise diagnostic, qualifying and review requirements. Forthcoming changes will strengthen the Criteria and help to ensure:

prescription of Ig is consistent with current evidence and expert opinion;
sustainability of Ig supply by ensuring continued availability for patients who derive genuine health benefits;
treatment decisions involve careful consideration of alternative therapies, prescribing the lowest effective dose, and appropriate weaning from Ig therapy; and
ethical expenditure of government funds in accordance with relevant national safety and quality standards for health care.

It is a requirement of the National Safety and Quality Health Service Standard (Blood Management Standard, Action 7.6) that health service organisations support clinicians to prescribe and administer blood products such as Ig in accordance with national criteria.

P187. Transfusion acquired haemoglobinopathy: muddying the waters

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Background

Regular blood transfusion, including red cell exchange transfusion, is routinely used in the treatment of patients with major haemoglobin disorders to improve anaemia and prevent serious disease related complications. To ensure optimised treatment, pre and post transfusion haemoglobin analysis by capillary electrophoresis is routinely performed in our laboratory. Transfusion associated haemoglobinopathy is a rare complication which can cause spurious and misleading results.

Case 1

An unknown haemoglobin variant (10%) was found in a 9 y/o female post exchange transfusion for sickle cell disease. Transfusion acquired Hb J was suspected which raised issues around donor screening and deferment from future donations.

Case 2

Electrophoresis on a 13 y/o male Burmese refugee with known transfusion dependent thalassaemia revealed 6% Hb E, elevated Hb F and transfused Hb A. Genotyping showed severe Beta 0 thalassaemia, with Hb E likely of donor source, necessitating a changed treatment plan with regular intensive transfusion.

Case 3

Recently arrived 8 y/o Indian female presented with severe anaemia and leucoerythroblastic blood picture. Claiming only 2 previous transfusions ever and none in last 3 months, electrophoresis revealed 10% Hb E in addition to a mildly elevated Hb A2 and Hb F for age. This was not suggestive of a significant thalassaemia syndrome however, subsequent genetic testing indicated compound Hb E/Beta + thalassaemia heterozygosity. Inaccurate transfusion history was probable in this case leading initial investigations to consider more sinister causes for leucoerythroblastosis.

Conclusion

Clinical diagnosis and management of haemoglobinopathy can be complex where transfusion acquired haemoglobinopathy may result in misdiagnosis. Accurate transfusion history may be challenging in recent migrants/asylum seekers. Haemoglobinopathy screening blood donors is not routine practice in Australia. Transfusion acquired haemoglobinopathy should be considered with unexpected findings. Genetic testing was essential in confirming diagnoses of cases presented, to ensure informed, appropriate patient treatment and family counselling.

P188. Marked change in ordering and use of blood products for Coronary Artery Bypass Surgery after the introduction of 'Rotocol' protocol

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Background

Cardiac surgery orders and uses more fresh blood products in our institution than any other department. Prior audit demonstrated high rate of products ordered and not used. Recent literature recommends the use of ROTational ThromboElastoMetry (ROTEM®) and platelet function testing (Multiplate) to guide blood transfusion practice to component specific replacement, potentially reducing transfusion. Collaborating with cardiac anaesthetists and ICU the transfusion department developed a protocol called the Rotocol for cardiac surgery which incorporates a ROTEM algorithm, multiplate testing and directions for transfusion, this commenced in May 2018.

Aim

Assess the initial impact of the Rotocol program on ordering and use of blood products

Method

Review of patient records receiving primary Coronary Artery Bypass Graft (CAGS) one month prior and one month after the introduction of POP and compare these results to an initial audit conducted in 2016-2017.

Result

Red cell and platelet ordering and use in primary CAGS has markedly reduced since the introduction of the Rotocol program compared to historical data and the immediate month prior.

Red Cells	Number of patients	Ordered	Used (%)	Not used (%)	CT Ratio
2016-2017	50	50	16 (31%)	36 (69)	3.25
April-May 2018	20	32	13 (40%)	19 (60)	2.5
May-June 2018	22	9	9 (100%)	0 (0%)	1
Platelets	Number of patients	Ordered	Used (%)	Not used (%)	Ordered Transfused Ratio
2016-2017	50	37	18 (58%)	19(52%)	2
April-May 2018	20	14	7 (50%)	7(50%)	2
May-June 2018	22	3	2 (67%)	1(33%)	1.5

Conclusion

Patients receiving surgery for CAGS since the introduction of POP there has been less fresh blood products ordered and transfused. Ordering patterns for platelets and red blood cells have reduced because of the goal-directed transfusion program and reduced expectations of blood product requirements. This has enabled better resource allocation of platelets and red blood cells.

P189. Group O RhD negative red blood cell units: the discord between demand and supply

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Background

Victoria has seen a 21% reduction in demand for red blood cells (RBC) since 2011, similar patterns are seen nationally and internationally. Demand for group O RhD negative units in Victoria has increased by 19%, or 17% of all RBC issues. In contrast Australian O RhD negative donor population is 9%. Wastage of O RhD negative units has declined from 10% to 3% in the same period.

Victoria Data	2011	2017	Percentage change
Total RBC issues	210,593	176,685	□16%
O RhD neg issues	24,594	29,263	□19%
O RhD neg issues as a proportion of total issues	12%	17%	□41%*

The Australian Red Cross Blood Service developed guidelines for the use of group O RhD negative RBCs (2008) to ensure availability for patients for whom there is no alternative.

Aims

To document the use of O RhD negative units and compare against the 2008 Guidelines, to better understand the increase in demand.

Methods

Audits circulated to all Victorian health services. Questions included patient demographics, ABO and RhD group, specific transfusion requirements, and urgency. Algorithms were developed to determine alignment of O RhD negative unit to 2008 Guidelines.

Results

Preliminary data to June 2018 shows a large variance from 2008 Guidelines (range 0-100%, mean 64%). Reasons for noncompliance are often unique to individual health services, e.g. regional “hubs” receiving rotational stock from satellite sites with short expiry results in high “used to avoid time-expiry”; routine transfusions of O RhD negative units to patients with other ABO groups due to not holding a full ABO inventory.

Summary

Data shows improvements are required to meet the 2008 Guidelines. With an increased understanding of how O RhD negative units are used strategies can be implemented to reduce inappropriate demand to better reflect the true need. Blood Matters will provide individual report cards to health services, including recommendations for improved practice.

P190. Infusions of Intragam 10® increase serum free light chain measurement in plasma cell myeloma patients with secondary hypogammaglobulinaemia

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Introduction

Plasma cells (PCs) secrete immunoglobulin or light chains. The detection and measurement of these proteins is used in diagnosis and monitoring of PC dyscrasias. The serum free light chain (SFLC) assay measures FLC in the serum by immunoturbidimetry.

PC myeloma (PCM) is complicated by secondary hypogammaglobulinaemia (SHG). SHG patients with infective complications are treated with infusions of intravenous immunoglobulin (IVIg) (1). IVIg infusions prior to measurement of SFLC can affect the result (2). Limited data is available about FLC in IVIg products but significant variation between preparations exists (3). Hypothesis: administration of IVIg increases free light chains.

Method

SFLC assays (*The Binding Site* Freelite®; SPAPLUS® analyser) were performed on samples collected immediately before and within one hour after infusions of IVIg in PCM SHG patients. In one patient, SFLC assays were performed daily for 5 days after infusion.

Results

6 patients with PCM and SHG had 7 sets of pre- and post-IVIg SFLC measurements. For patients receiving Intragam 10® (N=4) the median difference pre- and post-infusion for kappa and lambda light chains was 20.8 mg/L and 48.5 mg/L (NR: kappa 3.3-19.4, lambda 5.71-26.3). For non-Intragam® (N=3) products the median difference pre- and post-IVIg for kappa and lambda was 3.8 mg/L and 1.4 mg/L, respectively (see graphs). In two Intragam 10® patients the interpretation of disease status would be altered. In the patient with sequential SFLC assays, the changes resolved within 24 hours.

Conclusion

Administration of Intragam 10® increases SFLC in PCM patients. Precision of the Freelite™ assay is reported as 1.6-3.4% (4). The difference with Intragam 10® is greater than this coefficient of variance (CV), in contrast to non-Intragam 10® products where the difference remains within this CV. This may represent differences in the manufacturing process.

We recommend performing SFLC for disease monitoring prior to IVIg administration to avoid misinterpreting disease activity based on transiently elevated results.

References

1. National Blood Authority. "Access to intravenous immunoglobulin". <http://www.blood.gov.au/Intravenous-Ig> . Accessed on 3/6/2018.
2. Raines G, Webb A, Morgan S *et al*. Elevation of free light chain measurement after infusion of immunoglobulin. *Abstract at HAA ??Year*.
3. Sakem B, Matozan K, Nydegger U *et al*. 2013. Anti-red blood cell antibodies, free light chains and antiphospholipid antibodies in intravenous immunoglobulin preparations. *IMAJ*. 15:6 17-621
4. The Binding Site Freelite® sFLC immunoassays. Accessed at <https://www.wikilite.com/freelite-immunoassay-instrumentation> on 26/06/201

P191. The cessation of inverting whole blood prior to centrifugation

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Every year the Australian Red Cross Blood Service collects and processes 1.3 million blood donations which are then delivered to hundreds of healthcare providers around the country.

During whole blood collection, packs are continuously inverted to ensure even distribution of anticoagulant and then are transported to major processing centres for separation into red cells, platelets and plasma. Prior to separation at the processing centre, the blood packs are gently inverted again.

A review on the inversion process of whole blood packs in the processing centre prior to centrifugation was performed. A preliminary evaluation conducted in 2016 at the Brisbane Processing Centre, demonstrated that the cessation of inverting whole blood packs prior to centrifugation did not adversely impact blood component quality.

The Blood Service is currently undertaking a three month pilot at the Melbourne Processing Centre. The purpose of the pilot is to confirm that the cessation of inverting whole blood packs prior to centrifugation does not impact blood component quality and that the test results are reproducible at a second processing centre.

During the preliminary evaluation, a total of 141 whole blood donations were randomly selected not to be inverted prior to centrifugation. These components were segregated from routine inventory pending 100% Quality Control testing in accordance with the Council of Europe. This was to ensure the quality and safety of the prepared blood components was acceptable, prior to the release into inventory. The following quality control attributes were tested:

Component Type	Attribute	Specification	% Acceptance
Red cells	Volume (mL)	>220	75
	Haemoglobin (g/Unit)	≥40	75
	Haematocrit (L/L)	0.50 – 0.70	75
	Leucocyte Count (x10 ⁶ /Unit)	<1.0	90
	% Haemolysis (at end of storage)	<0.8	75
Pooled platelets	Volume (mL)	>160	75
	Platelet Count (x10 ⁹ /Unit)	>240	75
	Leucocyte Count (x10 ⁶ /Unit)	<0.8	90
	pH (at end of storage)	6.4 – 7.4	75
Fresh frozen plasma	Volume (mL)	250 - 310	75
	Platelet Count (x10 ⁹ /L)	<50	75
	Leucocyte Count (x10 ⁹ /L)	<0.1	75
	Plasma Hb (g/L)	No abnormal colour or visible clots.	100

Statistical analysis (unpaired t-test, two-tailed, 95% confidence interval) demonstrated no statistical or clinical significance between the current process (inverted) and the modified process (not inverted) for all component parameters.

Results from the preliminary evaluation concluded that the elimination of inverting whole blood packs prior to centrifugation, produced blood components of equivalent quality to those that had been inverted. It is hypothesised that results from the confirmatory three month pilot will reproduce the same test results at the second processing centre.

“Australian governments fund the Australian Red Cross Blood Service to provide blood, blood products and services to the Australian community.”

P192. Effect of dietary probiotics on anti-A/-B titres – pilot study and implications for major ABO-incompatible transplants

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Aim

Examine the relationship between baseline dietary probiotic intake and anti-A/-B titres and see if increasing or decreasing intake affects titres.

Methods

Baseline probiotic intake and anti-A/-B titres were determined in 20 non-AB volunteers in Christchurch, followed by a week of increase or decrease in probiotic intake - in those with relatively low or high baseline intake respectively, then re-determination of anti-A/-B titres. Descriptive statistics are used to present results.

Results

Volunteers, aged 19 – 64, of whom 7, 5, and 8 respectively were group O, A, and B, baseline probiotic intake scores ranged from 0 – 14 (median, 11). Group A participants were older than O or B participants. Baseline titres (anti-A/-B, IgM and IgG together), ranged from 8 – 512. Anti-B titres were lower than anti-A titres, baseline titres appeared to correlate negatively with age, and group O participants had higher titres than non-O people. Twelve and eight participants respectively reduced or increased probiotic intake. In those increasing intake, average fold rises in anti-A IgM, IgG titres, and anti-B IgM, IgG titres were 0, 1.2, 0.3, and 0.6 respectively with 3/8 showing a two-fold rise in one or other titre. In those decreasing intake, average fold fall in anti-A IgM, IgG titres, and anti-B IgM, IgG titres were -0.3, -1.1, -0.2, and -0.4 respectively with 3/12 showing a two-fold fall in one or other titre. Three participants achieved decreases in IgG anti-A that were not only serologically, but also clinically, significant.

Conclusions

This pilot study suggests that reducing dietary probiotic intake has small, potentially useful, effects on anti-A/-B titres. This may be relevant for patients scheduled for major ABO-incompatible transplants who may need plasma exchanges to reduce titres. A larger study involving better supervised, longer, periods of probiotic intake reduction will help to determine if this method may be clinically useful.

P193. Comparison of the Ortho1 Vision® Max analyser to the Ortho AutoVue® Innova System

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The Ortho Vision Max analyser is a high throughput automated instrument designed for immunohaematology testing using gel card technology. The analyser has four probes, two load stations and two centrifuges. Processing functions include pipetting, serial dilutions, reagent handling, incubation, centrifugation, reaction grading and interpretation using digital imaging. The analyser may be used as a standalone instrument or interfaced to a Laboratory Information System. This comparison study was performed by parallel testing of routine patient samples (Adults, Neonates and Cords) against our existing Ortho AutoVue analyser.

Tests Evaluated	Tests performed
ABO and Rh(D) Typing	n=114
Three cell antibody screen	n=73
Direct antiglobulin test (DAT) monospecific and polyspecific	n=10 and n=9
11 cell antibody identification panel (AID)	n=13
Crossmatch of donor red cells versus patient plasma	n=16 patients, n=25 units

Concordant results were obtained for 113/114 ABO and Rh(D) typings. The ABO discrepancy on both analysers was due to a mixed field reaction from a patient undergoing blood group conversion post-transplant. The Rh(D) typing was related to cord sample integrity. Reverse grouping reactions were weaker on the Vision in 23% of samples compared to the 10% reported by Lazarova². None of these gradings affected the interpretation of the groups.

Of 73 three cell antibody screens 16 were positive but four produced a higher reaction strength grading on the Vision Max.

Cord sample DAT testing produced two result discrepancies: positive on the Vision Max but negative on the AutoVue.

12/13 AID results were comparable with one sample failing to show reactivity against select homozygous cells. Crossmatching results on both analysers was identical.

Flagging alerts on both analysers were consistent.

Parallel testing demonstrated that the Vision Max was able to produce comparable results with the AutoVue instrument and is recommended for routine use for the tests included in this study.

¹Ortho Clinical Diagnostics, 1001 US-202, Raritan, New Jersey, United States

²Lazarova E, Scott Y, van den Bos A, et al. Multicentre evaluation of the new Ortho Vision analyser. *Transfusion Medicine*, 2017,27, 354-361.

P194. Evaluation of a new RhD Monoclonal Ortho ABD cassette

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Background

Ortho group cassettes use the same RhD Monoclonal reagent for forward and reverse group and group checks. A new cassette for performing the forward group check using a different monoclonal antibody was released and validated at our site.

Aim

To compare and evaluate the effectiveness of the new Ortho Clinical Diagnostics ABD cassettes containing the new RUM1 clone against the current D7B8 clone in detecting Variant D.

Method

Test fresh patient samples on both the current batch of Ortho D7B8 clone ABD cassettes and the new Ortho RUM1 clone ABD cassettes. Compare and evaluate the Rh (D) grading between the different cassettes.

Result

Of the 185 patient samples tested, 184 samples were concordant and 1 sample discordant (99.5% concordance rate). The discordant sample was from a known weak D patient which consistently came up negative in the Anti-D well of the ABD D7B8 clone cassette. When run on the RUM1 cassette the reaction was a 1+, therefore indicating that the RUM1 clone was more sensitive and/or able to bind to a section of the Rh (D) antigen that the D7B8 clone was unable to.

Conclusion

Use of two different clones for RhD testing would increase the likelihood of detecting variant D patients.

P195. The redevelopment of BloodNet - BloodNet 5

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BloodNet is Australia's online blood ordering and inventory management system. It is a web-based application that allows staff in health facilities across Australia to order blood products in a standardised way quickly, easily and securely from the Australian Red Cross Blood Service (Blood Service).

BloodNet was originally developed as ORBS by QLD Health in 2007-08. The National Blood Authority (NBA) rebranded it as BloodNet and coordinated a national implementation between 2010 and 2012. By 2016, the NBA had delivered a series of upgrades and enhancements and BloodNet version 4 was being used daily throughout the country.

Data from BloodNet is used to:

- support supply, supply planning and demand management
- determine the daily quantities and locations of blood stocks across the country
- monitor wastage and
- monitor the movement of blood and blood products.

In late 2016 the NBA commenced a major redevelopment of BloodNet. The aim was to release a new version (BloodNet 5) with a transformed user experience that is simpler, clearer and faster while still meeting privacy and accessibility obligations. The emphasis was on an enhanced user experience and a greater capacity to deliver important data which benefits the NBA, jurisdictions and health providers.

User research was undertaken to ensure the new BloodNet was designed and developed around user needs. The BloodNet User Reference Group (BURG) was consulted throughout the redevelopment and provided feedback through regular reviews and testing.

BloodNet 5 was successfully released to users on 1 July 2018. It is used at 428 health facilities and has 6243 registered users. BloodNet processes over 200,000 orders annually, tracks over 2.3 million individual units per annum and processes ~98% of fresh blood products issued by the Blood Service nationally. It enables the NBA to provide a safe, secure and affordable blood supply for all Australians.

P196. The challenges associated with implementing Patient Blood Management guidelines effectively.

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Aim

This study was undertaken to understand the common barriers and facilitators to implementing Patient Blood Management (PBM) guidelines effectively.

Method

We conducted a systematic scoping review according to the Arksey and O'Malley framework (Arksey & O'Malley, 2005). Following title, abstract and full-text screening, we selected articles for review. To be eligible for inclusion studies must have described experiences of implementing interventions to support the utilisation of the PBM guidelines.

Result

We extracted data from each paper into a bespoke data extraction form that sought to identify the barriers and facilitators to implementing PBM guidelines. We then mapped this information to the Theoretical Domains Framework (TDF) to understand which theories supported the most effective interventions, and to provide recommendations for future implementation plans developed by health facilities.

Conclusion

This study identified the most common barriers and facilitators to implementing PBM guidelines, in addition to theories which support the utilisation of interventions investigated by the included studies. We propose a set of interventions that have been demonstrated to be the most effective, as per our systematic review, and strategies to overcome the associated barriers.

References:

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P197. PBM – XXX Hospital Experience: From trial to truth

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Aim

To audit the blood transfusion practice at **XXX** Hospital and implement a Patient Blood Management system to improve the quality of transfusion practice.

Method

Audit of transfusion practice

A retrospective audit of RBC usage was undertaken in June 2016. This indicated that the inappropriate use of RBC transfusions was as potentially as high as 30%. The most common patient group receiving these transfusions was those with iron deficiency anaemia. On average this patient group received 2.5 units each.

Intravenous or oral iron would have been the most appropriate treatment in such patients.

RBC gatekeeper trial

An active “gatekeeper” for RBC requests was trialed.

November 2016, for 19 days (Monday-Friday 08:00-16:00)

Results:

182 requests in total. 9-10 requests per day

328 RBC requested in total (1.8 per patient)

240 RBC approved(1.32 /patient = 27% reduction)

88 RBCs saved = cost saving of \$ 25,000

Average Hb pre-transfusion 79gm/L

The trial highlighted, ferritin was not a reliable marker of iron deficiency in hospitalised patients. Many iron deficiency anaemia patients had normal or raised ferritins (due to an underlying infection or inflammation). Ret-He was found to be an excellent marker of iron deficiency
PBM implemented December 2017.

The CNS main roles are:

Early identification of patients with iron deficiency anaemia by reviewing automatically generated blood result lists.

Arranging pro-active treatment of iron deficiency with IV iron

Gatekeeping of RBC requests. This is ‘unique’ for a PBM initiative in **XXX**

Early Results

Total number of RBCs transfused is reducing at a faster rate than prior to the PBM commencing (Number of transfusions per thousand of population is on a decreasing trend) despite the increase in population.

Financially, net savings since the implementation of PBM in December 2017 are currently \$244,000 (to May 2018)

The trial demonstrated the need for a permanent PBM team at **XXX** hospital.

P198. Improving neonatal and paediatric clinical outcomes through patient blood management education

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Aim

In the first half of 2018 a suite of neonatal and paediatric patient blood management elearning courses were released, based on the national Patient Blood Management (PBM) Guidelines: Module 6 Neonatal and Paediatrics. Courses include:

- PBM for neonates and paediatrics (introduction)
- Neonatal: Preterm
- Fetal and neonatal alloimmune thrombocytopenia (FNAIT)
- Paediatric: Haematology/Oncology
- Paediatric: Surgical
- Paediatric: Major haemorrhage
- Paediatric: Iron deficiency anaemia

The aim of the courses is to educate clinicians on patient blood management and safe transfusion in neonatal and paediatric settings, improve patient outcomes and increase awareness of the national PBM guidelines.

Method

A retrospective analysis of course completion statistics and course completion questionnaires is being undertaken by voluntary online surveys to investigate the uptake, practical use, perceived value and effectiveness of the courses.

Results

Course completions for the neonatal and paediatric courses released from March to June 2018 are currently in excess of 1000.

Analysis of learner evaluation questionnaires showed that learners agreed/strongly agreed that the program:

improves knowledge	100%
will improve patient safety and outcomes	83%
assists in the identification of near misses	75%
will result in change to clinical practice	58%

Conclusions

Analysis of user evaluation data demonstrates that the neonatal and paediatric patient blood.

P199. Correlation of N-terminal pro-B-type natriuretic peptide levels and cardiac magnetic resonance imaging T2* in patients with β -thalassaemia major

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Aim

Cardiac death secondary to myocardial iron toxicity occurs in 50% of patients with transfusion-dependent β -thalassaemia major. N-terminal pro-B-type natriuretic peptide (NT-proBNP) seems to be a useful tool for early detection of cardiac haemosiderosis. We designed this study to determine whether plasma NT-proBNP levels are predictive of cardiac iron concentration, based on heart T2* assessment by magnetic resonance imaging (MRI).

Materials and Methods

We evaluated plasma NT-proBNP levels in 50 patients with β -thalassaemia major, aged 18 to 46 years, with preserved left ventricular systolic function, all of whom had undergone cardiac MRI within 3 months before the study. Next, three groups were defined based on heart T2* value as : group A, patients without evidence of cardiac iron overload (T2*>20ms); group B, patients with mild to moderate cardiac iron overload (10ms<T2*<20ms); group C, patients with severe cardiac iron overload (T2*<10ms).

Results

NT-proBNP level was not similar among the three groups (p=0.03), being significantly higher in patients in group C (1,104.2 \pm 350.5 pg/mL) than in patients in group B (565.9 \pm 116.9 pg/mL, p=0.03) or group A (563.5 \pm 162.5 pg/mL, p=0.04). The analyses indicate that NT-proBNP levels did not correlate with cardiac iron concentrations (r=0.152, p=0.148).

Conclusion

Based on our study, measurements of NT-proBNP levels are not sufficient for early detection of cardiac iron overload. However, NT-proBNP measurements might be used as a tool to guide iron chelation therapy in patients with severe cardiac iron overload. The determination of their clinical use still requires multicentre studies.

Keywords

Pro-brain natriuretic peptide, magnetic resonance imaging, beta-thalassaemia, iron overload

P201. Effective hospital and blood service collaboration - transfusion management of a case of haemolytic disease of the fetus and newborn

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Background

King Edward Memorial Hospital Transfusion Medicine team works closely with the Australian Red Cross Blood Service (Blood Service) to ensure effective delivery of blood products and assessment of antibody levels to manage a severe case of Haemolytic Disease of the Fetus and Newborn (HDFN).

Case Report

We report a case of a 37 year old A Rh D Negative cceeFy(a-b+) G4P5 patient with Anti D+C and a history of HDFN in two previous pregnancies who also developed Anti-Fya during her fifth pregnancy. Her current partner was A Rh D Positive CCD.eeFy(a+b-). The patient's first two pregnancies were uneventful. Sensitisation is most likely to have occurred between the delivery of the second baby and late in the third pregnancy. The third and fourth babies were only mildly affected. In this pregnancy an initial intra uterine transfusion (IUT) was performed after the patient presented at 26 weeks with decreased fetal movements and a fetal Hb of 31g/L. The Blood Service Red Cell Reference Laboratory performed regular Anti-D quantitations. Through use of IVIg, selected typed fresh and irradiated red cells for five IUTs and monitoring of titres and quantitation, a good outcome was achieved. The newborn blood group was Group O Negative DAT Negative due to multiple transfusions. The original cordocentesis was A Positive DAT 4+. The Baby required three further red cell transfusions due to bone marrow suppression.

Discussion

When managing a complicated HDFN case, specialist management by the maternal fetal medicine team is of primary importance. However, this case also emphasises the excellent communication and coordination required between the hospital Transfusion Medicine Unit and the Blood Service Order Fulfilment and Red Cell Reference teams who work together to ensure effective monitoring of the patient and ensure the timely provision of typed blood for both the mother and baby.

P202. Summary of a multimodal approach to successfully reducing blood wastage at King Edward Memorial Hospital

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Aim

Our multidisciplinary Transfusion Medicine Team implemented a number of interventions to target blood wastage and ensure the best use of donor blood.

Method

The process was developed with key stakeholders and interventions ratified through the Hospital Transfusion Committee.

Intervention 1: Reduce blood product inventory to '1 hours' use of stock on site. Short expiry units rotated to larger PathWest sites for urgent use.

Intervention 2: Ensure compliant internal transport and storage of blood products. Work in partnership with theatre staff to implement a register to track all blood to and from theatre fridge.

Intervention 3: Target wastage of blood products with external blood transport failures. Assess the audit trail of all transfers and utilise PathWest shippers and temperature loggers to ensure transport conformity.

Intervention 4: Limit the allocation of sets of paediatric red cell minipacks to high risk neonates only. Neonatal audit highlighted a clear association between transfusion and gestational age and birth weight. High risk neonates <1 month old born at <28 weeks gestation were the primary cohort receiving >1 more than one red cell transfusion. Single minipacks are routinely issued unless a Neonatologist requests a reserved set.

Results

The interventions significantly reduced blood wastage costs from \$149,288 in 2012 to \$39,073 in 2017 without any adverse effects observed in our patients. External transport wastage costs were reduced from \$19,885 in 2012 to \$5,202 in 2017. Changes to neonatal red cell minipack allocation reduced wastage from 518 units in 2012 (53%) to 25 units in 2016 (6%). Cumulative savings of \$351,085 were made from 2013-2017 compared to wastage in 2012.

Conclusion

Strategies to reduce wastage are encouraging with demonstrated benefits to the blood supply. Hospital and laboratory staff embraced the opportunity to participate in the journey to ensure the very best use of the gift of donor blood.

P203. Deformation behaviour of stomatocyte, discocyte and echinocyte red blood cell morphologies in a uniform flow channel – A numerical study

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The aim of the study is to investigate the deformation behaviour of red blood cells (RBCs) having different morphologies during its passage through a uniform flow channel. RBCs are vital for sustaining the life, and carry oxygen and carbon dioxide between lungs and body tissues. Less deformable RBCs can obstruct capillaries, require higher transit time to navigate the microcirculation and can lead to adverse post-transfusion outcomes. RBC deformability is linked with its morphology. Some pathophysiological conditions and hematologic disorders [1], stomatocytogenic and echinocytogenic agents [2], and in-vitro storage [3] can change RBC morphology. A numerical study is employed with coarse-graining (CG) and smoothed particle hydrodynamics (SPH) methods to determine the minimum energy configuration of CG-RBC membrane, and to predict RBC behaviour during flow. Deformation behaviour of RBC is investigated for stomatocyte-II, discocyte and echinocyte-II morphology at different orientations to the flow direction. At a flow velocity comparable to an arteriole, RBC adopts the parachute shape profile irrespective of its initial morphology or orientation to the flow direction. Furthermore, the transit time for a RBC in its discocyte shape requires slightly more transit time whereas the echinocyte is the first to exit the flow channel, however, this difference in transit time for different morphologies is not significant. The study is capable of predicting stomatocyte, discocyte and echinocyte flow behaviour during their passage through microfluidic devices, ventricular assist devices (VADs) and blood cell separation etc., and currently being extended to capillary flow conditions. It is aimed to extend the current study to predict RBC morphology at altered extracellular ionic strength and pH conditions; to predict post-transfusion flow behaviour when stored at these modified extracellular conditions; and by this means to suggest improvements to existing additive solutions for in-vitro RBC storage.

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P204. Abdominal aortic aneurysm repair in a patient with anti-Jk3: an exercise in teamwork and PBM

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Background

Anti-Jk3 antibodies have been implicated in haemolytic transfusion reactions (HTR). The Jk-null phenotype is rare with the highest incidence in Polynesians (0.9%). Transfusion in rare blood groups is difficult with limited availability of antigen negative red cells and the risk of HTR with incompatible units. There is limited evidence regarding strategies to ameliorate HTR.

Case Presentation

A 57-year-old Tongan woman with anti-Jk3 antibody required semi-urgent open abdominal aortic aneurysm repair. Blood loss >5L was predicted due to difficult access (morbid obesity and massive uterine fibroids). Jk-null blood available at short notice included 3 imported and 4 cryopreserved units. Family screening identified 3 Jk-null relatives however their directed donations were not available at the time of surgery. Anticipated transfusion requirements exceeded available compatible blood and methylprednisolone 1g IV and IVIg 0.4g/kg was administered 6hrs preoperatively to minimise HTR. Intraoperative transfusion commenced with 2U Jk(a-b+) red blood cells. Further red cell transfusion was avoided through the use of cell salvage, careful surgical technique and haemostatic support with platelets and plasma products with surgery being successfully completed. No clinical signs of HTR were observed and there was no laboratory evidence of haemolysis at acute or follow up assessment.

Discussion

In the setting of critical bleeding and emergency surgery in patients with rare antibodies it may be impossible to meet antigen negative red cell requirements. Evidence for the use of corticosteroids and intravenous immunoglobulin in management of HTR is limited to case studies and routine cannot be recommended. The demand for Jk-null red cells is unpredictable and transfusion support relies on targeted phenotyping and family members are an important source of potential donors. Targeted patient blood management strategies are required to reduce the need for transfusion and communication between treating clinicians and the Blood Service is essential in minimizing wastage of precious resources.

P206. So what has changed

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To ascertain the impact of RMIT University Transfusion Science workshop participation on the skills and attitudes of attendees and the likely acceptance of different delivery of workshop content an online survey was conducted of past participants.

A questionnaire seeking feedback on (a) the conduct and content of the workshops, (b) the impact attendance had on understanding of theoretical aspects of Transfusion Science, confidence in communicating that understanding and their serological problem solving, and (c) preferences for different formats of workshop delivery in the future. The survey was conducted using the Qualtrics™ online survey tool. A questionnaire link was emailed to 373 past workshop participants.

73 responses were received giving a disappointing response rate of 20%. 97% rated the workplace relevance of content as very good to excellent. 94% indicated a positive outcome on their confidence in understanding theoretical aspects of Transfusion Science and their ability to communicate that to their peers. 77% gave a positive outcome in communicating that to medical and nursing staff. 91% percent reported a positive outcome on their serological problem solving ability.

When ranking preferences for the format of future workshops, the majority favoured the current five day workshop on campus, a third favoured lectures being offered online prior to attending a three day practical workshop either during the week or over a weekend, slightly less than a third favoured the current 5 day workshop conducted over a weekend. The least favoured option was to have all content delivered online.

Workshop content has been shown to be relevant to the workplace, participant confidence in serological problem solving and in communicating their understanding to peers is positive. Preference for workshop delivery is to maintain the status quo, however, external factors may see an increase in online content delivery in the future.

P207. Utilisation of electronic tools for selection of Red Cell Units for paediatric patients in a newly integrated Paediatric and Adult Transfusion Laboratory

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Aim

We undertook to develop electronic tools to assist in red cell unit selection for transfusion in paediatric patients, to be utilised in a newly integrated paediatric and adult Transfusion laboratory.

Methods

The Perth Childrens Hospital opened 10th June 2018, and is a 300 bed state of the art specialist paediatric hospital and trauma centre. The hospital is serviced by the Western Australian public pathology laboratory located approximately 8 minutes walking distance away. This laboratory also services a 600 bed adult tertiary hospital, the principal WA hospital for neurosurgery, liver transplants and WA's only comprehensive Cancer Centre, and is the referral laboratory for 19 regional laboratories located up to 2,500 kilometres away.

We developed and introduced two separate electronic tools in accordance with national and international guidelines utilising Microsoft Excel rules:

Program 1: automatically generates the requirements for age of red cells, irradiation and CMV in small "top up" and large transfusions following entry of required date of transfusion and date of birth.

Program 2: automatically calculates the collection and expiry dates for irradiated or non-irradiated red cell units based on age of red cells required for that particular day

Results

The introduction of these electronic tools have been received with enormous enthusiasm and are valuable in a laboratory whose primary focus had been adult transfusion. These tools provide surety and confidence to scientists, enable productivity to be maintained in an environment of cost reductions and ensure patient safety. They can be easily modified as national and international guidelines change.

Conclusion

We have developed a simple yet powerful tool for electronic calculation of red cell unit selection in paediatric patients based on national and international guidelines for utilisation in an integrated paediatric and adult Transfusion laboratory and have been critical to the quality of service and clinical outcome.

P208. Platelet-rich plasma sequestration in cardiac surgery- prospective controlled study

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Aim

We tested the platelet count and induced platelet aggregation during and after platelet-rich plasma (PRP) sequestration. We hypothesised that platelet count and aggregation are protected.

Methods

Written informed consent, local ethic committee approval.

Elective surgery CPB>2 hours. Initial hematocrit >0,35 (800 ml of whole blood processed) RBC+PRP sequestration simultaneously, PRP retransfused after the CPB.

CPB: X- coating, centrifugal pump, UFH:ACT>400s, TXA 30mg/kg.

Cell saver: CPD-A bags, EDTA vacutainer, manufacturer protocol.

Platelet count- flow cytometry. Optical aggregometry: collagen, ADP, ristocetin and epinephrin induced aggregation. Whole blood sample before surgery, from processed PRP, after retransfusion, after surgery. TEG guided transfusion therapy..

SPSS 22:: Fisher exact test for qualitative, Student, Mann-Whitney for quantitative parameters.

Results

Sequestration group: 18 patients (94% male), control 12 patients (80%M). Both group comparable by age (67 both), EuroSCORE (3,37 vs 3,62%), aortic(61 vs 49%), redo surgery(22 vs 14%). Antiplatelet medication withdrawn. No difference in perioperative (605 vs 564ml) postoperative (711 vs 652 ml) blood loss, transfusion of RBC (1,6 vs 2,4 TU), FFP (1,7 vs 1,7 TU), PLT (1 vs 0 TU), fibrinogen, PCC, additional TXA (18 vs 14%), reexploration because of bleeding (16 vs 14%), ICULOS (4 vs 3,5 days), HLOS (11,5 vs 10,5 days), 30day mortality (1 vs 0). Platelet count decreased (185 to 136 vs 230 to 136). Platelet count after CPB was lower in PRP (105 vs 196 p=0,001) but not at the end (136 both). Significant decrease of collagen (43 vs 5,3%), ADP (79 vs 4%) and epinephrin (37 vs 5%) mediated aggregation but preserved values of ristocetin (95 vs 99%) mediated aggregation recorded.

Conclusion

The using of PRP sequestration have no impact on bleeding, transfusion therapy and clinical outcome in complex cardiac surgery. It preserves platelet count and ristocetin, but no other receptor mediated platelet aggregation.

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P209. When to wake up your on-call Haematologist for out of hours DOAC testing?

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Aim

Can routine coagulation results be used as evidence to either initiate or delay specific Direct Oral Anticoagulant (DOAC) testing out of hours?

Method

A retrospective analysis of coagulation tests was performed on patients on DOACs who presented to Royal Hobart Hospital from Jan/2015 to April/2018. Data for all DOAC (Apixaban, Rivaroxaban and Dabigatran) testing was extracted from the laboratory information system. DOAC results that were paired with traditional coagulation testing (PT/APTT/TT) were tabulated and individually assessed for suitability by reviewing Digital Medical records of the patients. Those patients with co-morbidities, interfering anticoagulants or receiving transfusion support were excluded from the analysis. The remaining data points were graphed to determine if a meaningful pattern existed that could assist in patient management.

Results

DOAC	PT		APTT		TT	
Apixaban	n=51	R ² =0.46	n=51	R ² =0.24		
Rivaroxaban	n=78	R ² =0.53	n=78	R ² =0.40		
Dabigatran	n=36	R ² =0.51	n=38	R ² =0.36	n=28	R ² =0.78

Conclusion

Except for Dabigatran where TT is a reliable indicator of presence of anticoagulant in circulation, routine coagulation testing cannot provide a reliable metric to initiate/delay out of hours testing for patients on Rivaroxaban and Apixaban. Better Clinician/laboratory communication is essential for identifying patient's specific anticoagulation treatments and the exact nature of out of hours testing. Testing for urgent samples with bleeding/surgical implications will continue to be reviewed by the on-call Haematologist and processed on a case by case basis.

P211. Integrated bioinformatics solution to improve compatibility testing for transfusion

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Aim

The overall objective of this study is to provide a new basis for pretransfusion testing by accurate characterization of the complete blood group variant profile from complex Next-Gen Sequencing (NGS) data.

Method

We are developing a novel algorithm for the typing of 36 blood group system using NGS data. The algorithm is divided into three steps: 1) Extract single nucleotide polymorphisms (SNPs) and copy number variations (CNVs) from NGS data; 2) Identify the known blood group (BG) alleles from SNPs and CNVs including those resulting from conversion, crossover and other recombination events; 3) Prediction of novel BG from rare variants without a current blood group phenotype association and variants that may encode novel antigens. Finally, all three steps of the algorithm will be integrated into a user-friendly software. We are using publically available and in-house sequenced genome data for the development of the software. The accuracy of the software will be assessed by comparing results with serologically predicted BGs.

Results

The first step of software development is completed, wherein the software accepts fastq files with user-provided parameters and performs alignment, quality control, and detection, annotation and filtering of SNPs and CNVs. Additionally, we have created an in-house database, QUT BG, which contains the genetic profiles of known BGs obtained from experimentally validated online resources such as ISBT, RhesusBase, and Erythrogen. Currently we are working on predicting known BG using the identified genetic profiles and QUT DB.

Conclusions

The novel algorithm developed in this study will overcome the clinical limitations such as usability and accuracy of the existing methods for BG genotyping and matching.

P212. Iron Deficiency in Pregnancy- a new approach to an often neglected issue in women's health

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Aim

To implement systems to improve antenatal detection and management of iron deficiency (ID) and iron deficiency anaemia (IDA) in pregnant women, to optimise iron stores and haemoglobin at delivery.

Method

A clinical practice improvement project was initiated at Toowoomba Hospital, in partnership with the Australian Red Cross Blood Service, based on previously successfully collaborations.¹ Women who booked at or before 20 weeks gestation from 1st September to 31st December 2017 were included. All patients had FBC and ferritin levels taken at the first visit, at 28 weeks, and at 36 weeks. Using the algorithms supplied and following discussion with the women, they were commenced on oral iron supplementation if required. Educational handouts were given to support these conversations.

Data regarding blood results, delivery, and interventions such as iron infusion or blood transfusion is being collected for analysis.

Result

Toowoomba hospital delivers 2,000 babies annually. Data revealed an average of 75% of women had ferritin levels less than 30 µg/L, indicating iron deficiency. Discussion with the women revealed that few had been asked to take iron supplementation and most chose non-therapeutic doses, as suggested by pharmacy assistants, because there was previously no education available to support the decision making process.

Feedback from midwives (73% of respondents) and medical staff (23% of respondents) has been extremely positive with 100% agreeing or strongly agreeing that the algorithms were easy to use and guided decision making. All answering indicated they would recommend the tools to be used to compliment practice. 86% of respondents indicated that they 'learnt something new' and 'my practice is (will be) changed and improved.'

Conclusion

These results indicate the acceptance and utility of routine screening for iron deficiency early in pregnancy, allowing early identification and correction prior to delivery.

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P213. Post-transfusion purpura: case report and literature review

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Post-transfusion purpura (PTP) is a rare syndrome characterised by development of sudden thrombocytopenia 5-12 days after transfusion. The exact incidence is unknown with estimates of 1:50,000 to 1:100,000 transfusions. The pathogenesis is through transfusion causing an anamnestic immune response against a specific human platelet antigen the patient has been alloimmunised to through previous pregnancy or transfusion. Paradoxically, recipient antigen-negative platelets as well as donor platelets are destroyed. Platelet drop is profound, falling below $10 \times 10^9/L$ in the majority of cases. Laboratory tests to confirm the diagnosis involve demonstrating platelet alloantibodies as well as absence of the corresponding antigen on the patient's platelets.

We present the case of a 55 year old woman who presented following trauma. She required urgent surgery and received two units of blood. She received three doses of intravenous cephazolin and ibuprofen for post-operative analgesia. She was noted five days after transfusion to have developed thrombocytopenia and by day seven her count was $14 \times 10^9/L$. She received IVIG 1g/kg for two days based on our provisional diagnosis of PTP with immediate improvement. Her platelet genotype returned as 1aa 2aa 3ab 5aa 15ab. Her HPA Antibody screen was positive for an anti HPA-1b alloantibody consistent with PTP. Drug-antiplatelet antibody screen for cephazolin was negative. An anti HPA-15b antibody was also identified. Notably, the secondary emergence of an autoantibody following the alloimmune response has been postulated as a mechanism behind why recipient antigen-negative platelets are also destroyed.

This patient's case is uncommon due to both its occurrence in the era of leucodepletion and her results of both an alloantibody and seemingly autoantibody. We use this case to encourage clinicians to consider PTP as a differential for thrombocytopenia and we delve further into the pathophysiology, diagnosis and treatment of this rare disease.

P214. Reversing oral antiplatelet agents with platelet transfusion: a review

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Aspirin, clopidogrel, prasugrel and ticagrelor are oral antiplatelet agents that are widely used for the prevention of cardiovascular or neurovascular thrombotic events.

Despite their effectiveness in reducing thrombotic events, they are associated with an increased risk of bleeding which includes major bleeding and fatal bleeding. Management of patients treated with an oral antiplatelet agent who require urgent surgery or are bleeding is challenging for clinicians. No antidote is available to reverse oral antiplatelet agents, and their platelet inhibiting effect persists for 3 to 10 days after the last dose.

Platelet transfusion can reverse the haemostatic defect produced by antiplatelet drugs by providing a source of uninhibited platelets from a donor. The efficacy of platelet transfusion is influenced by 1) the binding of the antiplatelet agent to its receptor, aspirin, clopidogrel and prasugrel bind irreversibly to their receptors, whereas ticagrelor reversibly binds to the platelet receptor; 2) the half live of the antiplatelet agents; 3) the quantity of platelets transfused; and 4) the time between the last dose of oral antiplatelet and the platelet transfusion.

Individual in vitro reversal experiments, cohort studies, and randomised controlled trials provide limited information on platelet transfusion for the reversal of oral antiplatelets. We have performed an extensive review of all available literature which is informative. Platelets are most effective at reversing oral antiplatelets if transfused after the agent is cleared from the circulation. There are three distinct patterns of reversal of oral antiplatelet agents. Aspirin can be fully reversed from about one hour after ingestion with 1-2 apheresis units of platelets. Clopidogrel and prasugrel can be partially reversed as donor platelets provide a linear improvement in aggregation. Ticagrelor is the most difficult to reverse, and the response to donor platelets is dose- and time-dependent.

Detailed knowledge of the optimal timing and quantity of platelets to transfuse is essential to prevent or treat bleeding in patients who take oral antiplatelets, and to utilise finite blood products appropriately.

P215. A 5-year retrospective cohort study of the impact of anaemia in a tertiary hospital setting

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Aim

To investigate the association between nadir haemoglobin, mortality and length of stay in all hospitalised patients within a single tertiary centre.

Method

Retrospective cohort study of all patients admitted for at least 48 hours to a tertiary centre between July 2010 and June 2015. Anaemia status was measured using nadir haemoglobin results and was grouped into 3 categories: moderate to severe (<100 g/L), mild (between 100–119 g/L for females and 100–129 g/L for men), or not anaemic (>120 g/L for females, >130 g/L for males).

Result

In our sample, 56.6% (45,675/80,765) of inpatients were anaemic during their hospital stay. Anaemia was independently associated with higher odds of in-hospital mortality, even when mild (odds ratio 1.59, 95% CI 1.36 to 1.86, P = 0.001). Anaemia was also associated with increased length of stay in both emergency and elective patients, however the increase was significantly longer in emergency admissions (mild anaemia: incidence rate ratio, 1.52, 95% CI 1.48-1.56, P< 0.001; moderate to severe anaemia: incidence rate ratio 2.18, 95% CI 2.11-2.26, P<0.001) compared to elective admissions (mild anaemia: incidence rate ratio 1.30, 95% CI 1.21-1.41, P<0.001; moderate/severe anaemia: incidence rate ratio 1.69, 95% CI 1.55-1.83, P<0.001). Independent of anaemia, red blood cell transfusion was associated with 2.23 times higher odds of in-hospital mortality (95% CI 1.89-2.64, P<0.001) and 1.31 times longer length of stay (95% CI 1.25-1.37, P<0.001).

Conclusion

In our hospital sample, the majority of patients were anaemic during admission. Over one-third of patients not anaemic on admission developed anaemia during their hospital stay. Anaemia, even if mild, is independently associated with increased mortality and hospital length of stay; however, transfusion to treat anaemia is an independent and additive risk factor. These findings, if replicated in other jurisdictions, have significant medical and economic implications for health systems.

P216. A frozen inventory of red cells for disaster response: a feasibility study

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Background and Aim

Maintaining a supply of red cells, especially group O Rh(D)-negative red cells, is essential for the Blood Service's emergency preparedness. In 2017, a mass casualty situation in the United States exhausted the local supply of O negative red cells. A frozen inventory of red cells might prevent this. However, the current process for freezing rare red cells is unsuitable, limited by a 24 hour post-thaw shelf-life. Adoption of cryopreservation methods developed for the Australian Defence Force, particularly post-thaw storage in AS-3, could allow establishment of an inventory of frozen red cells with extended post-thaw shelf-life. Therefore, the aim of this study was to establish a suitable method of red cell cryopreservation.

Method

Red cells (day 7 post-collection; n=30) were glycerolised using an ACP-215 cell washer, and frozen at -80°C. Red cells were thawed at 37°C, deglycerolised and resuspended in AS-3 additive. Red cell indices, lactate, pH, potassium, 2,3-diphosphoglycerate (2,3-DPG), lactate dehydrogenase (LDH) and haemolysis were measured pre-freeze and post-thaw (days 0, 1, 4, 7, 14, 18 and 21).

Results

The average haemoglobin (Hb) post-thaw was 42.6 ± 3.6 g/unit. The overall post-thaw Hb recovery was 85%. The average haemolysis on day 14 post-thaw was $0.63 \pm 0.14\%$. LDH release correlated with haemolysis throughout storage ($R^2=0.8582$). The average haematocrit (Hct) was 0.522 ± 0.043 L/L; 10 units had an Hct below 0.5 L/L. An Hct of 0.5 L/L could be achieved by selecting red cells with pre-freeze volumes >250 mL. On day 14 post-thaw, lactate production and potassium release were acceptable (5.32 ± 1.38 mmol/L; 31.18 ± 4.19 mmol/L). 2,3-DPG was depleted by day 4 post-thaw, which may be reversible once transfused.

Conclusion

Preliminary data indicates freezing red cell components from inventory is feasible and the post-thaw shelf-life could be extended by suspension of red cells in AS-3.

P217. The role for genomics to solve complex red cell blood group serology problems: a targeted blood group exome sequencing approach

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Aim

To report on the clinical utility of targeted exome sequencing for blood group genotyping in a national reference laboratory setting.

Method

We previously evaluated a targeted exome sequencing approach for extended blood group genotyping in a reference laboratory (Schoeman *et al.*, 2017, 2018). Over the past 27 months we received 176 samples from the Blood Service Red Cell Reference Laboratory with a request for sequencing to resolve a problematic blood group status. Next Generation Sequencing (NGS) was performed using the TruSight One (TSO) Sequencing Panel and MiSeq platform. Manual data analyses of single nucleotide variants and copy number variants were performed as reported previously (Schoeman *et al.*, 2018).

Result

For 159 samples, data analysis targeted the gene(s) for one blood group system; for the remaining 17 samples all blood group-related gene variants were analysed. More than half of requests (57%) were related to the RH system and the requests were mostly prompted by weak or partial serology results unresolved by SNP microarray typing.

TSO sequencing assisted in resolving or confirming serology/SNP typing results for over 95% of cases. These included 4 family studies; two involving low frequency Rh antigens (one novel), one a sickle cell patient with a (C)ce^S haplotype and the fourth a novel low frequency Augustine antigen (now AUG:3). Seven additional novel variants; across the MNS, RH, KEL and LW systems; were identified in 6 samples. Investigation is ongoing for the remaining 5% of cases and includes the application of gene-specific long-range PCR.

Conclusion

Targeted blood group exome sequencing is a powerful and accurate auxiliary tool in the reference laboratory arsenal. Limitations of 2nd generation NGS (e.g. short sequence read lengths), do not enable resolution of more complex cases and necessitates additional testing such as long-range PCR. Already, NGS incorporating ultra-long reads is a promising future tool to overcome this limitation.

References:

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P218. The implementation of a nurse-led pre-op anaemia clinic improves wait time from referral-to-review in treatment of iron deficiency patients

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Aim

This clinic was set up in July 2017 as part of the Ministry's directive to adopt the Patient Blood Management (PBM) model. It aims to investigate the cause of anaemia, provide proper diagnosis and commence treatment before an elective surgery.

Method

A cross sectional study done in 2016 demonstrated anaemic patients requiring pre-op assessment waited > 7 days for their first review, leading to a delay in treatment. Data was collected from July 2017-April 2018. All new referrals were independently managed by a nurse specialist using a protocol formulated from guidelines. Cases were escalated to the relevant specialties if they require further evaluation for bleeding or underlying malignancy.

Results

38 new referrals were received, consisting of general surgery (32%); orthopaedics (32%); colorectal surgery (16%); gynaecology (11%), ophthalmology (8%) and CTVS (1%). The median age was 60 (28 to 95). Of these cases, 78% were seen on the same day and within 1-3 days of referral. Comparatively, only 12% were reviewed within 1-3 days and none were reviewed on the same day as referral from July-December 2016. 81.6% of the patients seen were able to proceed with planned surgery, while the remaining 11.4% were unfit or opted out due to personal reasons. The maximum increase in Hb after haematinics was by 3.9g/dL which was reflected in an orthopaedic case while the minimum increase was by 0.2g/dL in a breast malignancy case. The mean Hb increase was 1.73g/dL. The timeframe from referral-to-review is crucial as prompt initiation of treatment is necessary to optimise patients' haemoglobin before surgery.

Conclusion

This nurse led clinic has proven to improve the wait time for anaemic patients requiring pre-op assessment leading to effective treatment. The next phase would be to ensure as many of this type of patients get managed appropriately and study secondary outcomes such as peri-operative transfusion rates.

P222. Transfusion under triple threat: bringing the past alive for future generations

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Background

Japan's 2011 earthquake, tsunami, and nuclear crisis interrupted collecting, testing, processing, and distributing allogeneic blood in the six north-eastern prefectures of Honshu, our largest island. Hospitals with autologous and/or research blood collection programs prepared to emulate Australian Emergency Donor Program (EDP) protocols with hastily recruited volunteer donors.

Crisis Outcome

As subsequently published (*Transfusion Medicine Reviews* 27:29–35), this was a disaster of mass fatality rather than mass injury, for which increased collections outside the affected areas, delivered through ad-hoc transportation networks, met demand. Major medical centres have since been tasked with conveying hard-earned expertise to future generations.

Educational Challenges

Medical school classes were postponed as our institution responded to the 2011 crisis, although some students remained on campus to be of service. Today, no students in our 6-year curriculum have direct experience of our disaster response.

Education Then

Year 5 students, in groups of 6-8, spend 1-1/2 days in transfusion medicine. Historically, Tuesday afternoons were in serology lab, where each student blood typed 10 "patients". Wednesday mornings began with "The Strange Case of Penny Allison", followed by splitting into two subgroups for (1) bench time with a lab scientist and (2) autologous blood collection and/or progenitor cell apheresis with a medical team. Students go to the local blood centre Wednesday afternoons.

Education Now

Curricular changes in 2018 forced us to move serology lab from Tuesday to Thursday. It starts with a whiteboard exercise, interrupted by a phone call summoning the physician - and students - to an emergency. Upon arrival, it is 11 March 2011. A briefing takes everyone through the first days of our earthquake, tsunami, and nuclear crisis, and leads to each student blood typing 10 "volunteer emergency donors". Thus far, one such simulation has been videotaped for analysis

P223. Systematic testing of donors when their whole blood donations are repeatedly discarded due to red cell processing issues

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Background

Whole Blood donations from donors with the sickle cell Haemoglobin (HbS) trait can block leucodepletion filters, resulting in leucodepletion failure. Failure of leucodepletion increases the potential for transfusion reactions within recipients and CMV transmission risk. Therefore, red cell components found to have filtration or clotting issues are discarded.

Aim

To follow up on whole blood donors whose donations have been repeatedly discarded due to issues with leucodepletion filtration.

Methods

The project commenced in April 2016 and this report is till June 2018. Donors with either consecutive, or a total of 3, discarded whole blood donations were identified. These donors were deferred and a letter was sent to the donor's general practitioner suggesting further investigation using standard tests. These tests included a full blood count, reticulocyte count, blood film, ferritin, high performance liquid chromatography (HPLC), lactic acid dehydrogenase (LDH), serum electrophoresis (EPG), direct anti-globulin test and cold agglutinin. Donor consent was obtained for the study team to analyse the results and the donor was managed according to the findings. Permanent deferral from blood donation was made when HbS trait, cold agglutinins or a paraprotein were identified.

Results

163 donors were identified as having multiple whole blood donations discarded. Responses were received for 104 (63.8%) donors. HbS trait was found in 43 (41.3%); no cause in 31 donors (29.8%), cold agglutinins identified 22 (21.1%) and a paraprotein found in 3. Chronic Lymphocytic Leukaemia was detected in 1 donor.

Conclusions

Donors with repeatedly discarded whole blood donations are now systematically reviewed and excluded from blood donation. Whole blood processing failure often arises from the HbS trait, presence of cold antibodies or paraproteins. A number of donors had no known reason warranting further investigation. This review has become a routine part of donor and component management.

P224. Assessment of transfusion-related immune modulation in cardiac surgery patients

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Background

Transfusion-related modulation of the recipient immune response may contribute to adverse patient outcomes including increased rates of infection and mortality. Coronary artery bypass grafting (CABG) is a complex surgical procedure which triggers a systemic inflammatory response and may involve transfusion. Dendritic cells (DC) and monocytes are key immunoregulators and their dysfunction may contribute to adverse patient outcomes associated with CABG and/or transfusion; however, understanding of this is limited.

Aims:

To prospectively assess changes in DC and monocyte immune profile in CABG patients.

To investigate whether transfusion further modulated this immune profile and contributed to adverse patient outcomes.

Method

An ex-vivo whole blood culture model was used to assess patient DC and monocyte immune profile at 5 time-points (admission, intra-operative, ICU, day-3, day-5). Lipopolysaccharide was used in parallel to model a bacterial complication. Association between DC and monocyte immune profile and adverse outcomes (prolonged intensive care unit (ICU) length of stay (LOS; >24hrs); post-operative atrial fibrillation (AF)) was assessed (Spearman; $P < 0.05$) for the overall patient cohort ($n=49$) and for the transfusion sub-group ($n=7$).

Result

The DC and monocyte immune profile was significantly modulated post-CABG with evidence of failure to respond to bacterial stimuli (immunoparalysis). Modulation of both DC and monocyte co-stimulatory and adhesion molecules and inflammatory cytokines was associated with prolonged ICU LOS and post-operative AF. CABG-associated modulation of the DC and monocyte immune profile was less evident in patients who received transfusion, however these patients were more likely to have prolonged ICU LOS (71% of transfusion recipients vs 33% for non-transfused patients).

Conclusion

CABG resulted in immunoparalysis of DC and monocytes. Dysfunction of DC and monocyte cytokine production was associated with prolonged ICU LOS and post-operative AF. Transfusion recipients had a different immune profile and spent longer in ICU.

P225. Underlying inflammation influences immunoregulatory cell immune responses in a model of platelet concentrate and packed red blood cell transfusion

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Background

Transfusion of packed red blood cells (PRBC) and platelet concentrates (PC) has been associated with increased rates of infection and mortality, with storage duration a possible contributing factor. Underlying inflammation may further contribute to these poor patient outcomes in transfused patients. The relationship between the level of underlying inflammation, the storage period of blood components and immunomodulation remains unclear.

Aim

To use an established in-vitro transfusion model to investigate whether changes in dendritic cell (DC) and/or monocyte phenotype following exposure to PRBC or PC are impacted by the level of underlying inflammation.

Method

Freshly collected whole blood ("recipient") was cultured (37°C, 5%CO₂, 6Hrs) with either a 1 unit (10%) or 2-3 unit (25%) "transfusion" of fresh (day (D) 2) or stored (D5) PC-supernatants (PC-SN) or fresh (D2) or stored (D42) PRBC-supernatants (PRBC-SN) and lipopolysaccharide (LPS; 0, 0.25, 0.5, 0.75, 1µg/mL; modelling different levels of underlying inflammation). DC and monocyte responses were investigated using flow cytometry (IL-6, IL-8, IL-10, IL-12, IL-1α, TNF-α, MIP-1α, MIP-1β, MCP-1, IP-10). Repeated measures one-way ANOVA with Tukey's post-test (P<0.05) was used to assess effect of transfusion dose, storage and level of underlying inflammation.

Result

Regardless of dose (10% or 25%), exposure to fresh PC-SN or PRBC-SN in combination with low LPS concentrations (0.25, 0.5µg/mL) resulted in suppression of DC and monocyte cytokine production. A 10% dose of stored PC-SN or PRBC-SN resulted in minimal modulation, regardless of level of underlying inflammation. However, modelling a 25% dose of stored PC-SN or PRBC-SN, co-cultured with low-mid range LPS concentrations (0.25-0.75µg/mL) resulted in significantly reduced DC and monocyte cytokine production. At higher LPS concentrations, the effect of both fresh and stored blood components on monocyte and DC responses was less evident.

Conclusion

The impact of PC-SN and PRBC-SN transfusion on DC and monocyte immune responses was more evident in the presence of lower levels of underlying inflammation.

P226. Mass(ive) transfusion education: one million and counting

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Background

In 2006 it was recognised that there was a need for a consistent educational approach to improving the safety and quality of transfusion practice. This needed to be accessible by staff across all health sectors and professions – public/private, metropolitan/rural, all professions - who are part of the transfusion chain.

BloodSafe eLearning Australia (BEA) was developed to fill this gap by providing online education. Developed initially for South Australia, approval for national funding resulted in the program being available free-of-charge to all Australian states and territories.

Results

The program currently has more than 500,000 registered learners, who have completed more than one million courses, and is used by more than 1500 hospitals, universities and other organisations.

Twenty-six courses, based on guidelines and standards published by ANZSBT and NBA, cover clinical transfusion and PBM in a range of clinical settings. Courses are endorsed by medical specialty colleges Course development is undertaken using a '5E' educational framework to engage learners through exploration, explanation and elaboration, and evaluation of learner knowledge and program objectives.

Stakeholder feedback shows that the program provides credible, consistent education that is cost-effective and reduces duplication. It is 'best-practice' elearning that is readily accessible and allows institutions to focus on the development of practical transfusion skills.

User evaluation shows that the courses have a positive impact, with 89% of respondents stating they gained additional knowledge and more than 87% reporting they will/can make changes to their work practices to improve patient safety and outcomes. External reviews show the program has strong governance and provides value for money.

Conclusion

The BloodSafe eLearning Australia program provides education to a large number of health professionals across Australia. These courses provide users with a consistent and reliable knowledge base that translates into changes to practice and improved patient outcomes.

P227. Mass Serological Screening of Blood Donors for the Vel-negative Rare Blood Type with a Monoclonal anti-Vel Reagent: The French Experience

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Aim

Mass screening of rare blood types is challenging for blood donor testing laboratories, as most reagents are of limited supply, poor quality or unavailable on the market. Molecular typing can be helpful if the molecular basis of the rare type is characterized. This approach, however, remains costly and not easy to implement for mass donor screening. Newly developed monoclonal blood grouping reagents may allow coping with this issue.

Method

A collaboration between several French teams resulted in the production of a human monoclonal anti-Vel, clone SpG213Dc3 (Danger Y et al. *Vox Sang* 2016), with an adapted protocol for the PK7300 high-throughput blood grouping instrument (Beckman-Coulter).

Result

From October 2015 to April 2017, 981,650 donations were systematically tested for Vel, making it possible to find out 339 Vel- donors confirmed by the National Immunohematology Reference Laboratory, both at the phenotypic (two different sources of human antisera) and molecular levels (*VEL*⁻⁰¹/VEL*⁻⁰¹* genotype). The prevalence of the Vel- phenotype calculated on 494,792 donors was 6.1 in 10⁴ (95% CI, 5.5-6.8 in 10⁴), significantly higher than the commonly reported prevalence of 4 in 10⁴ in Caucasians (calculated on 10,000 individuals "only").

Conclusion

Anti-Vel is a highly clinically significant antibody and Vel- blood is necessarily required for patients with alloanti-Vel. Finding Vel- blood is often challenging worldwide; it is even more difficult when the patient is group O and shows additional common alloantibodies. This work allowed to considerably increasing the stock of Vel- blood at the French National Rare Blood Bank, which currently contains 370 Vel- RBC units from 97 donors. Of note, 26 units are O, D-C-E-, K- and 41 O, E-c-, K- (no O, C-e-, K-). We plan to apply the same mass donor screening strategy in the future by developing other monoclonal reagents, such as anti-Co^a, anti-Ge², anti-Js^b, anti-Hr^s and anti-Hr^B.

P228. Establishing a robust programme of antenatal haemoglobinopathy screening within a tertiary obstetric centre

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Australia has no national haemoglobinopathy screening programme, resulting in an unstructured and variable approach to screening women; following up abnormal results and supporting women/families in decision making regarding their care, our hospital was no different with a rather disjointed approach to screening and follow up.

In 2016 a nurse and midwife quietly set about improving the care for our women who may be affected by haemoglobin disorders and established a new model of screening with clearly defined roles and responsibilities. This was supported by improved guidelines and a programme of education which have been readily embraced by our staff who once again have readily accepted the challenge of change and play a very proactive role in recognising women at risk of haemoglobin disorders and encouraging screening.

Our practice change was led by passion and drive; no additional funding was available and required a subtle change of responsibilities only. It was supported by the multidisciplinary team and we are able to demonstrate how a structured approach to screening can be achieved; the key is identifying those women at risk.

We have analysed the data from 2017 and are using this to refine our screening process in the future; clearly there are areas we need to improve upon; but importantly we have improved the screening and follow up for our women. Our lessons and experience will be useful for any professional caring for women in Australia with child bearing potential, due to the changing nature of the demographics within the country. Although it is particularly pertinent to Western Australia as in 2016/17 24% of our births occurred in women with a family origin that places them at risk of haemoglobin disease.

We will discuss the next steps in this journey as we continue to learn from our women and their families.

P229. Loss of High Incidence Antigen in AML: A transfusion dilemma

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Loss of ABO blood group antigen in haematological malignancies is a well-known phenomenon (1), however the loss of the k (KEL2) antigen is rare. Here we describe a case of an AML patient with the loss of A (ABO1) antigen and k (KEL2) antigen and the challenges experienced in the pre and post allograft transfusion support.

Case report

A 42 year old male presented with high cytogenetics risk AML (Inversion chromosome 3, monosomy 7). Routine blood grouping and antibody screen revealed a mixed field reaction with anti-A and Anti-A,B reagents.

Method

ABO grouping and phenotyping were performed using standard serology techniques. Genotyping was performed using the Immucor BioArray HEA precise BeadChip. Targeted MPS (Massive Parallel Sequencing) was performed using MiSeq Sequencing platform and the TruSight™ one sequencing panel (Illumina).

Results

Further testing confirmed the initial findings of mixed field reactions with anti-A and anti-AB reagents in the forward group with the reverse group being Group A. The patient's phenotype was determined with no mixed fields observed and the k- phenotype was indicated. Genotyping on the initial sample returned an indeterminate call for the k phenotype. The sample was then referred for sequencing, which indicated that the patient is ABO*A.01/O*01.11 and KEL*01.01/*02, with probable phenotype of group A, K+k+.

Discussion

The loss of a high incidence antigen, such as k is rare. Given the low incidence of the k- phenotype in the Caucasian population (0.2 %), the provision of phenotype matched blood during the chemotherapy phase and post allograft recovery phase proved to be difficult. At the time of the initial request, there were no eligible donors with the same phenotype C-, k-, Fy(a-), Jk(b-) and S-. The patient was supported with k-, C-, to avoid potential alloimmunisation. The patient received a total of 36 units of RBC. The question/dilemma remains whether we could have transfused k+ units, given the sequencing result predicted k+ phenotype.

References

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P232. Caring for babies requiring transfusion – a focus on partnering with parents and ensuring excellence in practice.

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Aim: Transfusion is frequently required in neonates requiring intensive care management. In keeping with the release of Patient Blood Management (PBM) Module 6: Neonatal and Paediatrics guidelines, we aimed to ensure excellence in transfusion practice in the Neonatal Intensive Care Unit (NICU) and align local policies and practice to provide appropriate use of blood components in this vulnerable population.

Methods: Clinical practice improvement (CPI) methodology was used to determine interventions and key data monitoring: audit tool, staff feedback and parent feedback. Previous Standard 7 audits were reviewed and a baseline transfusion practice audit was collated. A NICU-specific parent handout about transfusion (largely informed by partnership with parents) and a video demonstrating a consent discussion were developed to assist in the consent process. NICU staff received additional inter-professional training in: obtaining informed consent, prescription, and safe administration of blood components. Parental knowledge, concerns, and feedback regarding transfusion practice was sought at baseline (survey) and upon project completion (experience trackers).

Results: Baseline audit showed inconsistent consent, monitoring and documentation processes in neonatal transfusions. Post-pilot audit showed improvement in these parameters. Clinicians surveyed (nursing and medical n=29) agreed that the parent handout was well set-out, easy to understand, and recommended that it be used to complement practice. The additional “Blood Month” training was well-received by staff and parental feedback about NICU transfusion was consistently positive.

Figure 1. NICU handout

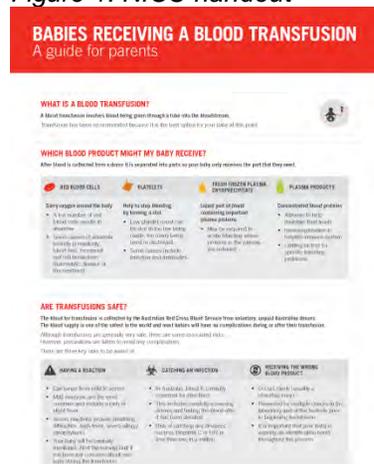


Figure 2. Parental feedback via experience trackers



Conclusion: A combination of staff training and parental CPI tools aligned with PBM Module 6 were well-accepted by clinical stakeholders and were associated with practice improvement. This CPI project demonstrated the potential to improve PBM and transfusion practice in this vulnerable population. It also developed NICU-specific consent information, not previously available, by partnering with parents to ensure excellence in transfusion practice. In the process, the strategies and tools developed may translate readily into other NICUs to support best practice.

P233. Developing a comprehensive sequence capture panel for red cell, platelet and neutrophil genotyping

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Aim

To develop a comprehensive exome capture panel targeting genes and regulatory regions encoding for red cell, platelet and neutrophil antigens.

Method

A total of 64 genes for 36 blood groups, platelet and neutrophil antigens were included in the panel design, as well as known regulatory regions. The initial design was submitted to Illumina concierge for design confirmation and the finalised panel consists of 2654 overlapping probes covering approximately 140Kbp target sequence. A collection of 16 well characterised test samples were chosen for the initial optimisation and testing of the panel. Allele and phenotype predictions were performed on VCF and BAM files using a combination of semi-automated and manual prediction methods.

Results

Coverage averaged 379x for all 16 samples, indicating considerably better performance than the TruSight One Sequencing panel, which is currently employed for blood group genotyping in our reference laboratory. Star allele combinations were predicted for all blood groups using a semi-automated python script excepting P1Pk, which failed to 'parse' in all 16 test samples. Semi-automated allele predictions consistently called the correct allele to match manual predictions for all SNP-based alleles except in two cases (both the ABO gene) and correctly called alleles for genetic loci matching the Hg19 reference sequence. Semi-automated prediction was unable to resolve *RHD* gene deletions or hybrids in the RH and MNS systems, however manual copy number variation analysis was successfully employed to resolve these instances.

Conclusion

Here we report on initial findings from a comprehensive red cell, platelet and neutrophil exome capture panel and semi-automated allele prediction script. The custom designed targeted panel demonstrates greater coverage and across target genes and higher throughput compared to the TruSight One Sequencing panel. The advantage of the greater throughput will allow its adoption for donor screening and discovery of rare blood groups.

P234. A laboratory network approach to reducing blood wastage

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NSW Health Pathology (NSWHP) East, Rural and Regional comprises 27 blood banks with 25,000 blood units transfused each year. In 2014/15, 1872 blood units were discarded at the cost of \$702,000. The National Blood Authority introduced in 2013 the Discard as a Percent of Issue (DAPI) to benchmark blood discards, and assigned DAPI targets for Health Facilities to meet.

From 2015, the following measures were introduced with the aim to reduce blood wastage and meet the DAPI targets:

- Raising awareness among scientific staff and laboratory managers.
- Setting blood stock levels that are appropriate for each Laboratory.
- Providing a monthly blood discard report for the network.
- Rotating blood units from small to larger centres when they reach their half-life.
- Training staff on proper blood inventory management practices:
- Do not stock rare blood types in small laboratory.
- Use older blood first.
- Use group compatible blood rather than group specific.
- Use O RhD Negative blood for patients of other blood types before they expire.
- Crossmatch blood only when required for transfusion.
- Regularly check crossmatched units, and consider releasing before ordering new stock.

As a result of the implemented measures, most laboratories maintained their DAPI below their set targets and/or achieved a DAPI comparable to their peer group. Blood discards in 2015/16 was lower by 28% compared with previous year. Further reductions in blood wastage of 42% and 25% were achieved in 2016/17 and 2017/18. The total annual cost saving has become \$554,000 (\$428 per unit).

Despite the significant improvement achieved in the last three years, 577 units were discarded in 2017/18. Out of these around 40% were due to clinical reasons. Our next step is to tackle the wastage resulting from clinical reasons, which requires different approaches to those implemented so far. Some interventions may not be cost efficient but there is more to blood than just the dollar value.

P235. Characterisation of microparticles present in cryopreserved sheep platelet concentrates

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Aim

In Australia, platelet concentrates (PCs) are routinely stored at room temperature for up to 5 days. This short shelf-life adversely impacts the availability of PCs in remote regional areas as well as in military settings. Cryopreserved PCs (cryo-PCs), frozen at -80°C, have a shelf-life of up to 2 years. Microparticles are submicron plasma membrane particles that can contribute to coagulation due to the presence of phospholipids. Cryopreservation of human PCs has been associated with formation of more microparticles and elevated procoagulant activity compared to liquid-stored PCs. A pre-clinical sheep model of cryo-PC transfusion will facilitate mechanistic studies and complement clinical trials. Therefore, this study aimed to characterise microparticles present in sheep cryo-PCs.

Method

Sheep cryopreserved PCs (cryo-PCs; n=6) were prepared by the addition of 5-6% DMSO, with minor modifications to standard procedures for human cryo-PCs. Sheep cryo-PCs were sampled pre-freeze, post-thaw and 24-hours post-thaw. Cryo-PC supernatant (SN) was separated with double centrifugation and stored at -80°C. Microparticle mean size and concentration was measured in ten replicates using nanoparticle tracking analysis system (NanoSight NS300, Malvern Instruments). Results are mean ± SEM.

Results

Prior to cryopreservation, sheep PCs contained a mean microparticle concentration of $3.28 \times 10^{11} \pm 0.24 \times 10^{11}$ microparticles/mL with a mean size of 144.8 ± 3.2 nm. Neither microparticle concentration nor size changed following cryopreservation, containing $4.13 \times 10^{11} \pm 0.44 \times 10^{11}$ microparticles/mL with a mean size of 140.6 ± 3.6 nm post-thaw. Furthermore, the microparticle concentration and size remained similar after storage at room temperature 24 hours post-thaw ($4.25 \times 10^{11} \pm 0.45 \times 10^{11}$ microparticles/mL, 136 ± 2.9 nm).

Conclusion

Microparticles were present in sheep-PCs; however, cryopreservation of sheep PCs did not lead to statistically significant changes in the concentration or size of these microparticles up to 24 hours post-thaw. Further investigation is required to determine whether the microparticles present in sheep cryo-PCs contribute to procoagulant activity in a manner similar to that of human cryo-PCs.

P236. Sheep platelet microparticles: comparison to human platelet microparticles and investigation of storage-associated changes

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Aim

Microparticles are submicron plasma membrane particles that due to the presence of phospholipids can contribute to coagulation. *Ex vivo* room temperature storage of platelet concentrates (PCs) has been associated with formation of microparticles and elevated procoagulant activity. Furthermore, microparticles present in PCs have been postulated to be potential mediators of adverse transfusion outcomes. To support the use of sheep as a model to investigate the effects of PC transfusion, this study aimed to characterise sheep platelet microparticles, assess storage-related changes and compare results to human platelet microparticles.

Method

Sheep buffy coat derived PCs in 30% plasma/70% SSP+ (n=5) were prepared with minor modifications to standard procedures for human PCs. Sheep PCs, and equivalent human PCs (n=5) were stored for 7 days at 22°C and sampled on day 2, 3, 5 and 7. PC supernatant (SN), prepared by double centrifugation, was stored at -80°C. The mean size and concentration of microparticles in PC-SN samples was measured in ten replicates using nanoparticle tracking analysis system (NanoSight NS300, Malvern Instruments). Results are mean ± SEM.

Results

At day 2 the mean size of microparticles in sheep PC-SN (127.2 ± 5.2nm) was no different to that of microparticles in human PC-SN (124.9 ± 3.7nm); however, the microparticle concentration was 2.85-fold less ($1.6 \times 10^{11} \pm 0.85 \times 10^{11}$ microparticles/mL in sheep PC-SN compared to $4.6 \times 10^{11} \pm 0.97 \times 10^{11}$ microparticles/mL in human PC-SN; $P < 0.0001$). Storage duration of human or sheep PCs was not associated with changes to microparticle concentration or mean size.

Conclusion

While sheep PCs contained a lower concentration of microparticles, similarities in the mean size and the similar absence of storage-related changes in both human and sheep PCs are suggestive that sheep may be a suitable model animal in which to investigate PC transfusion. Further investigation is required to confirm if the lower concentration of microparticles in sheep PCs is associated with decreased procoagulant activity.

P237. The importance of the test tube in an era of Column Agglutination Technology

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The Blood Service Red Cell Reference Laboratory (RCRL) employs a tube indirect antiglobulin test (IAT) technique as the method of choice for all red cell antibody investigations.

A recent sample referred for testing from a 39 year old male with a history of “difficult antibodies” highlighted the importance of maintaining this technique in routine blood banking as it is often utilised to resolve positive reactions that are not clinically significant, allowing serological crossmatch which can remove the need for referral to the RCRL and save time.

Most hospital and pathology blood banks no longer have access to tubes and rely solely upon column agglutination technology (CAT) as it requires minimal training, uses less sample volume and has proven sensitivity, specificity and reproducibility. It does however have a number of limitations such as the inability to allow the user to observe agglutination appearance and to perform a strict pre-warm method. Diluents used also contain antibiotics which can cause false positive reactions if a patient has developed drug dependent antibodies. These can all compromise an antibody investigation, leading to a reliance on the RCRL to resolve these problems by use of a tube technique.

With this particular case, tube techniques at room temperature and by IAT gave clear cut negative reactions, whilst a strong autoantibody was observed by CAT. This prompted the RCRL to conduct a look back study using a reporting tool to identify the number of reports issued over the past two years where the comment “Use of tube IAT is recommended for pre-transfusion and compatibility testing “ had been included in the text of the report. The reporting tool identified 90 investigations in NSW where the use of tube techniques had resolved the positive reactions that were not clinically significant.

P238. Introduction of a pre-operative patient blood management program for primary elective joint replacement surgery

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A pre-operative blood patient management program was introduced to optimize patient red cell mass prior to primary elective joint replacement surgery in our institution in May 2017.

Methods

Records of patients having primary elective hip or knee replacement between May 2017 and May 2018 were reviewed. Data relating to transfusion and iron status was compared to audit data from January to December 2014.

Results

In primary knee replacements 2017-2018 (n=43), compared to 2014 (n=56), transfusion index has decreased from 0.14 to 0.07. In primary hip replacements 2017-2018 (n=35), compared to 2014 (n=23), transfusion index has decreased from 0.3 to 0.08. Pre-operative anemia has decreased from 13% (n=10) to 6% (n=5). Frequency of pre-operative iron studies testing has increased from 13% (n=8) to 86% (n=67). The pre-operative treatment of low iron stores (ferritin <100mcg/L) has increased from 16% (1/6) to 53% (9/17). Length of acute admission has decreased from 7.8 in 2014 to 5.7 in 2017-2018. In 2017-2018, length of stay (LOS) was far greater in patients who had iron deficiency anaemia (n=4) with LOS of 14 days and in those who were transfused, with LOS of 7 days (n=4).

Several refinements were made to project workflow in early 2018. Among patients seen in pre-admission clinic from March to June, 100% (n=24) of these patients had iron studies tested pre-operatively. 100% (n=4) of patients with low iron stores were treated pre-operatively. Of the three patients who were transfused in this cohort, one was anaemic pre-operatively due to immunosuppression and renal failure. The remaining two patients had normal haemoglobin levels and ferritin levels >100mcg/L prior to surgery.

Conclusions

Length of stay and transfusion rates has reduced during between the two time-points, although this is likely multifactorial. The prevalence of iron testing has greatly increased, as has treatment of iron deficiency, with the introduction of the program. We aim to develop processes to address other intra-operative bleeding risk factors.

P240. Validation of regulated systems in preparation for ISBT128

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The Australian Red Cross Blood Service is entrusted with the supply of Australia's blood products. Every year 1.3 million blood donations are collected, tested and manufactured into blood components, then delivered to hundreds of healthcare providers around the country.

The Blood Service is implementing the Information Standard for Blood and Transplant (ISBT128) in 2018 in accordance with the National Blood Authority's barcode specifications paper 'Barcode Specifications for Blood and Blood Products Funded under the National Blood Arrangements'.

Implementation of ISBT128 involves changes to the critical information such as the donation identification number and component code data-structures, which are encoded within barcodes on the Blood Component label. Changes to such data-structures require updates to Information Technology systems, hardware and system interfaces. While seemingly simple, such a transformation means significant change through the Blood Service.

In order to ensure compliance with regulation and to maintain operational continuity, extensive mapping and testing of system data flow is required to ensure systems are adequately tested and validated prior to deployment. Additionally, due to the number of changes involved, prioritising and gradual deployment to mitigate risk and avoid a 'big bang' implementation was necessary.

This poster will demonstrate the overall approach taken by the Blood Service from planning to deployment to ensure regulatory compliance and validation was completed, for the successful implementation of ISBT128.

Australian Governments fund the Blood Service to provide blood, blood products and services to the Australian community

P241. Three years of Victoria's festive campaign-it's not the season to be wasting

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Aim

To report increased awareness and reduced red blood cells (RBC) waste over the festive period for three years, from 2015/16 until 2017/18 in Victoria.

Background

The RBC wastage reduction project commenced July 2014 to assist Victorian health services reduce RBC wastage to specified national targets.

The 'stop the waste' festive campaign was initially launched in October 2015, to inform health services that RBC waste peaks in January/February and explore reduction strategies.

Method

Each campaign begins with emails sent in August to help key stakeholders identify anticipated variations in practice and demand. Checklists, posters, and case studies (2016/17) circulated to promote discussion with the pathology/blood bank regarding anticipated changes in RBC needs. Communications to private hospital executives (2015-18) highlighting their role in waste reduction by recognising and reporting anticipated health service activity changes over the festive period. The campaign reminds staff to check inventory and monitor practices, comparing use and waste patterns from previous years.

Results

Overall, Victorian RBC waste continues to decrease; remaining consistently below national RBC wastage figures. Table 1 outlines RBC waste over the years the campaign has been running.

Table 1. Victorian RBC wastage

Year	Total RBC discarded (Jan and Feb)
2015	1,493
2016	1,099
2017	576
2018	563

In February 2018, Victoria reported the lowest ever RBC wastage rate of 1.8 per cent with 239 units discarded.

Summary

When the festive campaign commenced in 2015/16, a total of 2,133 red cells were discarded (November-February). The 2017/18 campaign, saw this number halved to 1,174 red cells discarded (a cost saving of approximately \$314,815); with no peak in February 2018. Increased awareness, regular communication, and engagement of health services/pathology/blood banks in the 'stop the waste' festive campaign have resulted in significant RBC waste reduction.

P242. Women at risk – obstetric blood management education for clinicians

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Introduction

Implementing obstetric blood management strategies is critical for the safety of pregnant women as: iron deficiency and iron deficiency anaemia in women of child bearing age is a public health issue 5-15% of Australian and New Zealand pregnant women have a postpartum haemorrhage (PPH) PPH rates are increasing in resource-rich countries.

Aim

A suite of online obstetric courses have been developed to inform and educate clinician's about the National Patient Blood Management Guidelines: Module 5, Obstetric and Maternity to help improve pregnancy outcomes.

Method

Three online courses, Obstetric Haematology, Obstetric Blood Management and Postpartum Haemorrhage have been created based on the national guidelines and current evidence. Courses are interactive and include clinical scenarios and videos of clinicians discussing best practice. Successful completion of a multi-choice assessment is required for learners to gaining a certificate.

Feedback is sought through an anonymous and optional electronic survey when course certificates are emailed to learners.

Results

The courses were released in August 2017 and have been endorsed by various professional bodies. There have been over 11,750 completions of these courses:

Obstetric Haematology – 3,444

Obstetric Blood Management – 2,534

PPH – 5,806

Survey feedback shows that the courses provide knowledge to users and will improve patient outcomes and safety.

	Obstetric PBM courses
<i>Improve knowledge</i>	91%
<i>Help identify a near miss or prevent an adverse event</i>	80%
<i>Change clinical practice</i>	70%
<i>Improve patient outcome/safety</i>	87%

Learners identified a range of areas where practice could be improved within their organisation.

Conclusion

Feedback from learners confirmed that the online obstetric PBM courses enhance knowledge and enable them to improve practice

P243. The Australian Haemoglobinopathy Registry: 2018 Snapshot

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Aim

The Australian Haemoglobinopathy Registry is a national register which aims to describe the epidemiology, management and clinical outcomes for Australian patients with thalassaemia and sickle cell disorders, and provide a resource for clinical research.

Method

Cases are identified by clinicians at participating sites. The dataset captures patient demographics, diagnosis, testing undertaken, medication and transfusion therapy, hospital presentations, and complications.

Results

The registry currently contains data on 354 patients from 6 sites across 5 states, with 4 more sites joining. This includes 210 adult patients (≥ 18 y), of whom 8.6% are α (HbH disease/other α thalassaemia), and 74.8% β thalassaemia (major, intermedia with major phenotype or HbE/ β thalassaemia compound heterozygotes), 15.7% sickling disorders (HbSS, HbSC or HbS/ β thalassaemia), and 2(1%) have another haemoglobinopathy. Of the 144 patients < 18 y, 19.4% have α thalassaemia, 26.4% β thalassaemia, and 54.2% sickling disorders.

Median age at June 2018 for α thalassaemia patients on the registry is 14.8 years (IQR 10.5, 36.9), β thalassaemia 39.1y (IQR 20.8, 48.0), sickling disorders 13.8y (IQR 9.0, 20.0).

40% of sickling disorder, and 97% of β thalassaemia patients receive regular transfusions. For patients with transfusion data available, adult β thalassaemia patients received a median 3 RBCs per transfusion (IQR 2.5, 3), every 4w. For regularly transfused sickle cell patients, available data show $> 85\%$ of transfusions being RBC exchange, and with a median of 4 RBCs (IQR 2, 5) every 4w. Alloantibodies were identified in 32.8% of β thalassaemia, and 18.9% of sickle cell patients (lower than previously reported for this group - which may reflect recent practice changes, including uptake of hydroxyurea therapy and better RBC matching).

Conclusion

Transfusion requirements in haemoglobinopathy patients are substantial. As the Australian Haemoglobinopathy Registry expands and follow up continues, it will become a valuable resource, providing analysis of evolving demographics, treatments and clinical outcomes.

P244. Hybrid glycophorins in the Australian blood donor population

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Aim

GYPA and *GYPB* genes of the MNS blood group system share a high degree of sequence homology and gene structure. Homologous exchanges between *GYPA* and *GYPB* result in the formation of hybrid genes encoding hybrid glycoporphins GP(A-B-A) and GP(B-A-B). Over 20 hybrid glycoporphins have been characterised. Each has a distinct phenotype defined by the profile of antigens expressed including Mi(a), MNS7. Anti-Mi(a) reacts with seven hybrid glycoporphins (GP.Vw, GP.Hut, GP.HF, GP.Mur, GP.Hop, GP.Bun, and GP.Kip) that have been reported in Caucasian and Asian populations. The Australian demographic is diverse, however, the prevalence of hybrid glycoporphins in the current Australian population has not been determined. The aim of this study was to determine the frequency of hybrid glycoporphins and serological profile of Mi(a)-positive hybrid glycoporphins in an Australian blood donor population.

Method

Blood samples from 5,098 Australian blood donors in Queensland were randomly selected and screened for Mi(a) using anti-Mi(a) monoclonal antibody (CBC-172, Japanese Red Cross) by standard haemagglutination techniques. Mi(a)-positive RBCs were further phenotyped using anti-Vw, -Hut, -Mur, -Hil, -Mi.III, and -Anek to characterise the profile of low-prevalence antigens on hybrid glycoporphins.

Result

Mi(a)-positive hybrid glycoporphins were detected in 11 out of 5,098 blood donors – a frequency of 0.22%. Of 11 Mi(a)-positive RBCs, serological profile for low-prevalence antigens revealed phenotypes consistent with 2 GP.Hut, 3 GP.Vw, 5 GP.Mur and 1 GP.Bun phenotypes.

Conclusion

Exposure to Mi(a)-positive hybrid glycoporphins sometimes stimulate antibody responses to Mi(a) and other low-prevalence MNS blood group antigens causing haemolytic disease of the fetus and newborn and haemolytic transfusion reaction. This study identified four distinct Mi(a)-positive hybrid glycoporphin phenotypes (GP.Hut, GP.Vw, GP.Mur and GP.Bun) providing data to support extended typing of donors to identify this low-prevalence, but immunogenic, antigen. Genotyping is underway to confirm the identity of these hybrid glycoporphins.

P246. Delayed clearance of fetal red cells after fetomaternal haemorrhage provoking Rh(D) alloimmunisation in a splenectomised patient despite repeated Rh(D) immunoglobulin

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In women administered Rh(D) immunoglobulin (RhDIg) in the setting of fetomaternal haemorrhage (FMH), clearance of detectable fetal red blood cells (RBCs) occurs typically within 48 hours of the sensitising event. However, there is little literature to guide the management of prolonged persistence of fetal RBCs postpartum. Supplemental RhDIg are recommended by both BCSH and ANZSBT guidelines if tests for FMH are persistently positive. Conversely, there are differing recommendations on the relative importance of RhDIg detection in maternal plasma. These guidelines are largely based on expert opinion.

Our patient was a 50-year-old primigravida whose past history included a distant splenectomy for immune thrombocytopenic purpura which was in remission. She was not overweight. She had become pregnant via *in vitro* fertilisation and had an uneventful antenatal course. She was Rh(D) negative and had therefore received routine antenatal prophylaxis with RhDIg. She underwent an uncomplicated elective caesarean section at 37 weeks due to her advanced maternal age.

Her baby was Rh(D) positive. FMH quantitation was estimated at 24.5mL by Kleihauer-Betke test and 22mL by flow cytometry using anti-HbF. Rhophylac 3000IU was administered intramuscularly 24 hours postpartum. This was repeated at day 3 intramuscularly and day 5 intravenously postpartum due to the persistence of greater than 20mL of fetal RBCs.

At 7 days, her Kleihauer-Betke test estimated 16.3mL fetal RBCs within her circulation and anti-D was detected. With specialist consultation, no further RhDIg was administered. It was hypothesised that her asplenia delayed clearance of fetal RBCs which would have been adequately coated with the administered immunoglobulin.

A follow up antibody screen at six months postpartum confirmed alloimmunisation. Given our experience, possible considerations in future cases include ongoing Rh(D) administration until complete fetal RBC clearance is achieved in spite of detectable RhDIg.

P247. The role of the multidisciplinary team in the obstetric management of anti-Co(a) antibody

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The multidisciplinary team is integral to the coordination of transfusion support in complex or high-risk obstetric care. We describe our approach to a pregnant woman with an antibody to the high incidence antigen, Colton^a (Co (a)).

A 39-year-old grand multigravida was referred for obstetric care due to the risk of haemolytic disease of the foetus and newborn (HDFN). The partner was Co(a) positive, confirming the risk of HDFN.

The local transfusion team including transfusion medicine specialist, transfusion nurses and blood bank scientists liaised closely with her obstetric team and Australian Red Cross Blood Service to facilitate care.

Antenatally, oral iron replacement was advised to treat iron deficiency and optimise maternal red cell mass. Antibody titre reached 256 and serial middle cerebral artery doppler ultrasounds were performed. No intrauterine transfusions were needed. If this had been required, an international search for suitable donors would have been conducted.

Preparation for transfusion support required close communication to prepare two fresh units of Co(a) negative RBCs, with further frozen Co(a) negative units available if required for the mother. For the neonate, the only fresh unit available was O Rh(D) positive, Co(a) negative, CMV negative, therefore urgent determination of Rh(D) status at birth was anticipated.

Induction of labour was planned, however the patient presented with premature rupture of membranes. Minimisation of blood loss during labour included active management of the third stage, with cell salvage on standby. Ultimately, the delivery was uneventful. The baby was A Rh(D) positive with positive DAT and eluate showing anti-Co(a) specificity. Double light phototherapy was required for two days, however the baby's haemoglobin was stable on discharge.

The mother was counselled regarding the risk of haemolytic transfusion reactions and HDFN in further pregnancies due to her anti-Co(a).

P248. Implementing a quality subcutaneous immunoglobulin home program for haematology patients using the push method of administration

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Aim

The introduction of subcutaneous immunoglobulin (SCIg) in Australia has provided patients with opportunity of self-administering their therapy at home. The flexibility of this treatment option has resulted in significantly improving the patient's quality of life. Currently in Western Australia, a small cohort of immunology patients are self-administering SCIg at home. The aim is to implement a consumer-focused quality SCIg program for haematology patients using the simplicity of the push method of administration instead of pumps.

Method

Implementation of governance requirements in accordance with the National Blood Authority SCIg access conditions.

The hospital transfusion nurse provides the SCIg education to the haematology patient in 2-3 sessions at the hospital. The partner or carer is encouraged to be actively involved in the program. The patient is provided with education resources including a PowerPoint education presentation and other support materials such as phone apps and patient diaries.

The patient is taught how to administer the immunoglobulin via push method in 1 or 2 subcutaneous sites. They are instructed to push the infusion for 5mls in 5 minutes then rest for 5 minutes and then repeat until infusion is completed.

A competency checklist after the 3 education sessions is completed to ensure that the patient understands to do the following: a) Administer SCIg safely b) Manage safe sharps disposal c) Recognise, respond and report adverse incidents. d) Accurate documentation of details of infusion and recording of batch numbers

Phone support is provided by the transfusion nurse and haematologist.

The patient provides SCIg program feedback and the evaluation data is used to modify and improve the service.

Results

Patient feedback has been extremely positive. Patients like to push the medication in 5 minute intervals and rest for 5 minutes.

Conclusion

The plan is to identify more appropriate haematology patients for the SCIg program.

P249. A Cold Case – The role of genotyping in solving a past Rh(D) discrepancy

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False positive Rh(D) typing in patients may result in anti-D immunisation from transfusion or omitting anti-D immunoglobulin prophylaxis in pregnancy. Known causes of this error include cold agglutinin reactivity in the monoclonal anti-D reagents and cross reactivity with some RhCE variants.

RHCE*01.11 (RHCE*ceRT) is caused by a single nucleotide polymorphism (SNP) 461G>C in Exon 3. The resultant amino acid change Arg154Thr expresses some D epitopes of group epD6 despite lacking all D-specific amino acids. This allele encodes c+e+w and reacts with some monoclonal anti-D.

In 2010, we investigated a donor with discrepant Rh(D) type during routine automated testing. Reactivity was variable between anti-D reagents and it gave inconclusive results with two RhD typing kits. Cold agglutinin investigations were negative. Using a combination of titres and adsorption/elution studies, it appeared that the patient's red cells possessed Rh(D) antigen. The expression of e was observed to be weakened. The RHD gene was not detected using in-house PCR tests targeting exons 4 and 7 by gel electrophoresis.

With the recently introduced Beadchip BioArray genotyping system, the stored DNA sample was reanalysed using the RHD assay and revealed a RHD deletion. Current availability of targeted DNA sequencing was also utilised and the donor was found to be RHD*01N.01/*01N.01 and RHCE*ce/ce.11 with a predicted phenotype of C-, c+, D-, E-, e+.

This case highlights the value of improved molecular testing techniques in confidently resolving previously discrepant results. The donor's red cells will be labelled as RhD positive, but as a recipient of blood in future, the donor should be regarded as RhD negative.

P250. Anti-Sc3 – A case study

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Antibodies to high frequency antigens can be detected during routine blood bank testing. Also referred to as 'high incidence' or 'public' antigens, for HFA classification, they must have an incidence of >90% but the majority have an incidence of >99%. They are generally clinically significant and can cause problems in blood bank testing due to their pan-reactivity. This can make it a challenging scenario to find compatible units in the event that a blood transfusion is required.

We investigated a patient with severe anaemia (49g/L) and active bleeding with a history of multiple transfusions in Papua New Guinea. Routine serological investigations performed at our laboratory indicated an antibody directed against an antigen in the Scianna blood group system. Subsequent molecular testing indicates the patient has no genetic variations found in the Scianna blood group.

Scianna is the 13th blood group System and consists of seven antigens including high incidence SC1, low incidence SC2 and very high frequency antigen, SC3, which is only absent on the null phenotype Sc:-1,-2,-3. This null phenotype is known to make a high frequency antibody anti-Sc3 and is more common in Pacific Islanders.

The referred patient in this case study has an antibody that reacted with all panel cells and weakly with their own. The reactivity was not destroyed with papain, trypsin or DTT treated cells. However, it was sensitive to cells treated with chymotrypsin. Inhibition with CD55 ruled out a Cromer related antibody. Adsorption studies ruled out additional allo-antibodies. Although serologically appearing as Sc:-1-2, the predicted phenotype by both HEA BeadChip and targeted DNA sequencing analyses indicates the patient is Sc:1-2.

In this case, serology indicates the patient is Sc:-1,-2 and has made an anti-Sc3 antibody. However, molecular testing can detect the presence of the SC*01 allele suggesting a predicted phenotype of SC:1,-2. It is necessary to perform long range PCR on this case to determine whether the anti-Sc3 is auto or allo, or, alternatively, a novel mutation.

P252. Antiplatelets and profibrinolytic activity of Citrullus colocynthis in control and high-fat diet-induced obese rats

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The current study aimed to investigate the effect of Citrullus colocynthis (*C. colocynthis*) hydro-alcoholic extract on blood haemostasis in control and high-fat diet (HFD) induced obese rats. In control rats, the extract significantly enhanced bleeding time and plasma levels of tPA and significantly decreased plasma levels PAI-1 and serum levels of thromboxane B2 leading to inhibition of platelets aggregation. In HFD induced obese rats, similar effects were seen and the extract was also able to reverse HFD induced increases in fibrinogen and VWF. Searching for the mechanism, *C. colocynthis* acts by (1) inhibiting of food intake, (2) inhibiting the activity of pancreatic lipase, (3) decreasing levels of TNF- α and IL-6 and (4) decreasing circulatory levels of the prothrombotic adipokine, leptin and enhanced circulatory levels of the antithrombic adipokines and adiopnectin. In conclusion, *C. colocynthis* has antiplatelets and profibrinolytic activity in both control and HFD induced obese rats.

P253. Global coagulation assays in anticoagulated venous thromboembolism patients: increased fibrin generation with reduced fibrinolysis

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Aim: Conventional coagulation testing is not sensitive enough to detect the anticoagulant effect of direct oral anticoagulants (DOAC) and anti-Xa levels only reflect drug levels rather than degree of anticoagulation. Global coagulation biomarkers such as calibrated automated thrombogram (CAT) and overall haemostatic potential (OHP) may provide a better assessment of an individual's haemostatic state. We aim to explore the role of these assays in assessing the anticoagulant effect in VTE patients as part of a larger prospective study using these assays to predict VTE recurrence.

Method: Patients on therapeutic anticoagulation for VTE treatment were recruited and citrated whole blood samples were obtained. The samples were double spun to obtain platelet-poor plasma for the evaluation of thrombin generation using CAT and fibrin generation using OHP and compared to previously collected normal controls.

Results: Fifty anticoagulated VTE patients were evaluated including 11 patients (22%) on warfarin, 34 (68%) on Rivaroxaban, 3 (6%) on Apixaban and 2 (4%) on enoxaparin. Compared to normal controls, anticoagulated VTE patients exhibited hypocoagulable CAT parameters ($p < 0.001$). Despite these findings, only 14/39 (36%) of non-warfarin patients had prolonged prothrombin time (PT) and/or activated partial thromboplastin time (APTT). Interestingly, fibrin generation parameters were significantly higher in VTE patients with reduced overall fibrinolytic potential despite being on anticoagulation. Fibrin generation did not correlate with von Willebrand antigen and factor VIII levels which were also found to be elevated (158% vs 101%, 143% vs 101%; $p < 0.01$) in VTE patients.

Conclusion: Global coagulation assays, particularly CAT, appear useful in the assessment of an individual's in-vivo anticoagulated status despite normal conventional coagulation studies. Paradoxically, fibrin generation is increased in these patients despite anticoagulation and the underlying pathophysiology will be further studied. This finding suggests that OHP assay is independent of the anticoagulant effect. Further prospective clinical correlative studies is ongoing.

Table 1. Laboratory parameters of anticoagulated VTE patients compared to normal controls

	Normal controls (n=97)	Anticoagulated VTE (n=50)	p-value
CAT parameters			
Lag time (min), median	3.1	5.7	<0.001
Endogenous Thrombin Potential (nM/min), median	1310.6	688.8	<0.001
Thrombin peak (nM), median	222.0	57.6	<0.001
Velocity index (nM/min), median	65.3	9.7	<0.001
OHP parameters			
Overall Coagulation Potential, mean	59.6	66.1	0.003
Overall Haemostatic Potential, median	27.5	33.5	<0.001
Overall Fibrinolytic Potential (%), median	52.1	48.2	0.007
von Willebrand antigen (%) , median	101	158	<0.001
Factor VIII (%) , median	101	143	<0.001

P256. Loss of transcription factor Gfi1b in the megakaryocytic lineage in mice

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Aim

Transcription factor Gfi1b is important for normal megakaryocyte differentiation and development. Investigation into a four-generation family with a bleeding disorder caused by a single nucleotide insertion into the *GFI1B* gene (c.880_881insC) included the establishment of a mouse model of the conditional knockout of *Gfi1b* through the megakaryocytic lineage. We aimed to examine the effect that the loss of function of this gene in this lineage has on the haematological phenotype of these mice and its correlation to the human phenotype.

Method

C57BL/6J mice generated at Walter and Eliza Hall Institute, Melbourne, were used in this study. Mice with floxed *Gfi1b* (*Gfi1b^{fl/fl}*) were cross-bred to transgenic mice expressing Cre recombinase under the platelet factor 4 (Pf4) promoter (*Pf4-Cre*) in megakaryocytes (*Pf4-Cre^{T/+}*). Mice with retained floxed alleles were controls. Analysis of the haematological system was carried out on harvested blood, tissue and organs. Statistical differences were determined by Student's t-test.

Results

There were significant differences between control and *Gfi1b* conditional knock-out (KO) (*Gfi1b^{fl/fl}* x *Pf4-Cre^{T/+}*) mice in all haematological indices, except white cell counts. Platelet counts showed a 70-fold reduction in KO mice compared to controls ($p < 0.0001$). Reduced red cell indices indicated blood loss due to severely depleted platelet numbers. Stress erythropoiesis was induced in the spleens of KO mice, with significant organ enlargement ($p = 0.0004$) and increased erythroblast populations. Megakaryocytes in bone marrow of KO mice showed increased DNA ploidy, and proliferation ($p < 0.001$). Electron microscopy showed malformed megakaryocytes in KO mice, in bone marrow and in spleen, with poorly defined platelet islands, few platelet granules, and irregular distribution of the platelet demarcation system.

Conclusion

Loss of Gfi1b function produces a severe bleeding phenotype in mice due to thrombocytopenia, and splenomegaly. The loss of platelet alpha granules and abnormal megakaryocyte morphology mirror the changes seen in patients with a mutant *GFI1B* gene.

P257. Implementation of a multidisciplinary surveillance team to improve inferior vena cava filter retrieval

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Background: Prolonged indwelling time of inferior vena cava (IVC) filters is associated with complications. Observational studies demonstrate 35% retrieval rates with significant loss-to-follow-up.¹

Aim: To evaluate the impact of a multidisciplinary surveillance program on timely retrieval and follow-up of IVC filters.

Methods: Prospective study of IVC filters inserted at a major tertiary centre from July 2017-March 2018. Consecutive IVC filters placed for venous thromboembolism (VTE) prophylaxis or confirmed VTE with contraindication to anticoagulation were identified via a central repository. The database developed was overseen by a multidisciplinary team of haematologists, anticoagulation stewardship pharmacist and nurse coordinators. The team reviewed patient records and intervened to facilitate IVC filter removal. Primary outcomes were retrieval rate and documented retrieval plan.

Results: A total 105 patients underwent IVC filter insertion. Fifty-two (50%) had a prophylactic indication for insertion and 53 were for confirmed VTE. Fifteen patients (14%) died during follow-up from causes unrelated to the IVC filter, and were excluded.

Over a median patient follow-up of 155 days (range 5-347), 59% (53/90) of IVC filters were retrieved. Average indwelling time was 131 days (range 5-284), with 4% retrieved before day 30, 30% before day 90 and 81% before day 180. Retrieval rates were 55% (24/44) in the prophylactic group versus 63% (29/46) in the therapeutic group (p=0.52).

Active engagement by the multidisciplinary team occurred in 51% (27/53) of successful filter retrievals. Of 37 patients with IVC filters remaining in-situ, plan for removal with ongoing review was in place for 30 (81%). Overall, 92% of the cohort had IVC filter retrieved or a documented plan. Seven patients lost-to-follow-up were all prophylactic insertions.

Conclusion: Implementation of a multidisciplinary surveillance program has derived a favourable IVC filter retrieval rate over a short period. This quality improvement strategy resulted in almost complete follow-up. Further enhancements to ensure more timely filter retrieval are proposed.

Reference:

Jia Z, Fuller TA, McKinney JM *et al.* *Cardiovasc Intervent Radiol.* 2018;41(5):675-82.

P258. Overview of real-world direct oral anticoagulant experience - patients on low-dose anticoagulants have higher rates of bleeding and thrombotic stroke

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Aim: Direct oral anticoagulants (DOAC) are increasingly in use due to the convenience of oral administration without requiring drug level monitoring. We aim to evaluate the local real-world DOAC use, in particular focusing on safety data.

Method: Retrospective evaluation of patients commenced or continuing on DOAC between September 2013 and September 2016 through Northern Health.

Results: 1079 patients were identified with median age 70 years (range 17-96). The indications for DOAC were atrial fibrillation (AF) 61.4% (n=663), venous thromboembolism (VTE) treatment 30.5% (n=329) and VTE maintenance/prophylaxis 8.1% (n=87). The most commonly prescribed DOAC was Rivaroxaban 60.8% (n=656) followed by Apixaban 28.7% (n=310) and Dabigatran 10.5% (n=113). Of these patients 29.7% (n=320) were on low dose anticoagulation. Forty episodes of clinically significant bleeding (ISTH-SCC score 3-4) (3.7%) were captured [Table 1]. The average HASBLED score of these patients was 2 and significant risk factors for bleeding included low dose anticoagulation, AF patients, concurrent antiplatelet use, prior bleeding and high falls risk.

In terms of thrombotic complications, there were 12 episodes of thrombotic stroke (1.8%) despite DOAC use with risk factors including low dose anticoagulation (p=0.03), prior stroke (p=0.04) and high falls risk (p=0.03). Nine patients on DOACs for VTE (2.2%) reported recurrence including a patient with active malignancy.

Conclusion: Our local safety data appears comparable to clinical trials although interestingly, low dose anticoagulation was a significant risk factor for both clinically significant bleeding (p=0.04) and thrombotic stroke (p=0.03). This may be due to a frailer population with significant baseline co-morbidities and shared risk factors for bleeding and stroke which has led to initial prescription of low dose anticoagulation. This data suggest that low dose anticoagulation does not negate their complications risk and careful prescribing with ongoing patient review for potential shift in their clinical situation is vital.

	Clinically significant bleeding (ISTH 3-4) n=40	No bleeding n=952	p-value
Age (median)	78 (32-89)	69 (17-96)	0.014
Atrial Fibrillation as indication	80.0% (n=32)	60.7% (n=578)	0.014
Low dose anticoagulation	45.0% (n=18)	29.8% (n=284)	0.041
Concurrent antiplatelet use	27.5% (n=11)	12.9% (n=123)	0.008
Prior bleeding	15.0% (n=6)	3.4% (n=32)	<0.001
High falls risk	32.5% (n=13)	16.4% (n=156)	0.008
	Thrombotic stroke n=12	No thrombotic stroke n=469	
Age (median)	79 (45-89)	75 (31-96)	0.553
CHA ₂ DS ₂ -VASc score	5	4	
Low dose anticoagulation	71.4% (n=10)	42.4% (n=275)	0.030
Concurrent antiplatelet use	7.1% (n=1)	17.7% (n=115)	0.303
Prior stroke	35.7% (n=5)	15.1% (n=98)	0.035
High falls risk	50.0% (n=7)	24.2% (n=157)	0.027

Table 1. Risk factors associated with clinically significant bleeding risk and thrombotic stroke in patients on DOAC

P259. Warfarin vs direct oral anticoagulants in venous thromboembolism – real world experience in Australia

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Aim: The introduction of direct oral anticoagulants (DOAC) has revolutionised the treatment of venous thromboembolism (VTE). Previous clinical trials have concluded that DOACs are non-inferior to warfarin in the treatment and prevention of VTE and at least as safe in terms of bleeding risk. However, real world data comparing the anticoagulants is limited and we aim to evaluate the demographics and safety outcomes during the warfarin era vs the DOAC era.

Method: Comparison was made of two separate retrospective local audits of VTE patients – one conducted during the warfarin era (July 2011 to December 2012, n= 617) and the other of those treated with DOAC (September 2013 and September 2016, n= 374).

Results: A total of 991 patients were reviewed: 62.3% (n=617) were on warfarin, 31.8% (n=315) were on DOAC for acute VTE treatment and 6.0% (n=59) were on DOAC for maintenance or prophylaxis. Of the patients on DOAC, 88.2% (n=330) were on Rivaroxaban and 11.8% (n=44) were on apixaban. There were more unprovoked VTE in the DOAC group. The patient demographics are outlined in the table below. Overall, there were 28 clinically significant bleeding (ISTH-SCC score 3-4) events in the warfarin group (4.5%) and 8 in the DOAC group (2.1%). The site of bleeding did not differ between both groups. In terms of recurrent VTE, 48 events were captured – 39 occurred on warfarin (6.3%) and 9 while on DOAC (2.4%).

Conclusion: This retrospective study found that patients on warfarin had a higher rate of VTE recurrence and clinically significant bleeding compared to patients on DOAC. The reason for this may be selection bias as high risk patients with other co-morbidities or those not meeting criteria for DOAC prescription continues to be prescribed warfarin over DOAC. Further studies are required to evaluate the comparative safety data of warfarin vs DOAC in VTE.

	Warfarin (n=617)	DOAC (n=374)	p-value
Age (median)	63 (16-96)	55 (17-90)	
Male	306 (49.6%)	187 (50.0%)	0.905
Provoked VTE	358 (58.0%)	107 (28.6%)	<0.001
History of prior VTE	139 (22.5%)	135 (36.1%)	<0.001
Acute VTE treatment	617(100%)	315 (84.2%)	<0.001
Complications:			
Recurrent VTE on treatment	39 (6.3%) 2.40 per 100 person years	9 (2.4%) 1.21 per 100 person years	0.005
Clinically significant bleeding	28 (4.5%) 1.71 per 100 person years	8 (2.1%) 1.08 per 100 person years	0.050
Site of bleed:			
Intracranial	6 (21.4%)	2 (25.0%)	0.834
Gastrointestinal	9 (32.1%)	3 (37.5%)	0.779
Other Bleeding Site	13 (46.4%)	3 (37.5%)	0.653

P260. Acquired Haemophilia and recombinant porcine FVIII replacement: An Australian case series

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Aim

To describe recent Australian use of recombinant porcine FVIII (rpFVIII) replacement therapy as a haemostatic agent in patients with acquired haemophilia.

Method

Four patients with acquired haemophilia treated in three different institutions around Australia in the last 12 (twelve) months were included in the study. A standardised proforma was developed and retrospectively applied uniformly by the treating Haematologists for collection of clinical and haemostatic data.

Results

The average time to diagnosis of acquired haemophilia from onset of symptoms was 3.5 days (range 1-8 days). Six bleeds were treated with rpFVIII, five of which were initially refractory to treatment with recombinant VIIa. RpFVIII was rated efficacious in 100% of bleeds by 24 hours. RpFVIII loading dose was 100 U kg⁻¹ (100-120 U kg⁻¹) and this increased the factor VIII level (via one-stage FVIII assay) from <1%-1.2% to 54%-306% taken 0.5-1.5 hours post infusion. Subsequent doses ranged from 40 to 60 U kg⁻¹ twice daily or daily for 3 to 13 days. No rpFVIII related adverse events occurred. Anti-porcine antibodies were measured at baseline for two of the four patients (0.6 and 1.1 BU respectively). The most heavily treated patient (13 days therapy with rpFVII) did not have an anamnestic rise in anti-porcine antibodies on follow up assessment (titre stable at 0.6 BU). Three of the four patients achieved complete remission and were weaned from immunosuppression. One patient died having achieved partial remission following an arterial ischaemic event. This event was temporally distant from the last dose of rpFVIII and clearly associated with pre-existing comorbidities.

Conclusion

This case series demonstrates that recombinant porcine FVIII is efficacious to treat acute bleeds in acquired haemophilia, including in those who are refractory to bypassing agents. Doses of rpFVIII were able to be titrated based on FVIII level and clinical response.

P262. Case report of perioperative anti-coagulation management of a patient with antiphospholipid syndrome undergoing mechanical heart valve surgery

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Introduction

There is limited evidence in the optimal perioperative anticoagulation management for patients with anti-phospholipid syndrome (APS) undergoing cardiac surgery.

Case

We present a 52 year old female patient with Systemic Lupus Erythematosus (SLE) and APS who underwent a successful on-pump mechanical mitral valve replacement for Libman-Sachs endocarditis with severe symptomatic mitral stenosis. Intraoperatively, 250 unit/kg of heparin was administered with monitoring of Activated Clotting Time (ACT) without a baseline ACT level. Protamine was given for an ACT value of 899 seconds with subsequent reduction to 171 seconds. Post-operatively, heparin infusion was started with an anti-FXa target of 0.3-0.7units/ml. She was transitioned to Danaparoid infusion (anti-FXa targets of 0.3-0.7unit/ml) due to thrombocytopenia with subsequent Heparin Induced Thrombocytopenia and Thrombosis (HITT) screening being negative. She was transitioned to warfarin therapy without any bleeding or thrombotic complications using these targets.

Discussion

Mitral valve is commonly affected in patients with SLE and APS and subsequent cardiac surgery has been associated with high mortality and morbidity mainly from thromboembolic complications. Optimal heparin monitoring is unknown due to difficulty in standardisation due to the interference of phospholipid antibodies with coagulation assays. Measurement of Thromboelastography (TEG) and Activated Clotting Time (ACT) intraoperatively have been shown to have inter-patient variability likely secondary to effects of Lupus Anticoagulant (LAC) on the assay. This has led to strategies of doubling baseline ACT and Activated Partial Thromboplastin Time (APTT) as targets, leading to administration of large doses of heparin associated with significant bleeding complications. Although anti-FXa levels have generally been targeted at 0.3 - 0.7 units/ml, there is poor evidence in this cohort of patients of optimal target levels. We report a case where no thrombotic or bleeding complications using targets of 0.3-0.7units/ml.

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P263. Efficacy of three factor prothrombin complex in achieving haemostasis in patients with major bleeding on anti-coagulation –Retrospective single center study

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Background

Non-vitamin K oral anticoagulant (NOAC) is used as anti-coagulation therapy for patients with thromboembolic disease and/or atrial fibrillation. There is uncertainty regarding the efficacy of 3-factor prothrombin complex concentrate (PCC) in NOAC associated major bleeding event (MBE). Prothrombinex-VF® is lysophilised coagulation factor containing Factor II, IX, and X and small amounts of Factor VII.

Method

Retrospective analysis of all patients who received Prothrombinex-VF® from January 2017 to February 2018 in our centre. Inclusion criteria was age >18, current anticoagulation therapy, MBE as defined by the International Society on Thrombosis and Haemostasis (ISTH) and <24 hours from last NOAC dose. Exclusion criteria were patients not for full resuscitation on admission. Primary outcomes were achievement of haemostasis (ISTH subcommittee measurements). Secondary outcomes were thromboembolic events, length of stay (LOS) and mortality.

Results

66 patients were collected with N=47 with warfarin associated MBE and N=19 with NOAC associated MBE. Overall, majority of patients had gastrointestinal bleed N=36 (53.7%), followed by intracranial bleeds N=18 (26.9%). Using Pearson Chi square analysis, more patients achieved haemostasis in the warfarin group N=42 (89.3%) with mean dose 27.5 IU/kg as compared to the NOAC group N=12 (63%) with mean dose 40.1 IU/kg (p=0.012). In the NOAC group, N=5 patients also received FFP in combination with Prothrombinex-VF® with N=2 not achieving haemostasis. Only 3 patients in total had a thromboembolic event (N=2 in warfarin group and N=1 in NOAC group). Mortality rate at 30 days was 6.5% in Warfarin group vs 10.5% in the NOAC group. Average LOS was 7.34 days in Warfarin group vs 11.5 days for the NOAC group.

Conclusion

3-factor PCC was not effective in achieving haemostasis for NOAC associated MBE (p=0.012) despite having higher mean dose. However effect of co-administration of FFP to improve haemostasis rates will require further research.

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Majeed, A., Ågren, A., Holmström, M., et al. (2017). Management of rivaroxaban-or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. *Blood*, 130(15), 1706-1712.

P264. The utility of flow cytometric platelet forward scatter as an alternative to mean platelet volume

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Aim

A number of studies have proposed a classification of inherited thrombocytopenia based on the mean platelet diameter (MPD) measured by image analysis on peripheral blood films. However this is labour intensive and not widely available. The mean platelet volume (MPV) generated by an automated cell counter can be used as a surrogate, but often cannot be recorded in macrothrombocytopenia. The aim of this study was to determine whether platelet forward scatter (FSC) generated on a flow cytometer could be used as an alternative to MPV.

Method

Platelet count and MPV was determined using a routine haematology (Sysmex) analyser on 41 patients, with either a suspected inherited platelet number disorder (n=25) or inherited platelet function disorder (n=16). Platelet FSC-Height was determined using a Fortessa-X20 flow cytometer on CD42b+ platelets, with normal ranges determined using healthy individuals. Mean platelet diameters (MPD) and Platelet Diameter to Large Cell Ratio (PDLCR) were determined on blood films analysed with ImageJ software on a cohort of 12 patients. Bleeding history was assessed using the ISTH bleeding assessment tool (BAT).

Result

An automated MPV could not be reported in 12 of the IPND patients (48%). There was a significant correlation between platelet FSC and MPD ($p < 0.0001$), PDLCR ($p < 0.0001$) MPV ($p < 0.0001$). Platelet FSC was inversely correlated to platelet count ($p = 0.0022$) and BAT ($p = 0.0199$). Despite a significant correlation between MPV and FSC, there was no significant correlation between MPV and BAT ($p = 0.52$), presumably non-availability of MPV measurements for the 12 IPND patients.

Conclusion

Platelet forward scatter measurements may be used as an alternative to MPV, especially in macrothrombocytopenia and those in which the MPV is not recordable. More patients are required to delineate reference intervals to enable the categorisation of inherited platelet disorders based on forward scatter and to determine the clinical utility of these parameters.

P265. Identifying efficacious thresholds for bleeding risk reduction in relation to Factor VIII levels in Haemophilia A patients receiving rVIII-SingleChain

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Aims

To assess the threshold levels of FVIII associated with significant reduction of bleeding risk, evaluate potential determinants of efficacy and quantify the relative risk of bleeding episodes based on FVIII activity levels.

Methods

rVIII-SingleChain is a single chain recombinant FVIII. Data for up to 2 years from 147 adults with 715 bleeding events from a Phase III study were utilized in the analysis, including all recorded bleeding episodes after the first infusion of rVIII-SingleChain. FVIII activity levels for each 12 hour time interval were simulated using a previously published population pharmacokinetic model. A Cox proportional hazards model was used to relate the time-to-bleed event data and various measures of FVIII exposure (>1%, >2%, >3% and >5%), as well as different dosing regimens (prophylaxis vs on-demand) to compare the risk of bleeding.

Results

Patients with simulated FVIII levels >1% had a 74% reduction in bleeding risk compared to patients with FVIII levels < 1%. Patients who maintained FVIII activity level >1% for 6 months or 1 year decreased the relative bleeding risk by 71% and 92%. Maintaining thresholds >2%, >3% and 5% further reduced the relative risk. The prophylaxis regimen showed a 91% reduction in relative risk compared with the on-demand regimen.

Conclusions

An rVIII-SingleChain treatment regimen maintaining FVIII levels >1% over time is an effective approach to control bleeding events. The relative bleeding risk is reduced by 92% when the FVIII activity level is maintained >1% for over a year. Higher FVIII levels further reduce the relative bleeding risk slightly. Prophylaxis regimens provide greater protection from bleeding than the on-demand regimen. This analysis quantitatively supports the rationale for optimized treatment regimens in adult haemophilia A patients by maintaining FVIII levels above 1%.

This research was supported by CSL Behring, King of Prussia, United States. The company was responsible for data analysis and abstract preparation.

P266. Long term safety and efficacy of rVIII-SingleChain in previously treated patients with severe Haemophilia A: Intermediate results of an extension study

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Aims

This Phase III multinational extension study investigates the long term safety and efficacy of rVIII-SingleChain in previously treated patients (PTPs) with severe haemophilia A.

Methods

PTPs with severe haemophilia A (endogenous Factor VIII < 1%) and >50 previous exposure days (EDs) to FVIII products were treated either on demand or prophylactically with rVIII-SingleChain 2 or 3 times weekly, or another regimen per the Investigator's discretion.

Results

As of 05 Sep 2017, 222 patients were enrolled. The median age was 20 y (1-64); 77 (34.7%) patients were 0- < 12 years, and 145 (65.3%) were ≥12 to ≤65 years old. The majority of patients were Caucasian (158, 71.2%); 50 (22.5%) Asian, and 12 (5.4%) were Black or African American. A minority of patients (10, 4.5%) were of Hispanic origin. A target of ≥100 EDs was achieved by 211 (95%) patients; the total cumulative EDs in the extension study was 65,522 in 494 treatment years. Of the 211 (95%) patients assigned to prophylaxis, 98 (44.1%) were treated 3 times weekly, and 84 (37.8%) patients were treated 2 times weekly. The median annualized spontaneous bleeding rate (AsBR) for all prophylaxis regimens, for patients treated 3 times weekly, and 2 times weekly was 0.35 (Q1, Q3: 0.00; 1.09), 0.35 (Q1, Q3: 0.0; 0.96), and 0.0 (Q1, Q3: 0.0; 1.46) respectively. Of a total of 2273 bleeding events, 2162 were treated with rVIII-SingleChain. Of these, 2120 were rated for haemostatic efficacy by the investigator: 85.8% were rated as either excellent or good and required 1 or 2 injections to achieve haemostasis. No PTP developed an inhibitor in the study.

Conclusions

rVIII-SingleChain has a favourable safety profile, and is effective and well tolerated for on demand and prophylaxis treatment in patients who have severe haemophilia A.

This research was supported by CSL Behring, King of Prussia, United States. The company was responsible for data analysis and abstract preparation.

P267. rVIII-SingleChain in Surgical Prophylaxis: Efficacy and Safety in 43 surgeries

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Aims

The surgical sub-studies of the Affinity program investigate the safety and efficacy of rVIII-SingleChain to control surgical haemostasis in children and adults with severe Haemophilia A.

Methods

Surgery was defined as a procedure requiring general, spinal or regional anaesthesia. Dosing of rVIII-SingleChain was based on the type of surgery, guided by the WFH recommendations. rVIII-SingleChain was administered as a bolus or a continuous infusion. The investigator rated haemostatic efficacy using a 4 point rating scale (poor/none; moderate; good; excellent); treatment success was defined as a rating of excellent or good.

Results

43 surgeries were performed on 32 patients aged between 5 and 64y (median, 32). 22 surgeries were orthopaedic while 21 surgeries were non-orthopaedic. 17 surgeries were related to haemophilia or its complications, and 1 surgery (appendectomy) was an emergency. Overall, rVIII-SingleChain was used as a bolus dose in 35 surgeries, and as a continuous infusion in 8 surgeries. No related AEs or SAEs were observed during the perioperative period. Haemostatic efficacy was rated as excellent and good in 38 (88%) and 5 (12%) surgeries respectively. Of the orthopaedic surgeries, 18 (82%) were rated as excellent, and 4 (18%) were rated as good.

Conclusions

rVIII-SingleChain, dosed by bolus or continuous infusion, was well-tolerated and effective in achieving surgical and perioperative haemostasis, with an overall treatment success of 100%.

This research was supported by CSL Behring, King of Prussia, United States. The company was responsible for data analysis and abstract preparation.

P268. Investigating age appropriate coagulation reference ranges to support patient blood management in the elderly – A pilot study.

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Aim

Reference ranges (RR) are vital for interpreting coagulation results. Current adult RR ranges have no upper age limit, even though there is evidence that coagulation function changes in older adults. The aim of this study is to compare coagulation results from a cohort of healthy older people against the current adult reference ranges for routine clotting assays and thromboelastography (TEG), to determine if the current RR are relevant to older adults or if age-specific RR are required.

Method

Blood donors aged 60yr or older were identified as representative of a healthy older population. Following ethics approval and consent, blood samples were collected from blood donors aged 60 years or older (n=30 male, n=30 female) at a single blood collection centre. Samples were tested by TEG, prothrombin time (PT), activated partial thromboplastin time (APTT) and derived fibrinogen. Statistical analysis included comparing results from the healthy older donor to adult reference ranges, using the GraphPad Prism statistical package.

Result

The mean age \pm SD of the healthy donors was 66.1 \pm 3.7 years (male 66.3 \pm 3.91; female 65.9 \pm 3.46). All PT results were within the adult RR. The majority of APTT results were in the lower half of the adult RR, and four (6.7%) were below the adult RR. All older donor derived fibrinogen results were within the adult RR however, levels were significantly higher in females ($P < 0.05$). From the TEG results, 11 (18.3%) CK-K and 14 (23.3%) CKH-K results were above the manufacturers RR.

Conclusion

Results from this pilot study show that healthy older donors tend to have lower APTT and some do not fit current TEG RR. A larger study is required to confirm if age appropriate APTT and TEG RR are required to support patient blood management of older Australians.

P269. Control of platelet function by post-translational modifications of integrin alpha 2b beta 3

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Aim

Integrin alpha 2b beta 3 (a2bb3) is the most abundant platelet receptor and plays a central role in haemostasis. Post-translational modifications are enzymatic modifications of proteins, such as glycosylation, which regulate many of their functions. We are interested in the post-translational modifications of disulphide bonds, including reduction and nitrosylation, within a2bb3 and their effect on platelet function. Modifications of disulphide bonds can be introduced by circulating thiol enzymes such as endoplasmic reticulum protein 5 (ERp5) and protein disulphide isomerase (PDI).

Method

The modifications of a2bb3 disulphides were studied by incubation of purified a2bb3 with thiol enzymes, followed by labelling with cysteine alkylators (maleimide and iodoacetamide). Platelet a2bb3 was purified from platelets of healthy donors and the disulphide modifications were detected by Western blot and mass spectrometry. The effect of disulphide modifications on platelet adhesion were measured by perfusing human platelets on biochips coated with fibrinogen or von Willebrand factor (vWF) in a microfluidics device.

Statistics

The amount of the reduced or S-nitrosylated form of a2bb3 disulphide and platelet adhesion, with or without treatment with thiol enzymes, were compared using the non-parametric T test.

Results

A specific disulphide, C177-C184, was found to be reduced in 10% of resting platelets. ERp5 increased the reduction of this disulphide to 30 % ($p < 0.05$). ERp5 and PDI induced denitrosylation of a2bb3 disulphides. In the microfluidics perfusion system, ERp5 caused a 3-fold reduction of platelet adhesion to fibrinogen (shear 1000 s^{-1} , $p < 0.005$) and a 15-fold increase of adhesion to vWF (shear 2000 s^{-1} , $p < 0.005$).

Conclusion

Our findings show that post translational modifications of a2bb3 disulphide bonds regulate platelet adhesion to fibrinogen and von Willebrand factor. This has important implications for informing the development of drugs targeting disulphide bonds in a2bb3 as antithrombotics.

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P270. Hospital acquired venothromboembolism and adherence to VTE prophylaxis policies: a loco-regional study

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Aim

To retrospectively determine the adherence to 2014 the Clinical Excellence Commission (CEC) hospital acquired VTE (HAT) prevention program in patients who developed HAT and the demographic information of patients with HAT using the CEC VTE prevention tool.

Methods

Patients with hospital-acquired venous thromboembolism (HAT) in Hunter New England Local Health District between January 2015 and August 2017 were identified and subsequently analysed in relation of VTE to age, gender, facility, division admitted under, duration of admission, duration between admission and VTE event, weight, pregnancy status, outcome, a determination of preventability of event, whether mortality (where it occurred) was related to VTE, and if VTE prophylaxis was used, and if this was appropriate. The appropriateness of VTE prophylaxis was determined using the CEC VTE risk assessment tool.

Results

The average age of patients with HAT was 66.7 years and occurred on average 12.2 +/- 2.9 days after admission, with a mortality rate of 10.1% (11/109), with 1.8% related to HAT.

Documentation of VTE assessment only occurred in 58.7% of the study population. Prophylaxis was prescribed in 56.9%. In those with HAT no prophylaxis was prescribed the majority at 80.9% did not a VTE assessment performed. Of the 71.6% (78/109) of patients who met guidelines for prophylaxis 23.1% (18/78) did not receive it.

Discussion and Conclusions

In this locoregional study of HAT there were a large proportion of patients who did not have VTE assessed and also those who were high risk for VTE and did not receive anticoagulation. This study identifies a gap in the implementation of VTE prophylaxis, and there is a need to improve VTE assessment and education, to improve patient outcomes. Electronic prescribing with computerised risk assessment linked to recommendations for prophylaxis and that continue to alert the users until a VTE assessment is performed may improve the rate of VTE assessment, as it has done in other centres. (1)

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P271. Comparison of Latest Viscoelastic Coagulation Assays in a Perioperative Setting

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Introduction

Point of care viscoelastic measures, namely TEG® and ROTEM®, are superseding laboratory assessments in the perioperative assessment and management of coagulation. The latest iterations of these devices have evolved to improve ease of use and are now cartridge based. The two cartridge-based systems have not been directly compared in the perioperative period.

Materials and Methods

Patients undergoing transcatheter aortic valve implantation were prospectively recruited. Samples (n=40) were obtained at four timepoints (post induction of anaesthesia, following 100 IU/kg heparin, post 1mg protamine / 100 IU heparin and 6h postoperatively). Each sample was concurrently assessed for standard laboratory tests (PT/INR, aPTT, thrombin clotting time, platelet count and direct fibrinogen), ROTEM[®] *Sigma* (Tem Innovations GmbH, Germany) and TEG6s[®] (Haemonetics Corporation, Switzerland).

Results

TEG6s required significantly less blood per test compared with ROTEM (300uL vs. 1.8mL). Conversely, TEG6s is an open system and required pipetting by the operator where as ROTEM is entirely closed. For extrinsically activated coagulation assays, clot strength measured by both correlated very poorly with PT but strongly with one another (R=0.7; TEG bias of 4mm \pm 0.1). Strong correlation with aPTT was evident for both clotting time and clot strength for the intrinsically activated coagulation assays measured with ROTEM (R=0.7 for both) and TEG (R=0.8 and R=0.5) and between methods (R=0.7 and R=0.9). Heparin was accounted for by the heparinase channel of ROTEM but not TEG where only 2/10 samples normalised.

Conclusions

The heparin effect was more consistently quantified by ROTEM. Strong correlation was observed between the two methods for most measures. Bias indicates that the results are not interchangeable.

P272. Drug-specific anti-Xa levels in obese patients taking rivaroxaban or apixaban

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Introduction and Aims

Three direct-acting oral anticoagulants (DOACs), including the inhibitors of activated factor X rivaroxaban and apixaban, are now approved in Australia for treatment of venous thromboembolism (VTE) or prevention of ischaemic stroke in patients with non-valvular atrial fibrillation (AF). Guidelines from the International Society on Thrombosis and Haemostasis recommend against the use of DOACs in obese patients with a body mass index (BMI) >40 kg/m² or a weight >120 kg due to limited efficacy data in this group.¹ We aimed to determine the prevalence of drug-specific anti-Xa levels suggesting inadequate anticoagulation in obese patients at our centre.

Methods

Drug-specific anti-Xa peak and trough levels were measured on 25 patients on either rivaroxaban (20 mg daily) or apixaban (5 mg twice daily) with a weight of >120 kg or BMI >40 kg/m². Peak levels below the published "on-therapy range" and trough levels of <25 ng/mL (lower limit of reliable levels in our laboratory) were considered as potentially reflecting inadequate anticoagulation.

Results

15 of the 26 patients were on rivaroxaban and 11 were on apixaban. Of those on rivaroxaban 7 were being treated for VTE and 8 for AF. Four of the 15 patients had a trough level of <25 ng/mL (lowest reported level in our laboratory) and 5 patients had peak levels below the published "on-therapy range". Of the 11 patients on apixaban 4 were being treated for VTE and 7 for AF. No patients had a level of <25 ng/mL and 3 patients had peak levels below the published "on-therapy range".

Conclusion

Our study shows that at least 25% of obese patients treated with rivaroxaban or apixaban had either a trough level below the lowest measurable level in our laboratory or a peak level below the published "on-therapy range" suggesting that these patients may be inadequately anticoagulated when treated with a fixed-dose DOAC.

References:

Martin et al. Use of the direct oral anticoagulants in obese patients: guidance from the SCC of the ISTH. *Journal of Thrombosis and Haemostasis* 16; 14: 1308-1313.

P273. Detection of Anthocyanins Effects to Alleviating Thrombotic Risk in Diabetes

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Background

Platelet hyperactivity has a significant role in initiating vascular thrombosis and subsequent cardiovascular disease (CVD). Several studies demonstrate resistance to currently used antiplatelet therapies such as aspirin (AS), especially in diabetes. The antioxidant activity of polyphenolic compounds including anthocyanin (AC) has been shown to reduce platelet activity and reduce CVD morbidity .

Aim

compare the antiplatelet effect of pure AC compounds in patients with type 2 diabetes mellitus.

Methods

Healthy human subject and patients with diabetes mellitus type 2 (n=50) were recruited in this study and divided into two groups. Each participant consumed 320 mg of AC/day in the form of capsules for 28 days. Fasting blood samples were collected at baseline (before) and after the treatment period. Flow cytometry was used to assess platelet activation by measuring platelet surface marker expression of CD41a and P-selectin. Platelet aggregation studies were performed by stimulating platelets with ADP, collagen or arachidonic acid. Full automated haematology analyser was used to obtain haematological indices. Biochemical autoanalyser was run to detect lipid profile, glucose, uric acid, and high sensitivity CRP.

Results

Flow cytometric analysis showed a suppressive effect of AC on the expression of P-selectin in both healthy and diabetes. There were reductions of ADP and collagen-stimulated platelet aggregation in both case and control groups. There were trends of lowering impact of AC on total cholesterol, glucose and triglycerides, but they were not significant.

Conclusion

The results show that AC may reduce platelet aggregation and activation as demonstrated by inhibition of ADP-stimulated platelet aggregation and P-selectin expression. These results provide greater insight into the effect of AC and the possible mechanism by which AC can reduce platelet function. Hence, AC may act as a complement to other anti-platelet agents to reduce the occurrence of thrombotic events.

P274. Nephrotic syndrome: an unexpected complication of haemophilia A

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Background

Haemophilia A is an X-linked bleeding disorder which has classic complications including haemophilic arthropathy, infections transmitted by plasma-derived factor concentrates and development of inhibitors. A wide range of renal diseases are associated with haemophilia; their pathogenesis being related to chronic viral infections, medication toxicity and age-related comorbidities e.g. diabetes and hypertension which are increasing as life expectancy improves for these patients.

Case Presentation

A 51-year old man with severe haemophilia A (Factor VIII <1%) presented with oedema, marked hypoalbuminaemia (10g/L), nephrotic range proteinuria (16g/24hrs) and deteriorating renal function (creatinine 124umol/L). Complications of haemophilia included arthropathy with severe kyphoscoliosis and paraspinal pseudotumour, epilepsy following intracranial haemorrhage and treated hepatitis C (HCV) with well controlled type II diabetes and obesity as notable comorbidities. Investigations revealed bland urinary sediment, cryoglobulinaemia (cryocrit 1%), normal complement, IgA lambda paraprotein <1g/L, ANA 1:80, negative ENA, ANCA, dsDNA and PLA-2-R antibodies. HCV antibodies were positive with HCV-PCR repeatedly negative since sofosbuvir/lepipasvir treatment for HCV genotype-1a infection 12 months prior. Differential diagnoses included membranous nephropathy and membranoproliferative glomerulonephritis however renal biopsy was not undertaken because anatomic and positioning issues prevented safe access despite detailed radiological assessment and bleeding risk outweighed the benefit of tissue diagnosis. Oedema improved with diuretics and urgent treatment with pulse methylprednisolone and rituximab was commenced, resulting in modest improvement in proteinuria (10g/24hrs) after 4 weeks.

Discussion

While rare cases of cryoglobulinaemia after HCV clearance have been described this is the first report of proteinuric kidney disease with HCV-associated cryoglobulinaemia in a haemophilic patient occurring after sustained virologic response to direct acting antiviral agents. This case features a rare complication of haemophilia and highlights the need for a rational approach to diagnosis for patients with bleeding disorders in whom invasive tests may not be possible

P275. The challenge of refractory ITP in pregnancy

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Background

Idiopathic thrombocytopenic purpura (ITP) is common in young women and presents a challenge in pregnancy where many treatment options are contraindicated or unstudied. While observational studies report good outcomes even with severe thrombocytopenia, the potential remains for maternal and foetal morbidity and mortality and consideration must be given to delivery method, anaesthetic choices and care of the neonate.

Case Presentation

A 20-year old woman became pregnant whilst receiving romiplostim for severe refractory ITP which had been minimally responsive to high dose corticosteroids and intravenous immunoglobulin (IVIg) since initial diagnosis 13 months earlier with severe thrombocytopenia (platelet count $10 \times 10^9/L$) during delivery of her first child. Platelet counts $<20 \times 10^9/L$ were associated with bruising and mucocutaneous bleeding; romiplostim was ceased and rescue therapy with dexamethasone and IVIg 2g/kg was commenced with mild and transient effect. Despite regular prednisolone and increased frequency of IVIg administration severe thrombocytopenia (platelet counts $<10 \times 10^9/L$) persisted and azathioprine was introduced at 13 weeks' gestation with moderate effect (platelet count $20-30 \times 10^9/L$) after 6 weeks. Morphology scan at 19 weeks' gestation did not reveal any foetal abnormality. We hope the azathioprine response will be maintained however management during the remainder of pregnancy will require collaboration between haematology and obstetric services and may include additional immunosuppressive therapy e.g. rituximab, vaginal delivery, haemostatic support if required and monitoring of the neonate for thrombocytopenia and bleeding complications.

Discussion

Treatment of ITP in pregnancy is difficult as many therapies are contraindicated or unstudied in pregnancy. In the absence of high-quality data guidance must be taken from case reports and expert opinions. This description of pregnancy without major complications despite prolonged severe thrombocytopenia and exposure to potential teratogens will add to the collective knowledge base to support clinicians treating ITP in pregnancy.

P276. Too much of a good thing: two cases of DIC-like coagulopathy in patients with decompensated cirrhosis after administration of Prothrombinex-VF®

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Background

Cirrhotic coagulopathy is a common management dilemma, with ongoing debate regarding the clinical use of prothrombin complex concentrates (PCC), including Prothrombinex VF.

Clinical Cases

We present two patients with advanced cirrhosis who were administered Prothrombinex VF. A 50-year-old male presented with decompensated Child Pugh C cirrhosis (CP-C) (MELD-Na 25). Coagulation profile on admission was INR 2.2, PT 26s, APTT 49s and fibrinogen 1.0 g/L. Prothrombinex VF 4000IU and vitamin K were administered prior to paracentesis.

A 52-year-old male with decompensated CP-C cirrhosis (MELD-Na 29), presented with per rectal bleeding. Coagulation profile on admission was: INR 2.8, PT 31s, APTT 72s. He was administered 3500 units of Prothrombinex-VF, IV Vitamin K, 8 units of cryoprecipitate, ceftriaxone, pantoprazole, and octreotide infusion. Urgent endoscopy and colonoscopy revealed haemorrhoidal bleeding.

Within 24 hours of Prothrombinex-VF administration both patients developed marked atraumatic bruising and bleeding from venous punctures. In both cases, coagulation profiles were consistent with a DIC-like coagulopathy (INR >10, PT >100s, APTT >200s, fibrinogen <0.4g/L). FFP and cryoprecipitate resulted in significant improvement within 24 hours. The only recognised trigger in both cases was Prothrombinex-VF administration.

Discussion

Prothrombinex-VF contains factors II, IX, X and small amounts of VII. In comparison, FFP contains prothrombotic and antithrombotic factors. As cirrhotic bleeds are driven by portal pressure, PCCs are appealing due lower required volumes. In advanced cirrhosis a condition of accelerated intravascular fibrinolysis and coagulation can occur. In cases such as those presented, unbalanced addition of prothrombotic factors can disrupt 'rebalanced' haemostasis and trigger a severe DIC-like consumptive coagulopathy. This phenomenon has been documented in severe liver disease with similar international PCC products, but not previously with Prothrombinex-VF.

Prothrombinex-VF is being administered to patients with cirrhotic coagulopathy in clinical practice and we would advise caution. If factor replacement is genuinely indicated, FFP represents the safer option.

P277. Evaluation of local platelet transmission electron microscopy (PTEM) reporting practices and implications for diagnosis of platelet storage pool disorders (PSPD)

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Aim

PTEM is considered the gold standard for test diagnosis of inherited platelet disorders. This study aims to evaluate the correlation between mean dense granule count (DGC) and percentage of platelets with zero DGC (%DGC₀) (RR \leq 10%) to determine whether reporting this additional variable may lead to clarification of indeterminate results, particularly with mean DGCs of 3-3.99 (RR 4-8).

Method

Retrospective data review of 103 testing episodes performed in a Queensland laboratory between 2016-2018 was performed. Following exclusion of activated or clotted samples, the data of 75 patients with a documented bleeding phenotype was analysed in Microsoft excel by regression analysis and Student's T Test with an adjusted significance level of 0.0083.

Result

In 75 patients, the DGC distribution of each sample was left-skewed with a median %DGC₀ of 16% (range 3-44) and mean DGC of 2.6 (range 0.8-4.52). In 34 patients diagnosed with a PSPD the mean DGC was 1.92 and 97% (n = 33) of patients had a %DGC₀ \geq 10% (mean 23.3%). Both this group and the total cohort showed poor correlation between % normal compared to %DGC₀, $r^2=0.49$ and $r^2=0.56$, respectively. The %DGC₀ was significantly higher in those with mean DGC 2-3 (16.11%) compared with those of 3-3.99 (9.9%) and \geq 4 (6.6%), $p = 0.000015$ and $p = 0.000019$, respectively. There was no statistical difference between %DGC₀ between mean DGC range of 3-3.99 and \geq 4 $p = 0.05$.

Conclusion

Patients with a mean DGC between 2-3 have a significantly higher %DGC₀ than those with mean DGC \geq 3 when the reference range of \leq 10% is applied. As such, reporting of this value may lead to improved stratification of indeterminate PTEM results.

P278. Combined haemodialysis and multiple idarucizumab doses are required for dabigatran reversal in severe acute kidney injury and bleeding

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Background

Dabigatran can be reversed with a single dose of idarucizumab in patients with normal renal function. We present a case of acute kidney injury with dabigatran toxicity requiring three doses of idarucizumab and daily haemodialysis.

Case Report

A 71-year-old man presented with acute gastrointestinal bleeding (haemoglobin 78g/L) and non-oliguric acute kidney injury (creatinine 1414umol/L) 6 weeks after a stroke and commencement of dabigatran (when he had normal renal function). Renal tract imaging, vasculitis and autoimmune screens were normal. His INR was 8.7 (initial APTT not available). Dabigatran was ceased and idarucizumab administered. Post-dose rebound coagulopathy occurred (APTT 89.7) indicating a further idarucizumab dose. Immediately following this dose a temporary dialysis line was inserted and the patient was commenced on increasingly efficient daily haemodialysis, at which time the dabigatran level was undetectably high. At 72 hours the patient was haemodynamically unstable with haemoglobin 64g/L and had rebound in coagulopathy (APTT 45), indicating a third dose of idarucizumab. We observed significant rebound in dabigatran and APTT both following the administration of idarucizumab and haemodialysis. The dabigatran level gradually declined to non detectable over 14 days of daily haemodialysis, when a renal biopsy revealed severe acute interstitial nephritis. Detailed medication history failed to identify a known causative agent. The patient was commenced on 60mg prednisolone daily and haemodialysis was withdrawn 6 weeks later following renal recovery.

Conclusion

This is the first report of biopsy proven dabigatran associated acute interstitial nephritis and also the first report of dabigatran toxicity requiring three doses of idarucizumab. Importantly, the three doses were not sufficient to reverse dabigatran and efficient daily hemodialysis was required to achieve complete dabigatran clearance. Multiple or higher doses of idarucizumab should be considered in patients with rebound coagulopathy.

P279. Isolation of patient-derived anti- β_2 GP1 antibodies using an NHS-activated column

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Aim

Anti- β_2 GP1 antibodies are strongly associated with increased risk of thrombosis and pregnancy complications. Although purified patient-derived anti- β_2 GP1 antibodies have been used to investigate their pathophysiological role, the efficacy and efficiency of antibody purification using N-hydroxysuccinimide (NHS) activated sepharose (or similar) columns have not been reported. Antibody purification can be challenging as β_2 GP1 adopts interchangeable J-shaped (active) and circular-shaped (inactive) conformations. We assessed the purification of patient-derived anti- β_2 GP1 using β_2 GP1-coupled NHS columns.

Method

Platelet poor plasma, containing anti- β_2 GP1 antibodies ($n=11$, confirmed by anti- β_2 GP1 immunoassay), were collected from patients with systemic lupus erythematosus and antiphospholipid syndrome. Plasma samples were applied to a Protein G column to isolate IgG fractions. IgG fractions were desalted, then applied to two in-house β_2 GP1-coupled NHS columns to purify anti- β_2 GP1 antibodies. Each β_2 GP1-coupled columns contained different commercially-available human β_2 GP1, coded as either H- β_2 GP1 (178 μ g/ml) or R- β_2 GP1 (680 μ g/mL). Eluted anti- β_2 GP1 antibodies were confirmed using immunoassay and gel electrophoresis.

Result

IgG fractions from three patients were purified using the H- β_2 GP1-coupled column, and from eight patients using the R- β_2 GP1-coupled column. Anti- β_2 GP1 antibodies were successfully isolated from one of the 11 samples using the R- β_2 GP1-coupled column. An immunoassay confirmed purification of anti- β_2 GP1 antibodies (42 units/mL). A single 50 kDa band on gel indicated IgG antibody fragment, rather than whole IgG (150 kDa), was isolated from the sample.

Conclusion

A relatively low concentration of β_2 GP1 (680 μ g/mL) was sufficient to purify anti- β_2 GP1 antibodies from one IgG sample. We speculate that conformation of β_2 GP1, rather than concentration, affected purification of anti- β_2 GP1, in that β_2 GP1 coupled to the NHS-activated column in the circular conformation may fail to purify anti- β_2 GP1 antibodies. Further, possible degradation of IgG may also affect purification of anti- β_2 GP1. The interaction of different conformations of β_2 GP1 with NHS-activated sepharose requires further investigation to assist with purification of anti- β_2 GP1.

P280. Where's Wally the antibody? Detection of IgG on platelets using immunocytochemistry

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Introduction

Platelets interact and possibly internalise IgG via FcγRIIIa receptors into α-granules. It is unclear how platelets react with IgG following activation. We investigated the effects of incubation time and platelet activation on the interaction between platelets and IgG using immunocytochemistry.

Method

Platelet rich plasma (PRP) was washed and incubated with 150 µg/mL healthy human-derived IgG (5, 10, 30 minutes) without activation (study 1). PRP was also incubated with IgG (150, 200, 300, 350 µg/mL) for 60 minutes without activation (study 2). Furthermore, a separate set of IgG-spiked PRP was activated with collagen after 10 minutes incubation. Platelets from both studies were collected by centrifugation, then mixed with Histogel to create cell blocks. Cell blocks were formalin-fixed, processed, embedded and cut (3 µm sections) onto superfrost-plus slides. Human IgG was detected with primary polyclonal rabbit anti-human-IgG and Dako Real Envision detection system. Sections were photographed and analysed with ImageJ-immunohistochemistry profiler software. The staining intensity data were statistically analysed using mixed effects linear modelling adjusted for repeated measures.

Results

Platelet clumps were densely stained near the surface of clumps, while individual platelets were completely stained in both studies. In study 1, washed platelets without additional IgG demonstrated the weakest positive staining. The staining intensity was higher with 30 minutes incubation compared to other times ($p < 0.05$), indicating more IgG attached to platelets. In study 2, activated platelets had stronger staining compared to non-activated platelets ($p < 0.05$), irrespective of IgG concentration.

Conclusion

Increased incubation time and activation of platelets appears to facilitate the binding of IgG to platelets. We speculate that IgG interacts with platelets following, but not during, platelet aggregation causing denser surface staining of platelet clumps. These techniques may be used to further investigate the interaction of pathogenic anti-platelet antibodies with platelets.

P281. MOHITO: A cocktail for quality improvement in heparin administration

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Introduction

There are 2 heparin infusion protocols used in the Western Sydney Local Health District for the management of acute coronary syndromes and venous thromboembolism. In NSW heparin was the 10th most common medication involved in a 2015 incident report. Addressing the management of heparin was recognised by the Clinical Excellence Commission's Anticoagulant Medicines Working Party as a priority for 2017.

Aim

The MOHITO (Management to Optimise Heparin Infusion Therapy Out west) study is a quality improvement project which aims to achieve 95% adherence to the Western Sydney Local Health District intravenous heparin therapy prescribing, monitoring and administration guidelines.

Method

The project utilises the plan, do, study, act model of clinical quality improvement. We have conducted an audit of 20 cardiology patients (most frequent user) who were prescribed intravenous heparin. Parameters included performance of baseline coagulation studies, documentation of the selected protocol and dose adjustments, number of therapeutic aPTT measurements, and the incidence of adverse events. In parallel with this audit we will conduct surveys to assess staff knowledge and use these data to tailor quality improvement measures such as structured education, increased senior clinician and pharmaceutical input, and the development of a heparin prescription form.

Results

The following errors were identified:

Error	% of cases
Baseline coagulation studies not performed	35
Indication for heparin not documented	90
Choice of protocol not specified	65
Dose adjustments not documented	5
Timing of adjustments not documented	40
Dose adjustments not adherent to protocol	10

Overall 50% of aPTT measurements were out of therapeutic range. 15% of patients had bleeding events with additional risk factors present in all cases (dual antiplatelets, abnormal liver function, recent surgery).

Conclusion

These data demonstrate poor adherence to the heparin protocol thereby increasing risks of adverse events. We propose to repeat this audit post implementation of improvement strategies to assess their impact.

P282. Low flow dynamics in extracorporeal membrane oxygenation significantly altered von Willebrand Factor function and conformation ex-vivo

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Aim

Bleeding remains one of the major risks of extracorporeal membrane oxygenation (ECMO) in patients with refractory cardiopulmonary failure. Changes in vWF function/conformation, due to susceptibility to shear stress, have been suggested to play a role in severe bleeding complications. We used an *ex-vivo* ECMO circuit to investigate the relationship between ECMO flow dynamics and vWF conformation/function.

Method

Heparinised human whole blood was circulated under standard physiological conditions for 6 hours (h) at two flow dynamics: ^Hhigh flow at 4Lmin⁻¹ (n=4), as during adult ECMO; ^Llow flow at 1.5Lmin⁻¹ (n=4), as during weaning. Blood samples were collected at baseline, 1, 2, 4 and 6 hours for ristocetin-induced platelet aggregation (RIPA), vWF multimer immunoblotting and haemolysis. Flow cytometry was used to examine the vWF binding platelet receptor, GPIb. Statistical analysis was carried out using ANOVA.

Result

No significant differences in changes of RIPA was observed between high and low flow. However, when compared to matched baseline, RIPA was significantly decreased at 6h in low flow setting ($p=0.0207$), which was absent in high flow. Interestingly, degradation in vWF conformation was only observed during low flow with significant reduction in molecular weight over time (^H33% vs ^L90% high molecular weight remaining). The free haemoglobin concentration was also higher following exposure to low flow (average 142.3mg/dL) compared to high flow ECMO (average 63.8mg/dL) at endpoint. While both flow dynamics had shown some activation of platelets with an increased percentage of GPIb^{moderate/weak} platelets overtime (^H $p=0.0286$; ^L $p=0.0127$), its surface antigen density was more profoundly reduced following low flow ($p=0.0397$) at 6h.

Conclusion

Our *ex-vivo* study suggests that trauma-mediated by low ECMO flow may be much greater than high flow. We hypothesised that the duration of blood-ECMO circuit contact may have a larger role in the reported bleeding and thrombotic complications in patients. However, further studies are required.

P283. Evaluation of global coagulation assays in patients with haematological malignancies

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Aim: To evaluate the utility of global coagulation assays (GCA) in assessing the clotting profiles of patients with haematological malignancies in comparison to normal controls

Method: Blood samples from patients were sent for routine laboratory tests and GCA testing. The GCA examined were (i) thromboelastography using TEG®, (ii) thrombin generation via calibrated automated thrombogram (CAT) and (iii) fibrin generation via the overall haemostatic potential (OHP) assay. Citrated whole blood was used for TEG® whilst platelet poor plasma was used for CAT and OHP. Results from these studies were then compared to previously collected normal controls (n=96).

Results: Thirty-two patients with median age 69.5 years were recruited. This included patients with multiple myeloma (n=15), acute myeloid leukaemia (n=3), chronic myelomonocytic leukaemia (n=1), myelodysplasia (n=3), chronic lymphocytic leukaemia (n=1), Hodgkin's lymphoma (n=1) and non-Hodgkin's lymphoma (n=8). Twenty (64.5%) of these patients were undergoing chemotherapy. Only two study patients showed prolonged APTT and/or PT. Compared to normal controls, the study group demonstrated significantly higher factor VIII, von Willebrand factor antigen, von Willebrand factor activity and D-Dimer levels (p<0.001). Study patients also showed hypercoagulable TEG® results with increased maximum amplitude (65.3mm vs 57.9mm, p<0.001) and reduced clot lysis (0.0% vs 0.6%, p<0.001). Thrombin generation parameters including peak thrombin and velocity index were significantly increased despite comparable endogenous thrombin potential. Fibrin generation parameters were also increased in our study patients (p<0.05) with preserved overall fibrinolytic potential. On sub-analysis, there were no differences between patients with MM and other haematological malignancies.

Conclusion: GCA appear more sensitive than conventional coagulation testing in profiling the haemostatic picture of patients with haematological malignancies. Thromboelastography, in particular, demonstrated a hypercoagulable state in our study patients alongside increased peak thrombin and fibrin generation. Future studies will be required to correlate these findings with the clinical risk of thrombosis.

Table 1: Comparison of investigation results between patients with haematological malignancies and normal controls

	Normal Controls (n = 96)	Patients Haematological Malignancies (n = 32)	with	p-value
Factor VIII (%)	101.0	185.0		<0.001
von Willebrand antigen (%)	102.0	194.0		<0.001
von Willebrand activity (%)	102.0	178.0		<0.001
D-dimer (ng/mL)	190.0	1155.0		<0.001
Thromboelastography				
R-time (min)	6.9	5.5		<0.001
a-angle (°)	58.0	59.7		0.390
Maximum amplitude (mm)	57.9	65.3		<0.001
Lysis 30 (%)	0.6	0.0		<0.001
Calibrated automated thrombogram				
Lag time (min)	3.1	3.5		0.096
Velocity index (nM/min)	65.0	92.0		0.022
Endogenous thrombin potential (nM.min)	1347.6	1369.2		0.458
Thrombin peak (nM)	222.6	263.1		0.008
Overall haemostatic potential assay				
Overall coagulation potential (%)	59.7	65.6		0.022
Overall haemostatic potential (%)	27.5	30.9		0.018
Overall fibrinolytic potential (%)	52.2	49.0		0.294

P284. Assessing renal function in patients receiving DOACs: Cockcroft-Gault versus estimated glomerular filtration rate

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Aim

In patients who are treated with a direct oral anticoagulant (DOAC), renal impairment may lead to impaired DOAC excretion and an increased risk of bleeding. Renal function was estimated by creatinine clearance (eCrCl) in the phase 3 trials which compared a DOAC to warfarin, however in routine practice, renal function is automatically provided on laboratory reports as estimated glomerular filtration rate (eGFR). The results of the different methods may not be interchangeable and may lead to DOAC prescribing that is inconsistent with prescribing guidelines. We compared results of eCrCl and eGFR to determine the impact on DOAC prescribing.

Method

Consecutive patients from the Hamilton General Hospital (Canada) who were treated with a DOAC for stroke prevention in atrial fibrillation, were studied. Results were calculated for eCrCl using the Cockcroft-Gault formula, and eGFR using the Modification of Diet in Renal Disease [MDRD] and Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formulae.

Results

185 patients were studied, mean age 76 years (range, 25 to 98), 85 (46%) female, serum creatinine range 49 to 310 $\mu\text{mol/L}$. Patients were treated with apixaban (88, 49%), rivaroxaban (49, 26%), or dabigatran (48, 25%). In patients with eCrCl ≤ 70 mL/min, the eGFR by both MDRD and CKD-EPI consistently produced higher results than eCrCl. In patients with eCrCl > 70 mL/min, eGFR results by MDRD and CKD-EPI tended to be lower than eCrCl. At least 46% of patients would have received DOAC treatment inconsistent with prescribing guidelines if renal function was determined using eGFR instead of eCrCl.

Conclusion

The difference in results between the eCrCl and eGFR can substantially impact DOAC dosing. For apixaban, rivaroxaban and dabigatran dosing, it is reasonable to use eGFR when the eGFR is ≥ 70 mL/min/1.73m². However, when the eGFR is ≤ 70 mL/min/1.73m², the eCrCl should be manually calculated to determine the appropriate dose of DOAC.

P285. Incidence of residual perfusion defects by lung scintigraphy in patients treated with rivaroxaban compared with warfarin for acute pulmonary embolism

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Background: Residual defects has been detected in over 50% of patients with acute pulmonary embolism (PE) treated with vitamin K antagonists but there is lack of data in patients treated with direct oral anticoagulants.

Aim: To estimate the incidence of residual perfusion defects detected by Ventilation Perfusion (VQ) scan at 3-6 months in patients with acute PE treated with rivaroxaban compared to warfarin.

Methods

Patients with first objectively confirmed symptomatic PE treated with rivaroxaban or warfarin who had follow-up ventilation perfusion (VQ) scan after 3-6 months of anticoagulation were identified from the Monash Health radiology database between 2015-2017 and 2011-2012 for rivaroxaban or warfarin treated patients respectively. Index and follow-up VQ scans were classified as normal or abnormal based on the radiologist report. We report our preliminary data for our planned cohort of 200 patients.

Results

One hundred and fifty-seven patients were included (mean age 57.1 years; 39.5% males; 51.6% unprovoked PE). In the overall cohort 46% had residual defects with a trend to lower incidence of residual defects in rivaroxaban treated patients 40.0% (95% CI 30.7 to 50.5), compared to warfarin 54.8% (95% CI 42.5 to 66.6) (OR 0.55 95% CI 0.29 to 1.05, P = 0.068). (Table 1). These results remain unchanged with again a trend towards lower incidence of residual defects in a subgroup of 62 rivaroxaban patients 41.9% (95% CI 30.5% to 54.3%) age matched (age \pm 5 years) with warfarin treated patients 54.8% (95% CI 42.5 to 66.6) (P = 0.15).

Conclusion

Our preliminary results are encouraging and suggest that patients treated with rivaroxaban may have better resolution of PE as detected by VQ scan at 3-6 months compared to warfarin.

Characteristic	Overall study cohort n = 157	Warfarin n = 62	Rivaroxaban n =95	P value*
Mean age, years (SD)	57.1 (18.2)	57.7 (17.5)	56.7 (18.7)	0.73
Male gender, n (%)	62 (39.5)	25 (40.3)	37 (38.9)	0.86
Unprovoked PE	81 (51.6)	32 (51.6)	49 (51.6)	0.89
Mean time to baseline scan, days (SD)	144.5 (32.0)	155 (27.1)	137.6 (33.3)	<0.05
Index scan VQ scan (%)	71 (45.2)	41 (66.1)	30 (31.5)	<0.05
Index Scan CTPA (%)	86 (54.8)	21 (33.9)	65 (68.5)	<0.05
Residual perfusion defects, n (%)	72 (45.9)	34 (54.8)	38 (40.0)	0.068

* Unpaired T Test for continuous variables, chi square analysis for categorical variables

P286. Thrombophlebitis post varicose vein surgery: is anticoagulation necessary?

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Aim: Patients may report limb oedema, lump and/or pain following varicose vein surgery and present to their local general practitioners (GPs) or emergency departments (ED). In our practice, we noted that there is significant heterogeneity in the management of these patients and we aim to determine the management approach of clinicians in patients suffering from limb oedema and/or pain following varicose vein surgery.

Method: A case study of a 67 year-old man presenting with left leg oedema and pain 6 days following varicose vein surgery (left saphenofemoral junction ligation, GSV stripping and stab avulsions) with a Doppler ultrasound reported as extensive superficial thrombophlebitis throughout the course of left great saphenous vein was sent as a survey (electronic and hardcopy) to GPs, ED physicians and haematologists (including registrars). The clinicians were requested to choose from 5 possible management options (Table 1).

Results: There were 115 responses from 52 GPs (45%), 31 ED physicians (27%) and 32 haematologists (28%), with marked heterogeneity seen across the different specialties (Table 1). Interestingly, the haematologists and/or haematology registrars were more likely to recommend anticoagulation (either full or prophylactic dose) compared to their other colleagues (25/32 vs 31/83, $p < 0.001$).

Conclusion: Limited superficial thrombophlebitis in the operated vein or its tributary soon after varicose vein surgery is a common (and often expected) post-operative occurrence due to associated surgical bleeding into the space previously occupied by the vein. There is usually no role for anticoagulation unless if there is evidence of deep venous thrombosis. Our survey showed that this is not well known in the medical community, which leads to unnecessary treatment with anticoagulation (49% in our survey). Further education to raise awareness amongst clinicians is required for patient safety.

Table 1 shows the breakdown of the different management approach across the specialties

	Prophylactic anticoagulation	Full anticoagulation	No anticoagulation	Aspirin	Unsure
GP & registrars	8	8	18	3	15
ED physicians & registrars	8	7	9	3	4
Haematologists and registrars	10	15	5	2	0
Total	26 (23%)	30 (26%)	32 (28%)	8 (7%)	19 (17%)

P287. Weight-based enoxaparin dosing for venous thromboembolism (VTE) >100kg gives similar anti-Xa levels to patients <100kg, with no increase in bleeding

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Background: In trials assessing VTE management, patients with obesity are under-represented or excluded. The ISTH advises against direct-acting oral anticoagulants in patients >120kg⁽¹⁾.

Objective: To assess weight-based enoxaparin dosing in VTE, comparing patients >100kg with those <100kg. The primary outcome was anti-Xa activity, as a surrogate for bleeding and recurrence, with secondary outcome measures of major bleeding and recurrence at 30 days.

Methods: A 5-year retrospective audit of patients with acute VTE prescribed enoxaparin 1mg/kg BD, with an anti-Xa level 2-6 hours post-dose. Patients with an eGFR <30 were excluded.

Results: 166 patients weighing >100kg with acute VTE were identified, and 63 were excluded for not fulfilling all criteria. 66 patients weighing <100kg were assessed for comparison.

Characteristics, anti-Xa levels and outcomes	Group 1 >100kg (n=103)	Group 2 <100kg (n=66)	p-value
Age (years), median (range)	49 (20-79)	70 (25-87)	<0.0001
Weight (kg), median (range)	130 (105-222)	75 (44-96)	<0.0001
BMI (kg/m ²), median (range)	43 (31.2-73.7)	24.7 (17.0-38.7)	<0.0001
eGFR (mL/min) 30-59, n (%)	10/103 (9.7%)	21/66 (31.8%)	0.0004
Provoked VTE, all causes, n (%)	63/103 (61%)	60/66 (90.1%)	0.0001
by cancer, n (%)	9/63 (14.3%)	34/60 (56.7%)	0.0001
Anti-Xa level (U/mL), median (range)	0.93 (0.36-1.54)	0.87 (0.15-1.41)	0.27
Anti-Xa >1.0U/mL with eGFR 30-59 mL/min	6/10 (60%)	13/21 (61.9%)	0.99
with eGFR >60 mL/min	36/93 (38.7%)	16/45 (35.6%)	0.85
Follow-up data (30d)	97/103 (94.0%)	59/66 (86.4%)	0.38
Major bleeding (30d)	0/97 (0%)	6/59 (10.2%)	0.0025
VTE extension / recurrence (30d)	0/97 (0%)	2/59 (3.4%)	0.0032

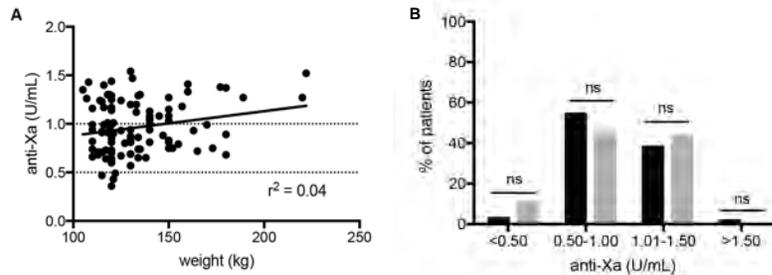


Figure 1. Anti-Xa levels were poorly predicted by weight (A). The distribution of anti-Xa levels in the obese patients was not statistically different to that in patients weighing <100kg (B), >100kg black, <100kg grey.

Discussion: Patients above and below 100kg dosed with 1mg/kg enoxaparin BD showed no significant difference in either median or distribution of anti-Xa activity. Regardless of weight, the majority of patients with an eGFR of 30-59 mL/min had anti-Xa levels >1.0U/mL. The obese patients did not suffer any major bleeding or VTE recurrence within 30 days. In comparison, the patients weighing <100kg, despite similar levels of anticoagulation, had higher rates of bleeding and recurrence. This was likely due to their older age and comorbidities, particularly renal impairment and cancer. These findings are consistent with the observation that bleeding risk is primarily determined by clinical characteristics rather than the anti-Xa activity alone.

Conclusion: These data support a weight-based dosing strategy for enoxaparin in obese patients with VTE, with no dose-capping, to ensure therapeutic drug levels. Routine anti-Xa levels in patients >100kg, particularly in those with moderate renal impairment, allow tailoring of doses to the therapeutic anti-Xa range.

P288. Anticoagulation in the Obese – A Multi-Centre Retrospective Audit with Clinical Outcomes

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Aim: To evaluate current anticoagulant prescribing in the obese and evaluate the role of drug specific Anti-Xa levels.

Method: Patients with a BMI >35kg/m² or weight >120kg receiving anticoagulants for venous thromboembolism (VTE) were identified at 4 sites across Australia. We collected demographic data, weight, height, indication, anticoagulant choice and rationale, laboratory drug monitoring, dose adjustments and clinical progress.

Results: We identified 52 patients of which 34/52 were female. Median age was 52 (range 27-87), median weight was 127kg (range 95-208) and median BMI was 42.1kg/m² (range 35.8-65.3). Prescribed anticoagulants included: rivaroxaban (39), apixaban (20), dabigatran (1), enoxaparin (19) and warfarin (16) with some patients receiving more than one anti-coagulant consecutively. Peak or trough drug specific levels were available for patients on rivaroxaban (19), apixaban (12), dabigatran (1) and enoxaparin (16).

Table 1: DOAC Drug Levels

Anticoagulant	Dose	Median peak level (ng/ml) (range)	Median trough level (ng/ml) (range)
Rivaroxaban	20mg	196 (90-453) (n=12)	32 (13-65) (n=7)
	15mg BD	196 (105-341) (n =3)	
Apixaban	5mg BD	141 (97-283) (n = 7)	48 (12-68) (n= 5)

6/39 (15%) patients on rivaroxaban had confirmed or presumed progressive thrombotic disease. Only 1 patient was on apixaban 2.5mg BD, and they developed a recurrent pulmonary embolus. 2/16 (12.5%) patients on warfarin had progressive thrombotic disease with a therapeutic INR and no recurrent events were seen on enoxaparin. Median enoxaparin dose to achieve therapeutic Anti-Xa (0.6-1.2 U/ml) was 0.89mg/kg (range 0.67-1.03). Bleeding complications were seen in 12/52 (23%) patients.

Conclusion: The optimal anticoagulation strategy in obese patients remains unclear. The recurrent thrombotic events in this population are concerning. Our study is limited by small numbers and missing data due to its retrospective nature. A prospective multi-centre registry is underway in Australia and New Zealand.

P289. Comparing physical activity and bleed rate among subjects with severe hemophilia A/B on prophylactic treatment with rFVIII Fc/rFIX Fc versus conventional rFVIII/rFIX

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Aim

To compare real-world changes over time in physical activity (PA) participation and annualized bleeding rates (ABR) in adult subjects with severe hemophilia A/B (HA/HB) receiving prophylactic treatment with extended half-life (EHL) products, recombinant factor VIII Fc fusion protein (rFVIII Fc)/rFIX Fc, versus conventional rFVIII/rFIX.

Methods

A retrospective chart review of HA/HB adults in the US from 2014–2015 (post rFVIII Fc/rFIX Fc approval) was conducted. Eligible subjects, randomly selected from 16 participating hemophilia treatment facilities, included males aged 18–35 years with severe HA/HB, without inhibitors, receiving prophylactic treatment ≥ 6 months, and who had not participated in hemophilia-related trials during the study period. Demographic/clinical characteristics, treatment, and PA participation data were collected from annual comprehensive exam visits and compared using either chi-square test or *t* test for baseline and Wilcoxon rank-sum test for outcomes.

Results

Of 170 subjects, 96 had HA (rFVIII Fc, n=45; rFVIII, n=51) and 74 had HB (rFIX Fc, n=29; rFIX, n=45). rFVIII Fc/rFIX Fc and rFVIII/rFIX groups were similar across baseline characteristics, except HB, where the rFIX Fc group reported lower total ABR at baseline (rFIX Fc, 1.93; rFIX, 3.07; *P*=0.10). Weekly frequency and duration of PA participation increased across most groups in 2015 versus 2014. Increased PA frequency was greater in rFVIII Fc (13.5%) and rFIX Fc (13.3%) groups than rFVIII/rFIX. Increase in PA duration was 18% for both rFVIII Fc and rFIX Fc groups compared with their counterparts. The rFVIII Fc group reported greater reductions in total and spontaneous ABR versus rFVIII (24% and 41%, respectively). Despite lower baseline ABR versus rFIX, the rFIX Fc group reported greater reductions in total and spontaneous ABR versus rFIX (7% and 37%, respectively).

Conclusions

In this real-world study, subjects treated with EHL rFVIII Fc/rFIX Fc reported substantially improved PA while maintaining good bleed control versus subjects receiving conventional rFVIII/rFIX. Large, prospective studies are needed to further evaluate the role of rFVIII Fc/rFIX Fc in improving PA.

P290. Longitudinal Hemophilia Joint Health Scores and life assessment (CHO-KLAT) in children with severe hemophilia A and long-term rFVIII Fc prophylaxis

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Aim: Evaluate longitudinal change in joint health and quality of life (QOL) with recombinant factor VIII Fc fusion protein (rFVIII Fc) using third interim data cut from the ASPIRE extension study (NCT01454739) in children who completed the Kids A-LONG pivotal trial (NCT01458106).

Method: Post-hoc analysis of subjects aged <12 years with Hemophilia Joint Health Score (HJHS) at Kids A-LONG baseline, ASPIRE baseline, and ASPIRE Year 1 and Year 2. QOL was evaluated using Canadian Hemophilia Outcomes–Kids Life Assessment Tool (CHO-KLAT) scores from children and parents, and in subjects from the HJHS analysis with measurements at Kids A-LONG baseline and ASPIRE Year 2. Change from Kids A-LONG baseline to last visit was analyzed (paired *t* test). QOL effect size was determined using Cohen’s *d* (≥ 0.8 indicates large effect size).

Result: Twenty-four subjects in the HJHS analysis had mean age 6.6 ± 2.1 years at Kids A-LONG baseline. Mean initial HJHS score was 1.63 ± 3.1 . Statistically significant improvement in HJHS score from baseline to ASPIRE Year 2 was observed (Table). There were improvements regardless of target joint status at baseline or pre-study regimen. Mean (standard deviation) child- and parent-reported CHO-KLAT baseline scores were 73.9 (14.0) and 70.4 (16.7), respectively. Statistically significant changes were observed for both child- and parent-reported scores. The effect size for child CHO-KLAT scores showed improvement over time. Compared with child scores, larger effect size was observed in parent scores at ASPIRE baseline, but was similar by ASPIRE Year 2. Parent effect sizes were sustained over time.

Conclusion: Functional joint outcomes improved significantly in children treated with rFVIII Fc for up to 3 years. Child self-reported QOL improved over time, and parent proxy scores were sustained over time. The large effect size in both child- and parent-reported scores indicates improved or sustained clinically meaningful outcomes when treated with rFVIII Fc.

Change Kids A-LONG Baseline	From	ASPIRE		
		Baseline	Year 1	Year 2
HJHS, mean (SD), n=24		-1.1 (2.78)	-1.3 (2.36)	-1.2 (2.77) ^a
CHO-KLAT, n=16 ^b				
Child score, mean (SD)		5.4 (12.2)	6.2 (10.8)	11.5 (9.7) ^a
Effect size		0.44	0.57	1.19
Parent score, mean (SD)		10.4 (10.3)	10.4 (11.2)	11.9 (11.1) ^a
Effect size		1.02	0.93	1.07
CHO-KLAT, Canadian Hemophilia Outcomes–Kids Life Assessment Tool; HJHS, Hemophilia Joint Health Score; SD, standard deviation.				
^a <i>P</i> <0.05.				
^b n may not be the same across all time points.				

P291. Long-term clinical outcomes of rFIXFc prophylaxis in adults aged ≥50 years with severe hemophilia B

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Aims: Recombinant factor IX Fc fusion protein (rFIXFc) is an extended half-life therapy approved for treatment of hemophilia B. B-LONG parent (NCT01027364) and B-YOND extension (NCT01425723) Phase 3 studies evaluated rFIXFc safety and efficacy in prevention and treatment of bleeding in previously treated subjects with severe hemophilia B. We evaluated clinical outcomes for >3 years in a B-LONG/B-YOND subgroup aged ≥50 years.

Methods: Treatment groups were weekly prophylaxis (WP; 20–100 IU/kg every 7 days), individualized prophylaxis (IP; 100 IU/kg every 8–16 days), modified prophylaxis (MP; tailored dosage), and episodic treatment (ET; on-demand dosage). In B-YOND, subjects could change groups at any time and appear in ≥1 regimen. Outcomes included inhibitor development, annualized bleeding rate (ABR) for subjects with target joints/target joint resolution, hemophilia quality of life questionnaire for adults (Hem-A-QoL), cumulative exposure, and factor consumption.

Results: Twenty-six subjects (median age [range], 56 [50–71] years) in B-LONG and/or B-YOND received rFIXFc (WP, n=13; IP, n=7; MP, n=3; ET, n=8). Baseline median (interquartile range [IQR]) ABR was 1 (0–5) and 20 (12–27) for subjects receiving prophylaxis and on-demand treatments, respectively. No subjects developed inhibitors. On-treatment overall ABRs were lowest for IP and highest for ET (Table). All 19 target joints resolved with prophylaxis. Mean (standard deviation) total Hem-A-QoL score changed by –3.9 (10) points from baseline to last visit for 9 subjects always on prophylactic treatment during B-LONG/B-YOND. Median (IQR) years of treatment and cumulative exposure days with rFIXFc were 3.42 (0.98–4.31) and 90 (44.0–198), respectively. Factor consumption remained stable.

Conclusions: We demonstrate >3 years of sustained bleed control, target joint resolution, and stable factor consumption, consistent with the overall study population, suggesting rFIXFc provides long-term clinical benefits for individuals with severe hemophilia B, irrespective of age and presence of target joints.

Table. Summary of ABRs in B-LONG/B-YOND

	Individualized Prophylaxis	Weekly Prophylaxis	Episodic Treatment
	n=7	n=13	n=8
Overall ABR ^a			
Median	1.14	2.13	12.83
IQR	0.48–2.64	1.16–4.35	8.96–20.59
	n=4	n=9	n=4
Overall ABR for subjects with baseline target joint ^b			
Median	1.56	3.17	17.07
IQR	0.24–4.18	1.16–4.35	7.19–22.52
ABR, annualized bleeding rate; IQR, interquartile range.			
^a Overall ABRs in the modified prophylaxis group (n=3) were 4.28, 6.44, and 7.70.			
^b Overall ABRs for subjects with target joint at baseline in the modified prophylaxis group (n=3) were 4.28, 6.44, and 7.70.			

P292. Long-term clinical outcomes of rFVIII Fc prophylaxis in adults aged ≥50 years with severe hemophilia A

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Aims: Recombinant factor VIII Fc fusion protein (rFVIII Fc) is an extended half-life therapy approved for treatment of hemophilia A. A-LONG parent (NCT01181128) and ASPIRE extension (NCT01454739) Phase 3 studies evaluated rFVIII Fc safety and efficacy in prevention and treatment of bleeding in previously treated subjects with severe hemophilia A. We evaluated clinical outcomes in an A-LONG/ASPIRE subgroup aged ≥50 years.

Methods: Treatment groups were individualized prophylaxis (IP; 25–65 IU/kg every 3–5 days), weekly prophylaxis (WP; 65 IU/kg every 7 days), modified prophylaxis (MP; tailored dosage), and episodic treatment (ET; on-demand dosage). In ASPIRE, subjects could change groups at any time and appear in ≥1 regimen. Outcomes included inhibitor development, annualized bleeding rate (ABR) for subjects with target joints/target joint resolution, hemophilia quality of life questionnaire for adults (Hem-A-QoL), modified Hemophilia Joint Health Score (mHJHS), and cumulative exposure.

Results: Twenty-one subjects (median age [range], 57 [50–65] years) in A-LONG and/or ASPIRE received rFVIII Fc (IP, n=14; WP, n=7; MP, n=3; ET, n=3). Baseline median (interquartile range [IQR]) ABR was 13 (6–22) and 27 (19–43) for subjects receiving pre-study prophylaxis and on-demand treatments, respectively. No subjects developed inhibitors. On-treatment overall ABRs were lowest for IP and highest for ET (Table). All 49 evaluable target joints resolved with prophylactic treatment. Mean (standard deviation) change from baseline in total Hem-A-QoL score and mHJHS was –1.9 (10.9) and –9.2 (11.43), respectively, for those always on prophylactic treatment. Median (IQR) years of treatment and cumulative exposure days with rFVIII Fc were 4.05 (3.04–4.26) and 293 (227–364), respectively. Factor consumption remained stable.

Conclusions: We demonstrate approximately 4 years of sustained bleed control and target joint resolution without inhibitor development, consistent with the overall study population, suggesting rFVIII Fc provides long-term clinical benefits for individuals with severe hemophilia A, irrespective of baseline status.

Table. Summary of ABRs in A-LONG/ASPIRE

	Individualized Prophylaxis	Weekly Prophylaxis
	n=14	n=7
Overall ABR ^a		
Median	1.77	2.01
IQR	0.35–5.26	0.25–4.76
	n=11	n=5

P293. Emicizumab subcutaneous dosing every 4 weeks is safe and efficacious in persons with haemophilia A with/without inhibitors-HAVEN 4 study

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Aim: Weekly subcutaneous emicizumab significantly reduced bleed rate versus no prophylaxis (only episodic bypassing agents [BPAs]), and versus prior prophylactic BPAs in adolescent/adult (HAVEN 1) and paediatric (HAVEN 2) PwHA with FVIII inhibitors, and similarly in adult/adolescent PwHA without inhibitors versus FVIII prophylaxis (HAVEN 3). Initial data from HAVEN 4 previously showed that subcutaneous maintenance emicizumab dosed 6 mg/kg every 4 weeks (Q4W) provided effective bleed control, and pharmacokinetics as expected, while being well tolerated, in haemophilia A (PwHA) with/without inhibitors. We aim to assess efficacy, safety and pharmacokinetics of emicizumab Q4W in PwHA with/without inhibitors in the HAVEN 4 expansion cohort.

Methods: Eligible patients: aged ≥12 years; severe PwHA and documented episodic/or prophylactic treatment with FVIII replacement or BPAs for ≥24 weeks prior to study entry. Emicizumab administered 3 mg/kg QW for 4 weeks then 6 mg/kg Q4W.

Results: Primary results from the expansion cohort will be presented. As of Dec 15, 2017, 41 patients were enrolled; 92.7% aged ≥18 years, 5 (12.2%) had inhibitors. Median (range) efficacy period, 25.6 (24.1-29.4) weeks. Effective bleed control was achieved (Table). Of 51 treated bleeds reported, 74.5% were traumatic. Approximately 40% of patients did not report any factor VIII or BPA use, neither to treat breakthrough bleeds nor for prophylaxis prior to activity/surgery. Emicizumab pharmacokinetics were as expected based on prior clinical data/modelling. The ~30-day elimination half-life of emicizumab supported the Q4W dosing regimen. A favourable safety profile was observed; 73.2% of patients experienced ≥1 adverse event (AE), the majority Grade 1–2; with only 1 serious AE (rhabdomyolysis deemed unrelated to emicizumab). No AEs of special interest (thromboembolism; thrombotic microangiopathy) and no AEs leading to emicizumab discontinuation or withdrawal from study were reported. Injection-site reactions were the most common emicizumab-related AE (22.0%).

Conclusions: Emicizumab Q4W is safe and efficacious in PwHA with/without inhibitors, and supported by pharmacokinetics. Efficacy data are consistent with that achieved in other HAVEN study dosing regimens.

Table: Bleed-related endpoints for Q4W emicizumab prophylaxis in PwHA with/without inhibitors				
	ABR, model based (95% CI)	Median ABR, calculated (IQR)	Patients with zero bleeds, % (95% CI)	Patients with 0–3 bleeds, % (95% CI)
Treated bleeds	2.4 (1.4; 4.3)	0.0 (0.0; 2.1)	56.1 (39.7; 71.5)	90.2 (76.9; 97.3)
All bleeds	4.5 (3.1; 6.6)	2.1 (0.0; 5.9)	29.3 (16.1; 45.5)	80.5 (65.1; 91.2)
Treated spontaneous bleeds	0.6 (0.3; 1.5)	0.0 (0.0; 0.0)	82.9 (67.9; 92.8)	97.6 (87.1; 99.9)
Treated joint bleeds	1.7 (0.8; 3.7)	0.0 (0.0; 1.9)	70.7 (54.5; 83.9)	95.1 (83.5; 99.4)
Treated target joint bleeds	1.0 (0.3; 3.3)	0.0 (0.0; 0.0)	85.4 (70.8; 94.4)	97.6 (87.1; 99.9)

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P294. Shear stress and fibrin exposure enhance platelet ADAM10 activity and trigger GPVI shedding

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Introduction

Fibrin and collagen bind to platelet glycoprotein(GP)VI and induce shedding of GPVI ectodomain (sGPVI). Unlike collagen, fibrin-mediated shedding does not require platelet signalling. A-Disintegrin-And-Metalloproteinase (ADAM)10 mediates collagen- and shear-induced sGPVI release from human platelets, however fibrin-induced ADAM10-mediated shedding has not been described. We evaluated molecular pathways mediating fibrin-induced GPVI shedding.

Methods

Fibrin- and collagen-mediated platelet aggregation were monitored by light transmission aggregometry. Platelet ADAM10 activity and sGPVI release following exposure to 5000s⁻¹ shear stress, collagen or fibrin were measured using an ADAM10 fluorescence resonance energy transfer assay and a sGPVI ELISA. Quantitative microscale volumes from thrombi formed under fluid shear stress on collagen-coated channels were captured using optical-micro-holography.

Results

Polymerised fibrin (thrombin + fibrinogen) induced α IIb β 3-independent platelet clumping and GPVI shedding. Accumulation was reduced 4-fold by GPRP (fibrin polymerisation inhibitor), but not by GPVI signalling inhibitors or metalloproteinase inhibitors. Polymerised fibrin exposure significantly reduced platelet GPVI expression, and increased ADAM10 activity compared to fibrinogen (p=0.008, n=6) or untreated platelets (p=0.004). Activity was reduced by 2 μ M GI254023X (ADAM10-selective inhibitor), GM6001 or EDTA (broad-range inhibitors), but not by GPRP or Src-family kinase inhibitors. Initial growth rates of individual thrombus volume increased with increasing shear rates (1605 to 7965 μ m³/min for 1800s⁻¹ and 7200s⁻¹, respectively, 2 donors). Thrombi volumes differed throughout the channel, with greatest variation at 7200s⁻¹ (min-max: 240-21096 μ m³, n=37, 4 donors).

Conclusions

Polymerised fibrin induced platelet accumulation, GPVI release and increased ADAM10 activity. Whilst monomeric fibrin treatment (+GPRP) reduced accumulation and shedding, ADAM10 activity remained elevated, suggesting fibrin-GPVI interactions enhance ADAM10 activity independent of platelet activation. Elevated sGPVI is predictive of mortality in injured patients and is strongly associated with sepsis progression. Assessing how shear stress and fibrin cooperate to trigger platelet activation and regulate GPVI shedding/ADAM10 activity will help establish key mechanisms underlying coagulation and platelet activation.

P295. Frameshift and stopgain NBEAL2 variants are common in Gray platelet patients

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Introduction

The Gray platelet syndrome (GPS) also known as α -storage pool disease was first described in 1971. The disease, with an autosomal recessive mode of transmission, is characterized by mild macrothrombocytopenia and platelets appearing grey on stained blood films. Most patients only experience moderate bleeding but in rare cases severe bleeding has been reported requiring transfusion. In 2011, 3 separate groups identified NBEAL2 as the gene linked to the disease. However, grey platelet is not a specific feature of GPS and other genes such as ANKRD26, GATA1, GFI1b, NBEAL2, SRC, TRPM7, VIPAS39 and VPS33B have also been associated with GPS-like platelet appearance.

Aim/Method

To improve diagnosis, we developed a platelet candidate gene array for Next-Generation Sequencing (NGS) targeting known genes important for platelet production and function including above genes.

Results

To date, 213 individuals have been genetically tested for investigation of inherited platelet disorder. Five patients were found to be compound heterozygous (N=3) or homozygous (N=2) for likely pathogenic NBEAL2 variants including 2 non-synonymous, 1 stopgain, 1 splicing variants as well as 1 frameshift insertion and 3 frameshift deletions. They all presented with macrothrombocytopenia and typical gray platelet appearance. Only one Indian patient was probably from a consanguineous family. For the second homozygous patient, a large deletion encompassing exon 44 could not be excluded.

Conclusion

From the literature, approximately half of the reported families are consanguineous with affected individuals homozygous for one variant which is different from our own observation. The associated NBEAL2 variants are diverse, as seen in our cohort, and spread from exon 6 to 50. Only one patient carrying the homozygous splice variant experienced severe bleeding post-surgeries supporting reports that patients with homozygous variants are more likely to suffer from moderate to severe bleeding. NGS is important to confirm a GPS diagnosis and optimize patient management and care.

P296. The Coagulopathy of Liver Disease assessed by Rotational Thromboelastometry and the Calibrated Automated Thrombogram

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Background and Aims

Coagulopathy in liver disease represents a complex spectrum of clinical bleeding and thrombosis due to its effect on both pro-coagulant and anticoagulant factors. Global coagulation assays such as rotational thromboelastometry (ROTEM) and thrombin generation assays such as Calibrated Automated Thrombogram (CAT) are promising tools with utility and differential strengths in predicting acute haemorrhagic and thrombotic risks. There is limited data on their relationship and how they can be used in complement in the clinical setting. We aim to study the relationship between these assays in patients with coagulopathic liver disease and to identify parameters which may be predictive of bleeding risks in this patient cohort.

Methods

Twenty cirrhotic liver patients with significant coagulopathy (defined as INR \geq 1.8 and/or platelets \leq 50 \times 10⁹/L) were studied. Conventional coagulation, ROTEM and CAT parameters were analysed for concordance.

Results

The following relationships were found between conventional coagulation, ROTEM and CAT parameters:

There was a positive correlation between PT with CT_{EXTEM} (r 0.71, p=0.0004) and APTT with CT_{INTEM} (r 0.58, p=0.0104).

An inverse correlation with PT and APTT with peak thrombin (r -0.79, p=0.0007) and endogenous thrombin potential (ETP) (r -0.79, p=0.0007).

Fibrinogen levels correlated strongly with MCF_{FIBTEM} (r 0.90, p<0.0001)

MCF_{EXTEM, INTEM, FIBTEM} showed strong correlation with peak thrombin and α -angle with ETP (r 0.70, p=0.0045).

A shorter MCF, longer CT and longer CFT were observed in the patients with a bleeding history. The CAT demonstrated a shorter lag time and ttPeak, a higher thrombin peak and a smaller ETP in the patients with a bleeding history compared to those with a thrombotic history

Conclusion

There is strong correlation between conventional coagulation tests and global coagulation assays in the coagulopathy of liver disease. ROTEM parameters appear to be more predictive of bleeding phenotype compared to CAT in this patient cohort.

P297. Evaluation of the ACL AcuStar analyser for use in a specialised coagulation laboratory

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Background/Aim

The ACL AcuStar is an automated benchtop analyser utilising chemiluminescent technology and offering fast turn-around-times and ease of use.

The objective of this study was to evaluate the AcuStar and compare results to established ELISA methods. Von Willebrand (VW) screening, Heparin Induced Thrombocytopenia IgG (HIT) and Beta-2-Glycoprotein 1 IgG (B2GP1) assays were assessed.

Methods

B2GP1: 52 samples previously assayed by ELISA (Genesis Diagnostics) were analysed on the AcuStar. Discrepant results were tested with the Phadia EliA method by an external laboratory.

VW: AcuStar testing on approximately 30 samples each for vW Antigen (vWAg), Collagen Binding (CBA) and Ristocetin Cofactor (RiCof) was undertaken and results compared to current methods (in-house vWAg ELISA, Life Diagnostics CBA ELISA, ACL RiCof latex immunoassay).

HIT: 29 positive and 26 negative samples by ELISA (Asserachrom HIT IgG) were assayed by AcuStar and results compared for qualitative agreement. Discordant results were sent for serotonin release assays (SRA) externally.

Results

B2GP1: The AcuStar assay showed 83% correlation with ELISA results. Of the discrepant results, the majority were positive by ELISA and negative by AcuStar. When tested by Phadia EliA, most discrepant samples showed agreement with the AcuStar.

VW: Good correlation was demonstrated between ELISA and Acustar vWAg ($R^2 = 0.98$), with reasonable correlation for CBA and RiCof ($R^2 = 0.82$ and 0.85 respectively).

HIT: Of the 55 samples tested, 12 did not correlate. All discrepant samples were ELISA positive to varying degrees, but AcuStar negative. Of these 12, 5 were of concern due to the strength of ELISA OD results. SRA testing of discordant samples compared favourably with the AcuStar.

Reproducibility studies on all AcuStar assays yielded acceptable inter- and intra-run CVs (mostly 5-7%). The manufacturer's normal ranges were successfully validated for the B2GP1 and VW assays. A lower cut-off for HIT positivity to that stated by the manufacturer will be adopted.

Conclusion

Validation of normal ranges, reproducibility and correlation studies for all assays were within acceptable limits.

P298. Plasminogen deficiency and ligneous conjunctivitis: A case report

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Introduction

Plasminogen is a circulating zymogen which fulfils a major role in fibrinolysis and wound healing. Plasminogen deficiency is a rare disorder and contributes to the development of pseudomembranes and ligneous conjunctivitis as a result of its function. We report the diagnosis, management and follow-up of a case of plasminogen deficiency at Monash Medical Centre.

Case Report

A 3 year old girl presented with 3 day history of pseudomembranous conjunctivitis and fever. She was treated with debridement and corticosteroid injection for 6 months. Due to the association of ligneous conjunctivitis and plasminogen deficiency, plasminogen levels were measured with a resultant level of 0.14 U/ml (Reference range 0.75-1.50 U/ml) and mildly reduced levels in both parents.

Method

A plasma donation from Australian Red Cross Blood Service, divided into segments for single use as eye drops, was kept frozen until use. This was utilised for treatment in the absence of accessible plasminogen concentrates. The product was administered four times daily for two months, thereafter tapered to daily use.

Plasminogen assay – chromogenic activity assay with streptokinase as activator on the ACL TOP instrument.

Histology – biopsy demonstrated prominent acellular eosinophilic material and inflamed granulation tissue.

Results

The conjunctivitis stabilised with the fresh frozen plasma and has not recurred to date. On more recent review, the patient has developed upper lid cicatricial entropion and early posterior sub capsular cataract, but is otherwise well.

Conclusion

Although plasminogen deficiency is a rare disorder, this case has been effectively managed as described, with no further lesions. The plasma eye drops served as an adequate source of plasminogen to prevent accumulation of fibrin deposits and prevent tissue damage in the setting of plasminogen deficiency.

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P299. NET-associated markers in heparin induced thrombocytopenia

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Aim: Heparin-induced thrombocytopenia/thrombosis (HIT) is an immune prothrombotic condition caused by the production of antibodies against a complex of heparin and platelet factor 4 [1]. Neutrophil extracellular traps (NETs) are strings of DNA admixed with cellular proteins, such as histone and myeloperoxidase (MPO), that are involved in the development of venous thromboembolism [2]. The aim of this study was to determine if NET-associated markers were increased in patients with HIT.

Method: Patients were included with a clinical diagnosis of, or suspected HIT based on 4T score and HIT antibody ELISA screen. Blood samples from 5 thrombocytopenia patients (high 4T, negative antibody screen), 5 confirmed HIT patients and 5 healthy controls were analysed for MPO cH3 double positive neutrophils (NETotic neutrophils) by flow cytometry. Twenty-one thrombocytopenia samples, 20 confirmed HIT samples and 22 healthy donor samples were analysed for NET markers in the serum: neutrophil elastase, MPO and double-stranded DNA (dsDNA) [3].

Statistics: The non-parametric T test was used to calculate the differences between the 2 groups of patients versus healthy controls.

Results: Patients with HIT had significantly higher % of NETotic neutrophils in the circulation (mean \pm SEM 6.7 ± 2.3) compared with thrombocytopenia patients (2.1 ± 2.2) and healthy controls (1.1 ± 0.8 , $p < 0.05$). Patients with HIT and patients with thrombocytopenia showed significantly higher elastase compared with healthy controls (445 ± 96 , 492 ± 99 vs 162 ± 34 pg/ml respectively, $p < 0.001$). Patients with HIT and patients with thrombocytopenia had higher dsDNA in the circulation compared to healthy controls ($p < 0.001$).

Conclusion: The percentage of NETotic neutrophils in the circulation is higher in patients with HIT compared with patients with thrombocytopenia from other causes (e.g. sepsis). Determination of NETotic neutrophils by flow cytometry may provide a useful marker to quantify and monitor NETosis in HIT.

References:

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P300. Prothrombin time as measured with STA® NeoPTimal is sensitive to Rivaroxaban effect

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Aim: Regular drug monitoring for Rivaroxaban, a direct oral factor Xa inhibitor, is not necessary due to its predictable pharmacokinetic. However, there are situations when urgent assessment is required. While anti-factor Xa level can be performed, this assay is not widely available in many institutions. Prothrombin time (PT) has been shown to be a useful and readily available method for detecting the rivaroxaban effect when sensitive reagents (e.g. STA® Neoplastine®) are used. We aim to investigate the effect of rivaroxaban on a new PT reagent, STA® NeoPTimal.

Method: We analyzed the PT using STA® NeoPTimal reagent on 30 patients receiving rivaroxaban 20mg daily for VTE treatment and the results were compared to the PT obtained using STA® Neoplastine® CI Plus and Dade® Innovin® reagents. Twenty-nine of these patients (97%) have eGFR >60ml/min/1.73m² and the median duration from time of last dose of Rivaroxaban is 7.73 hours (range 1 – 50.4).

Results: The PT measured using STA® NeoPTimal ($R^2=0.7873$) and Neoplastine® CI Plus ($R^2=0.7835$) closely correlated with the anti-factor Xa Rivaroxaban levels compared to the Dade® Innovin® ($R^2=0.5767$). STA® NeoPTimal reagent had similar sensitivity to STA® Neoplastine® CI Plus ($p=0.67$) and both were more sensitive compared to the Dade® Innovin® ($p<0.001$) reagent. Seven patients (23%) who reported taking their rivaroxaban within 2-5 hours prior to blood sampling (mean anti-factor Xa 119ng/mL) demonstrated a mean PT of 20 seconds (range 13.7-26.5) using the STA® Neoptimal and 19 seconds (range 13.6-23.3) using the STA® Neoplastine®. Of note, all but one patient with PT within normal range ($n=12$; range 11.6-15.3) measured using STA® NeoPTimal had anti-factor Xa <50ng/mL.

Conclusion: The PT measured using the new STA® NeoPTimal reagent is comparable to STA® Neoplastine® and may be appropriate to assess the anticoagulation effect of rivaroxaban in urgent situations, particularly when anti-factor Xa assay is unavailable.

P301. A case of acquired FXIII deficiency

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Aim

To present a case of a rare acquired bleeding disorder

Method

Case Report

We present a case of a 70 year old woman diagnosed with acquired factor XIII deficiency after developing bruising and bleeding not in keeping with the degree of thrombocytopenia from her MDS. She has a 7 year history of MDS with her initial bone marrow showing refractory anaemia with ring sideroblasts which was managed conservatively. Her thrombocytopenia progressively worsened and in 2017 and she started developing bruising after minor trauma. In the same year she had a complicated admission after presenting with haematemesis and epistaxis and extensive purpura. Upon discharge she went onto have further spontaneous bruising despite her platelet count ranging between 30-60 x10⁹/L. Bone marrow biopsy which showed MDS-RS-MLD and 4% blasts, and an ASXL1 mutation was detected (NGS panel). She developed extensive bruising at the bone marrow site, and a few months later had another episode of significant epistaxis requiring cauterisation. This led to further investigations for a bleeding disorder and it was noted on her coagulation studies that her FXIII activity was 14% using the Berichrom ammonia release assay¹. The remainder of her factor levels and von Willebrand screen were normal. A FXIII inhibitor was not detected using the Bethesda method². Given the significant bleeding diathesis, we have treated the patient with fortnightly Fibrogammin (plasma derived FXIII concentrate) and platelet transfusions. We have measured FXIII activity and antigen levels (using a latex immunoassay, "K-assay") at baseline and after administration of Fibrogammin which shows that activity to antigen levels correlate fairly well (Fig.1), and the half-life of factor XIII is approximately 13 days.

Conclusion

Acquired factor XIII deficiency is a rare disorder, and is usually due to autoantibodies against the FXIII-A subunit leading to reduced FXIII activation or activity and increased clearance from the circulation³. This predisposes the patient to bleeding complications and can potentially be fatal. Current management of bleeding is with administration of factor XIII concentrates.

References

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2. Auto- and alloantibodies against factor XIII: laboratory diagnosis and clinical consequences Muszbek et al., JTH 2018 (16): 822-832
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P302. Patient Experience: Providing Group Information Sessions for Subcutaneous Immunoglobulin

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Aim

The aim of the project was to bring patients together who were transitioning from Intravenous Immunoglobulins (IVIG) to Subcutaneous Immunoglobulin (SCIG) in an informal, relaxed information session where they could interact with each other and discuss the benefits of being able to have a greater input into the control, timing and convenience of having treatment outside a hospital setting.

Method

Patients were consulted on the idea of group information with others who would also be transitioning to the SCIG.

Consent was obtained and information times were organised for groups of 3 patients per session. Patients were chosen and placed in groups by looking at their compatibility to interact and assist those who may require additional support.

Patients were given the opportunity to test the equipment they would require to ensure that they could effectively manage administration in their own at home.

Results

Patients found group information sessions valuable in the context of a more relaxed atmosphere being able to engage with each other when learning the functions and setup of the equipment. Patients were keen to engage in conversation regarding the program and ways to support each other through the process.

Through these sessions patients that have commenced on the program have found that being able to administer treatment at home has made a significant improvement in their lives.

Conclusion

Both patients and staff found this method to be beneficial in the transition from Intravenous Immunoglobulin to Subcutaneous Immunoglobulin as patients were able to discuss between themselves and with staff ideas regarding how to make the transition as smooth and efficient as possible.

Through feedback from patients it has been found that patients are now making decisions regarding timing and administration of their treatment to fit into their lifestyle without having to attend a lengthy appointment each month.

P303. A study of older hip fracture patients prior to surgery, to identify anaemia and any association with alterations to haemostasis

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Aim

To measure the prevalence of, and progression of anaemia prior to surgery in geriatric hip fracture patients. To assess if alteration to haemostasis contributes to bleeding and anaemia.

Method

A pilot, prospective single centre descriptive study was undertaken in a regional hospital, on all patients aged 60 and over, admitted with a hip fracture. The World Health Organisation (WHO) definition of anaemia was used. Pathology databases and clinical records were reviewed to collect demographic and clinical data between admission and surgery. Analysis included full blood count (FBC) and routine coagulation tests; activated partial prothrombin time (APTT), prothrombin time (PT), international normalised ratio (INR), fibrinogen and global coagulation testing utilising thromboelastography (TEG6s). Paired sample students t tests were performed to measure changes over time in haemoglobin (Hb) and TEG variables.

Results

A total of 22 participants were included in the pilot study. The median (IQR) age was 82.5 years (11), with twice as many females (n = 16) as males (n = 6). 68% of the sample had intracapsular fractures (n = 15). On admission, 36.3% of patients were anaemic with mean Hb (SD) 127.5 g/L (12.3). On day 1, 46% were anaemic with mean Hb (SD) 118.7 g/L (16.2). The proportion of anaemic patients increased between admission and day 1 (p<0.015).

TEG6s	Admission (n=22) Median (IQR)	Day 1 (n=10) Median (IQR)	P
R (min)	5.2 (1.3)	4.5 (1.5)	0.047
K (min)	1.3 (0.6)	1.05 (0.58)	0.335
MA (mm)	63.4 (6.6)	65.5 (6.58)	0.769
A angle (degree)	72.6 (4.8)	75.7 (6.7)	0.674
LY30 (%)	0.0 (0.5)	0.0 (0.0)	0.314

TEG6s parameters did not significantly change between admission and day 1, with the exception of R time that was reduced on day 1.

Conclusion

The findings demonstrate that some older hip fracture patients become anaemic within a day of admission. Progression to anaemia in this cohort was not associated with alterations to haemostasis.

P304. A retrospective, observational study of BAX 855 in clinical practice in the United States

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Aim

To evaluate real-world utilization of extended half-life (EHL) BAX 855 (rurioctocog alfa pegol, SHP660, ADYNOVATE[®], Shire, Lexington, MA, US) in people with haemophilia A (PWHA) and to describe their clinical profiles before/after switching to BAX 855.

Method

Data were collected through case report forms, using medical records and direct communication with providers, PWHA, or their guardians. Assessments included disease severity, pain levels, number/location of target joints, prior HA therapy, reasons for switching, treatment duration, as well as dosing frequency, adherence and annual bleeding rates (ABRs) before/after switching.

Result

56 PWHA were included (mean age, 26 years); 89% (50/56) had severe HA. PWHA were from 23 states, received care from 44 providers (38 practices) and had ≥12 months of recombinant Factor VIII (rFVIII) therapy before switching to BAX 855. Mean affected target joints was 1.8. Baseline pain was mild–moderate for 93% (38/41 respondents). Most PWHA received standard half-life (SHL) Antihemophilic Factor (Recombinant) (ADVATE[®], Shire) before switching to prophylactic BAX 855 (73%; 41/56) or BAX 855 for breakthrough bleeding (67%, 33/49). Mean prior prophylactic treatment frequencies: 2.8/week for SHL, 1.8/week for EHL rFVIII. Mean dosing frequency for prophylactic BAX 855: 2.2/week; median time on prophylactic BAX 855: 12 months. Prior therapy adherence was complete–good for 68% (38/56). Mean ABRs on prior prophylactic therapies: 5.9 for SHL (n=35), 4.7 for EHL (n=3) rFVIII; mean ABR for prophylactic BAX 855: 1.7 (n=38). The most common reason PWHA switched to BAX 855 was reduced infusion frequency. Adherence to BAX 855 was complete–good for 80% (45/56).

Conclusion

PWHA who switched to BAX 855 reported improved adherence and lower mean ABR versus previous rFVIII treatment. PWHA who switched from SHL rFVIII reported lower mean dosing frequency with prophylactic BAX 855. These data support the important contribution of EHLs to the care of PWHA.

P305. Four-year bleeding frequency in haemophilia A patients on prophylaxis: data from the AHEAD study in 22 countries

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Aim: As new products become available, there is an increased need to compare their effectiveness in prophylaxis with standard products. We aimed to establish an effectiveness benchmark by assessing bleeding frequency in the AHEAD studies.

Method: These non-interventional, prospective, long-term cohort studies span 22 countries and include patients with severe or moderate (factor VIII <1–5%) haemophilia A (HA) treated with Antihemophilic Factor (Recombinant) (ADVATE®, Shire, Lexington, MA, USA). Preliminary data from prophylaxis patients with calculated annualised bleeding rates (ABR) at each time point were analysed in the International (INT, NCT02078427) and German (GER, German Clinical Trial Register DRKS 00000556) arms.

Results: 1117 patients (715 INT, 402 GER) were enrolled. Numbers of prophylaxis patients with ABR data for analysis were 611, 478, 371, and 251 in years 1, 2, 3, and 4, respectively. Over the 4-year period, prophylaxis patients had a median ABR of 1.7/2.4 (INT/GER) in year 1, 1.3/2.2 in year 2, 1.5/1.9 in year 3, and 1.0/2.1 in year 4. Over the 4-year period in the INT and GER arms combined, a median of 38.0% of prophylaxis patients had an ABR of <1, 13.9% an ABR of 1–<2, and 10.2% an ABR of 2–<3 each year.

Table. Percentage of Prophylaxis Patients Achieving ABR Levels By Year: Combined INT And GER Arms

	Year 1	Year 2	Year 3	Year 4
ABR	n=611	n=478	n=371	n=251
<1	37.0%	37.6%	38.3%	39.0%
1–<2	14.4%	13.4%	14.3%	13.6%
2–<3	11.1%	8.4%	9.7%	10.8%
≥3	37.5%	40.6%	37.7%	36.7%

Conclusion: These data show that ~40% of patients on prophylaxis had an ABR of <1 in routine clinical practice. About half of patients had an ABR <2. The AHEAD studies jointly represent one of the largest long-term prospective HA cohorts, providing a reliable benchmark for new products or therapeutic approaches.

P306. Recombinant von Willebrand factor dosing considerations: rapid stabilization of endogenous plasma FVIII Levels in subjects with severe von Willebrand disease

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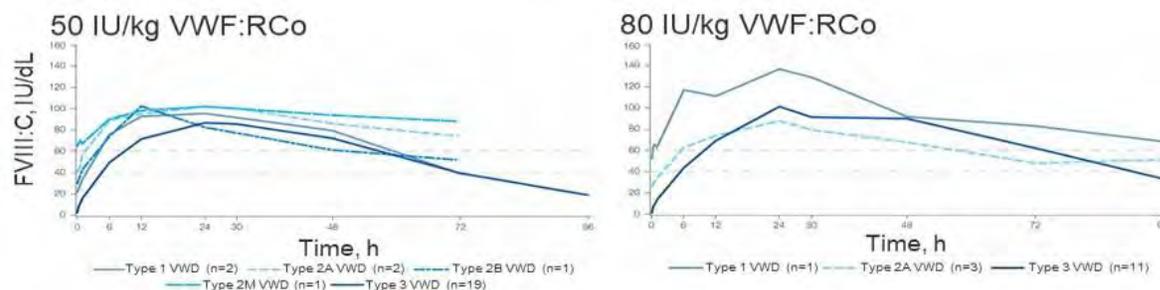
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Aim: We analyzed prospective clinical trial data to better inform dosing decisions related to recombinant von Willebrand Factor (rVWF) treatment and the pharmacodynamic effect of administering rVWF on endogenous FVIII:C.

Method: Two phase 3 clinical trials were included in this post-hoc analysis: an on-demand study (NCT01410227) and an elective surgery study (NCT02283268). All subjects had severe VWD. Subjects who received rVWF alone at doses of 50 or 80 IU/kg VWF:RCo were included in the analysis of mean endogenous FVIII:C over time.

Result: Analysis included 25 subjects treated with rVWF 50 IU/kg VWF:RCo and 15 treated with 80 IU/kg VWF:RCo. rVWF alone resulted in rapid and sustained increases in endogenous FVIII:C, regardless of the VWD type (Figure 1). FVIII:C increases at a mean rate of 7.7 IU/dL per hour (range: 1.0–17.2). Among 36 subjects with a preinfusion FVIII:C level of <40 IU/dL, the mean (range) time to reach 40 IU/dL FVIII:C was 5.1 h (0.8–11.5) in all subjects and 5.6 h (1.6–11.5) in subjects with type 3 VWD. Subjects with type 1, 2A, and 2B achieved the 40 IU/dL level faster (1.5, 4.2, and 0.8 h, respectively).

Figure 1. Mean FVIII stabilization for subjects with severe VWD who received rVWF alone



Conclusion: Treatment with rVWF alone results in rapid stabilization of endogenous FVIII:C, which was more rapid in subjects with higher baseline FVIII:C levels. A rise in FVIII:C to hemostatically effective levels (≥ 40 IU/dL) was reached in the majority of subjects within 6 h, and sooner in subjects with higher FVIII:C levels at baseline.

P307. Rurioctocog-alfa pegol prophylaxis: efficacy, safety, and immunogenicity in previously treated pediatric patients from the US, Europe, and the Asia-Pacific region

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Aim: Rurioctocog alfa pegol (BAX 855, SHP660, ADYNOVATE[®], Shire, Lexington, MA, US) is an extended half-life factor VIII (FVIII) built on the full-length Antihemophilic Factor (Recombinant) (ADVATE[®], Shire), approved for treatment of children and adults with hemophilia A (HA). We evaluated the hemostatic efficacy, safety, and immunogenicity of prophylactic BAX 855 in previously treated pediatric patients by geographic region.

Methods: A post-hoc analysis of a phase 3 multicenter study (NCT02210091) which included pediatric patients with severe HA. Patients were enrolled into 2 age-based cohorts (<6 years, 6 to <12 years) and received twice-weekly prophylaxis with 50 ± 10 IU/kg of BAX 855 for 6 months or ≥50 exposure days. Breakthrough bleeds were treated with BAX 855, with dose determined by bleeding severity/type. Outcomes included: annualized bleeding rate (ABR) and incidence of adverse events (AEs), including development of inhibitory antibodies to FVIII.

Result: 66 pediatric patients received ≥1 BAX 855 infusion. ABR was evaluated overall, by age group (<6 years, n=32; 6 to <12 years, n=34) and by geographic region, with 14/66 patients (21.2%) from Asia-Pacific countries and 52/66 patients (78.8%) from Europe and the US. As expected, most patients (63/66; 95.5%) did not have hemophilic arthropathy. The point estimate for the overall mean ABR (95% CI) was 3.0 (2.2–4.2). ABRs were generally low across age groups and geographic regions. Younger patients had fewer bleeding episodes than older patients overall and within regions. A mean ± SD of 94.1 ± 2.4% and 93.2 ± 5.5% of prophylactic infusions in the younger and older pediatric patients, respectively, adhered to the infusion schedule. No treatment-related serious AEs were reported. No patients developed treatment-emergent neutralizing antibodies to FVIII.

Conclusion: BAX 855 demonstrated efficacy and safety in previously treated pediatric patients with HA regardless of geographic region. No patients developed neutralizing antibodies to FVIII.

P308. First Australian Report of DIAPH1-Related Thrombocytopenia

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Aim

An integrated understanding of the platelet phenotype associated with *DIAPH1*-macrothrombocytopenia is lacking. We aimed to evaluate clinical and laboratory features of this disorder.

Method

Comprehensive platelet functional and structural analysis was performed on two related individuals (father and son) identified with a *DIAPH1* mutation by next generation sequencing.

Results

The heterozygous c. C3637T point mutation of *DIAPH1* is predicted to generate a premature stop codon at amino acid 1213 (p.R1213X) of the *DIAPH1* protein altering its function. This mutation segregated with macrothrombocytopenia (mean platelet diameter, 3.9 μ m; mean platelet count, 80x10⁹/l). Neutrophil Döhle-like bodies were not seen by immunofluorescence microscopy. Platelet surface expression of $\alpha_{IIb}\beta_3$ and glycoprotein Ib-IX was increased consistent with the increased platelet size. Platelets lacked a functional defect and showed normal aggregation to all agonists tested by flow aggregation studies. Interestingly, procoagulant platelets were increased at baseline but had a reduced procoagulant response to thrombin by flow cytometry with GSAO labeling. Normal dense granule content was seen by whole mount electron microscopy. Sectioned transmission electron microscopy revealed platelets that were heterogeneously enlarged, some rounded with prominent peripheral microtubules. Alpha-granules appeared increased and some appeared abnormally large and elongated, suggesting that *DIAPH1* may impact on granule formation. The open canalicular system appeared increased as did platelet glycogen and vacuolation. Increased microtubule stability was suggested on super-resolution imaging (dSTORM) by failure of tubulin rearrangement after thrombin activation. In addition, mild asymptomatic neutropenia was observed (mean 1.23x10⁹/l) in both individuals who also had severe sensorineural hearing loss detected in the first two decades of life.

Conclusion

DIAPH1 mutations should be considered in patients with macrothrombocytopenia, hearing loss and neutropenia. Further phenotypic associations will be important to better delineate the characteristics of this disorder.

P309. First presentation of congenital factor V deficiency in a young adult

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Congenital factor V deficiency is a rare autosomal recessive condition with an estimated prevalence of one in one million.

A 17 year old male presented to a regional emergency department with symptoms of headache, vomiting and drowsiness which developed after a head injury. A computed tomography scan of his brain showed a large extradural haematoma. The patient was transferred to a tertiary referral hospital under the neurosurgical service.

Coagulation studies performed on admission showed a significantly prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT) with a normal fibrinogen and normal thrombin time. The PT and APTT showed complete correction on mixing studies suggesting that a factor deficiency was present. Additional blood samples were collected for further investigations. The patient was given fresh frozen plasma which resulted in almost complete correction of the coagulopathy. He was subsequently taken to theatre for evacuation of the haematoma.

A series of factor assays (factors II, V, VII, VIII, IX and X) were then performed to determine the cause of the prolonged clotting times. The results from these factor assays showed a complete absence of factor V activity. A factor V inhibitor study was also performed which returned a negative result, thereby suggesting the deficiency was congenital.

The patient was continued on twice daily infusions of fresh frozen plasma with subsequent factor V levels rising to above 20%.

A bleeding history was taken post operatively and was significant for bruising following sporting activities as well as abnormal bleeding after mosquito bites. Subsequent testing of the patient's brother was also consistent with congenital factor V deficiency.

This case illustrates the importance of prompt investigation for congenital bleeding disorders in young patients who present with bleeding and unexplained coagulopathy.

P310. Effect of pre-operative DOAC levels on time to surgery

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Aim: Direct acting oral anticoagulants (DOACs) are increasing in prescription rates compared to warfarin(1). There is limited evidence about the optimal perioperative management of patients taking DOACs(2,3). Early hip fracture surgery (<48hrs from admission) has been shown to reduce mortality, however, surgery is often delayed due to anticoagulant medication(4). This study was conducted to assess if measuring pre-operative DOAC levels can expedite time to surgery (TTS) for this population.

Methods: Patients admitted between January 2016 and December 2017 were retrospectively identified from the Australia and New Zealand Hip Fracture Registry (ANZHFR). Anticoagulation prior to admission, time of last DOAC dose, transfusion data and complications were documented from the electronic medical records (BOSSNet). TTS was defined as time from presentation to initial emergency department to operation. DOAC levels were assayed via automated chromogenic analysis of direct factor Xa activity, using apixaban or rivaroxaban as a calibrator (STA-R Stago®) or Dilute Thrombin Time (Haemoclot, Hyphen-Biomed®) for dabigatran(5). Surgery would proceed if the pre-operative DOAC level was <50ng/mL.

Results: 75 patients (82.9±6.9yrs, 70% female) with a surgically managed acute hip fracture were identified on apixaban (n=45), rivaroxaban (n=24), dabigatran (n=6). 49 patients were identified on warfarin. 58 patients had pre-operative DOAC levels ordered. TTS was significantly longer in DOAC patients than warfarin (Table 1). 30-day mortality was 5.3% (n=4), with no deaths related to bleeding or thrombosis.

Table 1: Comparison of TTS

	Warfarin (n=49)	With DOAC level (n=58)	Without DOAC level (n=17)	P value with without level	P value vs DOAC warfarin
TTS mean±std (hours)	34.1±18.7	41.2±12.5	52.8±17.4	0.003	0.001
Operation in <48hrs	84%	78%	41%	0.004	

Conclusion: The measurement of pre-operative DOAC levels was associated with a higher percentage of patients undergoing hip fracture surgery within 48 hours and a shorter TTS.

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P311. Perioperative Management of Anticoagulants in Elective Surgery at a Tertiary Hospital

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Background

Many patients undergoing elective surgery are on anticoagulation. The BRIDGE trial illustrated that perioperative bridging with low molecular weight heparin significantly increased bleeding rates without reducing thrombosis. Whether these findings and anticoagulant guidelines translate into practice is unclear.

Aims

Evaluate -

1. Current perioperative management of patients taking anticoagulants.
2. Bleeding, thrombosis and rehospitalisation rates.
3. Concordance with guidelines and recommendations.

Methods

Retrospective analysis of consecutive adults undergoing elective surgery at a tertiary hospital between January 2017 and April 2018 who received anticoagulants pre-operatively. Concordance with NSW Clinical Excellence Commission guideline was rated according to thrombosis and bleeding risk tables and cofactors.

Results

Evaluated 145 patients, mean age 72±10.7 years. 84.2% received anticoagulation for atrial fibrillation. Interruption/bridging anticoagulation was rated guideline concordant in 140 cases (96.6%), with concordant decisions associated with prior ischaemic stroke (p=0.012), VTE (p=0.018) and active cancer (p=0.018). 3 had thromboembolism (2.1%), 31 received blood transfusion (21.4%) and 4 required rehospitalisation for bleeding or thromboembolism (2.8%). 35 (24%) were bridged – 10 (28.5%) received blood transfusion. 18 (16.4%) non-bridged patients were transfused. Appropriate decisions to interrupt/bridge were associated with lower rates of blood transfusion (p=0.04). Duration of anticoagulation cessation was only concordant in 45 patients (31.0%). Median anticoagulation cessation was 3 days: 75 patients (51.7%) had ≤ 3 days cessation. Patients with ≤ 3 days anticoagulant cessation had fewer transfusions (14.7%) vs patients with > 3 days cessation (28.6%) (p=0.033) but those with shorter anticoagulant cessation had more low bleeding risk procedures. There were no differences in concordance or complications rates between patient's taking DOAC's versus warfarin.

Conclusion

There is considerable concordance with guideline recommendations regarding decision to interrupt/bridge patients, however there was widespread discordance concerning duration of interruption to anticoagulation, suggesting requirement for further education.

P312. Assessment of inferior vena cava filter-related complications when used as either treatment or prophylaxis

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Background

Inferior vena cava (IVC) filters are frequently used as adjunct therapy in patients with confirmed venous thromboembolism (VTE) with contraindications to therapeutic anticoagulation. IVC filters may also be used for VTE prophylaxis in patients with major trauma who are deemed inappropriate for chemical thromboprophylaxis.

Aim

To investigate the rates of IVC filter-related complications in patients with IVC filters inserted for either confirmed VTE, or primary VTE prophylaxis in trauma patients.

Methods

Single centre retrospective audit of consecutive IVC filter placement from December 2015-December 2016.

Results

A total of 151 patients had IVC filters inserted. Sixty-three (42%) insertions were for confirmed VTE in patients unable to have therapeutic anticoagulation, and 58% (88/151) for prophylactic indications. Nineteen patients (ten in the VTE group and nine in the prophylaxis group) died during hospital admission and were excluded from the results.

Rates of complications are displayed in *Table 1*.

Table 1	Confirmed VTE group (N=53), %	Prophylaxis group (N=79), %	p value
IVC thrombosis	2 (3.8)	2 (2.5)	0.68
IVC occlusion	1 (1.9)	5 (6.3)	0.23
IVC penetration	2 (3.8)	1 (1.3)	0.34
Filter fracture	0	1 (1.3)	0.41
Filter tilt	6 (11.3)	3 (3.8)	0.09
Total complications	11 (20.8)	12 (15.2)	0.41

The rate of deep vein thrombosis (DVT) during the follow-up period was 11% (6/53) in the confirmed VTE group and 42% (33/79) in the prophylaxis group (p=0.0002). There were no fatalities from pulmonary embolism in either cohort.

Retrieval rates were 68% (36/53) in the confirmed VTE group and 62% (49/79) in the prophylactic group (p=0.49).

Conclusion:

There were no differences in IVC filter-related complications when comparing filters inserted for confirmed VTE or for primary prophylaxis in trauma patients. VTE diagnosis following IVC filter placement was significantly higher in the prophylactic group, but there were no fatal thrombotic events.

P314. The Venous Thromboembolism Cohort Study: An Update

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Background:

Venous thromboembolism (VTE) is a substantial burden on the Australian health care system. Recent changes in the availability of anticoagulants for treatment of VTE may impact treatment duration.

Aim:

The VTE Cohort Study was established in 2012 to increase understanding of the clinical outcomes of patients diagnosed with VTE in Victorian hospitals.

Method:

Review of consecutive VTE episodes entered on the central registry between 2012 and 2016.

Results:

409 entries are registered on the database. Of the available data, median age is 53 years, median weight is 85 kilograms and 202/404 (50%) patients are male.

Distal DVT occurred in 178/404 (44.1%) of patients, followed by proximal DVT in 170/404 (42.1%) and pulmonary embolism in 168/404 (41.6%). Less common types of VTE included upper limb DVT in 12/404 (3.0%), splanchnic vein thrombosis in 5/404 (1.2%) and cerebral vein thrombosis in 3/404 (0.7%).

Type of maintenance anticoagulation was available for 383 patients and the change in anticoagulant use has been reviewed prior to and after 2014. Results in **Table 1**. The most striking change is the increased use of the direct oral anticoagulant, rivaroxaban, which corresponds with a decrease in warfarin usage. Apixaban for treatment of VTE was listed on the Pharmaceutical Benefits Scheme in September 2015 which may explain the lower use in this cohort.

Maintenance anticoagulant	2012-2013 n=222, (%)	2014-2016 (n=161), (%)
Low molecular weight heparin	42 (18.9)	16 (9.9)
Warfarin	153 (68.9)	49 (30.4)
Rivaroxaban	11 (5.0)	65 (40.4)
Apixaban	0	4 (2.5)
Dabigatran	1 (0.5)	0
Fondaparinux	1 (0.5)	0
Study drug	3 (1.4)	0
No anticoagulation	10 (4.5)	22 (13.7)
Unknown	1 (0.5)	5 (3.1)

Conclusion:

The treatment of VTE continues to evolve, and the VTE Cohort Study continues to be a useful Australian resource in evaluating clinical outcomes and changes in treatment.

P315. Procoagulant Platelets are elevated in Essential Thrombocythaemia and segregate with JAK2V617F Mutation Status

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Aim

Essential thrombocythaemia (ET) is characterised by thrombocytosis and high thrombotic risk, yet standard platelet function testing does not predict thrombosis. Procoagulant platelets are pivotal in thrombin generation and elevated levels are associated with thrombotic disorders. We aim to characterise procoagulant platelets amongst ET patients, to determine response to disease modifying treatment and association with JAK2 mutation status.

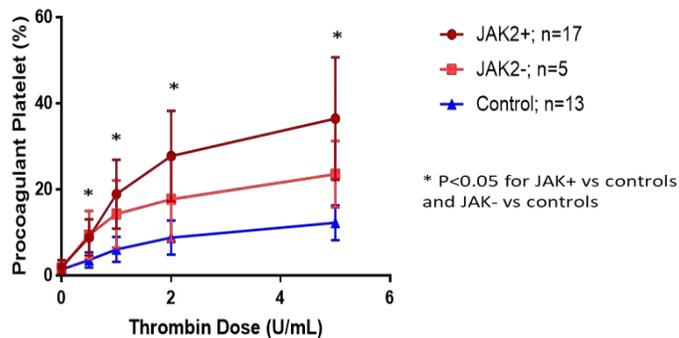
Method

Patients with ET and age range matched controls were recruited in two centres (Concord Hospital, Sydney, Australia and Singapore General Hospital, Singapore). Procoagulant platelets were measured by flow cytometry (GSAO and P-selectin expression) in whole blood: unstimulated and after ADP (5 μ M) or increasing doses of thrombin (0.5-5U/mL) with or without collagen 10mg/mL. Reticulated platelets and platelet aggregation were measured in a subset.

Result

75% were on anti-platelet therapy (aspirin 72.8%) and cytoreductive agents (hydroxyurea 59.1%; anagrelide 18.2%). In the Australian cohort, healthy controls (n=14) and ET (n=22) demonstrated similar procoagulant platelets percentages at rest and in response to ADP. There was significantly higher procoagulant platelet response in ET patients at all concentrations of thrombin with or without collagen. Stratification by JAK2V617F mutation status showed increased procoagulant response in JAK2+ patients at thrombin concentrations \geq 1U/mL with or without collagen. No difference is seen with stratification by cytoreductive treatment, platelet count, reticulated platelets or allele burden at diagnosis. Similar findings were detected at the Singapore site (18 patients, 13 controls). Patients receiving aspirin demonstrated suppression of aggregation but not their procoagulant platelet response.

Thrombin dose curve JAK2+ vs JAK2- with controls



Conclusion

ET patients have heightened procoagulant platelet response especially in the presence of thrombin. This appears to be independent of platelet aggregation response and immature platelets release but could be related to JAK2V617F status. The pattern of response observed differs from patients with coronary artery disease and suggests presence of underlying dissimilar mechanistic pathways that could be further explored.

P316. Evaluation of haemostasis in pregnancy using global coagulation assays

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Introduction

Pregnant women are at increased risk of venous thromboembolism (VTE). Routine laboratory tests are inadequate in evaluating overall haemostasis. Global Coagulation Assays (GCA) including thromboelastography (TEG), calibrated automated thrombogram (CAT), and overall haemostatic potential (OHP) assay, may provide a more holistic assessment of the coagulation pathway.

Aim

To evaluate the GCA in the assessment of term pregnant women.

Method

Non-labouring pregnant patients at ≥ 37 weeks' gestation was recruited prior to elective Caesarean section. Bloods were collected at a single preoperative time point for baseline tests and research samples, which included citrated kaolin whole blood for TEG and platelet poor plasma for thrombin and fibrin generation assays. The results were compared to previously collected non-pregnant healthy female controls aged 18 to 45 years (n=31).

Results

Nineteen women (median age 31 years) were recruited. Four patients (21%) had gestational diabetes and fifteen patients had a body mass index (BMI) ≥ 30 kg/m² at the time of delivery. All patients demonstrated positive D-dimer (median = 1830 ng/mL) and had median fibrinogen of 4.5 g/L. Pregnant patients were hypercoagulable on TEG with significantly increased maximum amplitude (MA) and α -angle and reduced lysis 30. CAT demonstrated elevated endogenous thrombin potential (ETP) and thrombin peak but no difference in velocity index. There was a trend towards higher ETP with increasing BMI (p=0.06) with no correlation with age, gestational diabetes or parity. The fibrin generation parameters were positively correlated to increasing fibrinogen level (Pearson's coefficient = 0.869 p<0.001), despite preserved overall fibrinolytic potential. Increased fibrinogen was also associated with higher MA (Pearson's coefficient = 0.56, p=0.016).

Conclusion

GCA can be used to delineate the hypercoagulable state in pregnant women. The contribution of BMI to hypercoagulability in the pregnancy may be detectable by GCA and warrants further study.

P317. Experience with the HEMSTOP bleeding risk questionnaire

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The HEMSTOP (Hematoma, hEmorrhage, Menorrhagia, Surgery, Tooth extraction, Obstetrics, Parents) questionnaire, a validated bleeding risk assessment tool, was introduced into use in the pre-admission clinic in our institution with the aim of reducing indiscriminate coagulation testing and to facilitate diagnosis and management of patients with bleeding disorders.¹

Methods

The records of all patients having elective surgery from November 2017 to February 2018 were reviewed (n= 360).

Results

62% (n=185) of patients completed the HEMSTOP questionnaire. Coagulation tests were requested in 42% of patients (n=150), compared to 67% in a 2015 local audit. The rate of ordering was comparable in those who did not complete the HEMSTOP: 50% (n=75); those who completed the HEMSTOP: 41% (n=75); and those with a HEMSTOP score of ≥ 2 (predicted to be at higher risk of bleeding): 46% (n=6). The HEMSTOP had been completed in only 50% (n=75) of patients in whom coagulation tests were ordered. 17% (n=26) of requested coagulation tests were abnormal. This was attributable to anti-coagulants in 69% (n=18).

13 patients (7%) scored ≥ 2 . Of these, the score was downgraded on anaesthetic review in 3 patients, and was explained by focal pathology or anticoagulants in a further 5 patients. Overall, a potential bleeding disorder was identified in 5 patients. One of these patients had abnormal coagulation tests. Subsequently mixing studies and Multiplate® were performed. This was the only patient of the 5 to receive a transfusion (day 5 post-operatively). No referrals to haematology were made and no other specific haemostatic testing was requested.

Conclusion

Although overall coagulation test ordering has reduced by 25%, ordering does not appear to be directed by the HEMSTOP questionnaire. Coagulation testing is frequently performed in the presence of anticoagulants with minimal clinical utility. Although a cohort of patients with potential bleeding risk was identified, other than in one case, this did not alter their management.

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P318. Oestrogen sensitive microRNAs: Important post-transcriptional players for regulating tissue factor and factor VIII

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Aim

High circulating oestrogen (E₂) is a risk factor to engender venous thromboembolism, although the molecular mechanism(s) remains to be elucidated. We previously identified two E₂-sensitive microRNAs (miRNAs), miR-365a-3p and miR-548aa which directly interact with tissue factor (*F3*) and factor VIII (*F8*) mRNA, respectively. In the current study, we investigated whether these miRNA candidates also affected F3 and F8 protein expression.

Method

HuH-7 liver carcinoma cells were transfected with 50nM miRNA precursors (negative control or candidate miRNAs) for 48h and 72h. Post-transfected cells were collected and assessed for mRNA and protein expression of candidate miRNA targets (F3 or F8), via real time polymerase chain reaction and Western Blot. Statistical significance was determined using the Student's t-test.

Result

The expression of *F3* mRNA was significantly inhibited by miR-365a-3p at 48h (58% reduction) and 72h (53% reduction) after transfection (P<0.05, n=3). There was also a ~30% decrease of truncated (48h) and full length (72h) F3 protein. The decline of *F8* transcript levels were only demonstrated 48h post-transfection of miR-548aa (25%, P<0.05, n=2). Full length and truncated F8 protein remained unchanged (P>0.05) after 48h transfection, however, a ~55% down-regulation of full length and truncated F8 protein expression was displayed 72h post-transfection (P<0.05).

Conclusion

In the HuH-7 cell model, miR-365a-3p suppressed F3 mRNA and protein expression following 48h and 72h transfection. Furthermore, the mRNA and protein levels of F8 were reduced by miR-548aa after 48h and 72h transfection, respectively. This data strongly suggests that E₂-responsive miRNA candidates regulate F3 and F8 via miRNA:mRNA interactions. Future research will focus on the effects of miRNA regulation of F3 and F8 protein function to identify miRNA-based biomarkers, and/or develop therapeutics, for thrombotic disorders.

P319. Emicizumab prophylaxis once-weekly or every two weeks provides effective bleed prevention in persons with hemophilia A without inhibitors–HAVEN3 results

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Aim: Subcutaneous once-weekly (QW) emicizumab prophylaxis is effective in haemophilia A (PwHA) with inhibitors. HAVEN 3 (NCT02847637) study assessed the efficacy, safety, and pharmacokinetics (PK) of emicizumab prophylaxis QW and every 2 weeks (Q2W) in adolescent/adult PwHA without inhibitors.

Methods: Severe PwHA patients without inhibitors aged ≥ 12 years were enrolled. Patients on prior episodic FVIII, with ≥ 5 bleeds over the previous 24 weeks, were randomized (2:2:1) to emicizumab prophylaxis: 3 mg/kg QW for 4 weeks, followed by 1.5 mg/kg QW (Arm A) or 3 mg/kg Q2W (Arm B) maintenance; or to no prophylaxis (Arm C). Primary efficacy objective compared treated bleed rates (Arm A vs C; Arm B vs C). Patients previously on FVIII prophylaxis received 1.5 mg/kg QW emicizumab maintenance in Arm D; those from a non-interventional study (NIS; NCT02476942) were included in intra-individual comparisons.

Results: 152 patients, aged 13–77 years (median: 38) were enrolled. Statistically significant and clinically meaningful reductions of $\geq 94\%$ were observed in treated, all, treated spontaneous, joint and target joint bleeds with emicizumab QW or Q2W versus no prophylaxis; $>55\%$ of patients receiving emicizumab QW or Q2W had zero treated bleeds and $>91\%$ had ≤ 3 treated bleeds. An intra-individual comparison showed a 68% reduction in treated bleed rate with QW emicizumab versus prior FVIII prophylaxis observed during NIS. Emicizumab was well tolerated; most common AE was injection site reaction (25%). No thrombotic events, antidrug antibodies, or de novo FVIII inhibitors occurred. Sustained emicizumab trough concentrations were achieved with both regimens.

Conclusions: Emicizumab prophylaxis QW or Q2W significantly reduced bleed rates in PwHA without inhibitors, with a favorable safety profile. Most notably, an intra-individual comparison demonstrated superiority of emicizumab over previous FVIII prophylaxis. Subcutaneous emicizumab prophylaxis may provide a highly efficacious and flexible management option, with reduced burden for PwHA without inhibitors.

Acknowledgement

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P320. Pulmonary cement embolisation

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Introduction

Percutaneous vertebroplasty is a common and effective procedure to relieve pain induced by osteoporotic fractures and osteolytic metastases. Pulmonary embolisation of the cement used for this procedure (polymethylmethacrylate) has been reported in the surgical and radiological literature. We present two cases of pulmonary cement embolization at our institution. We aim to increase awareness of this complication and review the literature.

Case 1

A 72-year-old female presented to hospital with dyspnoea two months following T12 vertebroplasty for an osteoporotic fracture. CTPA demonstrated hyperdense material within the pulmonary vasculature of bilateral upper lobes, with extravasation of cement into the paravertebral veins. She commenced anti-coagulation with rivaroxaban for six months. Repeat imaging demonstrated persistence of the cement emboli and transthoracic echocardiogram showed early pulmonary hypertension. Due to her risk of chronic thromboembolic pulmonary hypertension (CTEPH) she continues on indefinite anti-coagulation.

Case 2

A 76-year-old male developed pleuritic chest pain and dyspnoea one week following vertebroplasty for multiple osteoporotic crush fractures. CTPA showed right upper and middle lobe pulmonary cement emboli and paravertebral and azygous vein cement leakage. A therapeutic dose of subcutaneous enoxaparin was given for three days with improvement in his symptoms. He will complete six months of oral apixaban.

Literature Review

The incidence of pulmonary cement embolisation ranges from 3.5 to 23%, however in practice, many cases go undetected. The risk seems to be higher for vertebroplasty than for kyphoplasty. The thrombogenic cement can lead to progressive occlusion of pulmonary arteries. Therefore, six months of anti-coagulation is recommended. After this time, the foreign body is endothelialised and the risk of further thrombosis is reduced. The long term risk of CTEPH is unknown. No treatment is recommended for asymptomatic patients. Surgical embolectomy should only be considered in exceptional cases of central embolisation and haemodynamic instability.

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P321. Raised D-dimer post-cessation of anticoagulation is predictive of recurrent thrombosis in provoked VTE and distal VTE

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Introduction: Raised D-dimer post-anticoagulation cessation has been associated with increased risk of recurrence in patients with unprovoked major VTE. Whilst thrombosis recurrence is much higher in unprovoked events, recurrence after provoked venous thromboembolism (VTE) and isolated distal deep vein thrombosis (IDDVT) are not insubstantial, with recurrence rates of 2.3 and 3.9 per 100 event/years respectively in our recent real-world audit. There is limited data however on the use of D-dimer testing in patients who have completed anticoagulation for provoked VTE or IDDVT.

Methods: Retrospective evaluation was performed on 1024 patients with a diagnosis of VTE between January 2013 and December 2016 at a tertiary hospital. Patients were identified who had D-dimer tested within 90 days post-cessation of anticoagulation.

Results: 189 patients with post-cessation D-dimer were identified. Median age was 58 (18-92) and 55.3% (n=105) were female. Median follow up was 18 months (3-55). 33.3% (n=63) had IDDVT, 66.3% (n=126) had above knee DVT (AKDVT)/PE, 54.5% (n=103) of VTE were provoked. Anticoagulation was recommenced in 11 patients with provoked VTE, 13 patients with unprovoked VTE and 5 patients with IDDVT.

Of patients who remained off anticoagulation, elevated D-dimer post anticoagulation cessation was a significant risk factor for recurrence in the provoked VTE (relative risk (RR) 4.21, p=0.01) and unprovoked VTE cohorts (RR 4.55 p=0.008)[table 1]. Elevated D-dimer post anticoagulation cessation was also significantly related to risk for recurrence in the IDDVT sub-cohort (RR 4.09, p=0.007)[table 2].

Table 1. VTE recurrence rates in provoked VTE and unprovoked VTE (pts who remained off anticoagulation [AC])

		No VTE recurrence	VTE Recurrence	
Provoked VTE (n=103)	Normal D-dimer post cessation (n=65)	61 (93.8%)	4 (6.2%)	RR 4.21(95%CI 1.34-13.22) p-value=0.014
	Elevated D-dimer post cessation (n=38 [27 off AC])	20 (74.1%)	7 (25.9%)	
Unprovoked VTE (n=86)	Normal D-dimer post cessation (n=52)	46 (93.9%)	3 (6.1%)	RR 4.55 (95%CI 1.49-13.88) p-value=0.008
	Elevated D-dimer post cessation (n=34) [20 off AC])	13 (65.0%)	7 (35.0%)	

Table 2. VTE recurrence rates in all IDDVT (pts who remained off anticoagulation [AC])

	No VTE recurrence	VTE Recurrence	
Normal D-dimer post cessation (n=36)	32 (88.9%)	4 (11.1%)	RR 4.09 95%CI (1.46-11.5) p-value=0.007
Elevated D-dimer post cessation (n=27) [22 off AC]	12 (54.5%)	10 (45.5%)	

When provoked VTE were sub-categorised, raised D-dimer demonstrated the most statistical significance in VTE provoked by travel (RR 13.5 p=0.06).

Conclusion: D-dimer post cessation may have a clinical role in predicting VTE recurrence, with a positive D-dimer post cessation in the provoked VTE and IDDVT population associated with 4.21 and 4.09 relative risk of recurrence respectively. Further clinical research is required to evaluate these findings.

P323. Tinzaparin for anticoagulation in patients with renal impairment: results of a pilot program at Concord Hospital

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Background: Low molecular weight heparins (LMWH) are problematic in renal impairment due to accumulation. Tinzaparin has the highest molecular weight of all LMWH, thus relies least on renal clearance. Dosage is weight-based at 175units/kg once daily, with no renal adjustment in patients with creatinine clearance greater than 20ml/min. We aimed to explore if tinzaparin would be a useful addition to the pharmacy formulary at Concord Hospital.

Methods: Patients were eligible if creatinine clearance by Cockcroft-Gault (CG-CrCl) was 20 to 50ml/min during period of requirement for heparin anticoagulation. SAS approval was gained for each patient. Tinzaparin anti-Xa levels were measured 4 hours after administration at days 2, 7 and 14 and levels correlated with both CG-CrCl and CKD-EPI eGFR. Patients were reviewed monthly if they continued on tinzaparin.

Results: Eighteen patients were established on tinzaparin from June 2017 to January 2018 with cancer-associated thrombosis (n=7); bridging to warfarin (n=4); breakthrough thrombosis on anticoagulation (n=4), and acute thrombosis (n=3). No patients reached the pre-specified anti-Xa level of >1.4 required for downward dose adjustment, one patient had a dose increased in response to low anti-Xa levels. Three patients experienced mild bleeding complications: epistaxis (1; dose-reduced); small abdominal wall haematoma (2). Bleeding was not predicted by CG-CrCl, CKD-EPI eGFR or tinzaparin levels. Tinzaparin levels correlated with CKD-EPI (p=0.02) on day 2 but not CG-CrCl. Three patients died during follow-up, attributed to causes outside of tinzaparin use.

Conclusions: These results confirm previous findings of safety and effectiveness using therapeutic tinzaparin in patients with CrCl 20-50ml/min, leading to its approval for the pharmacy formulary at Concord Hospital. Tinzaparin is an attractive alternative with once daily dosing, particularly in cancer-associated thrombosis with renal impairment whilst maintaining the safety profile of LMWH.

P324. Influence of travel, marathon running and compression socks on haemostatic activation

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Aim: Travel and exercise are associated with increased thrombotic risk. Compression socks may reduce haemostatic activation during exercise. We investigated the effect of pre-marathon travel on haemostatic markers and the influence of compression socks on coagulation following a marathon.

Method: 42 runners travelling domestically (DOM) and 25 runners travelling internationally (INT) were recruited. Both DOM and INT runners were allocated to wear compression socks (SOCK: DOM (n=19), SOCK: INT (n=15)) or no compression socks (CONTROL: DOM (n=23), CONTROL: INT (n=10)). Venous blood samples were obtained 24h prior-to and immediately post-marathon and analysed for thrombin anti-thrombin complexes (TAT), tissue factor (TF), tissue factor pathway inhibitor (TFPI) and D-Dimer.

Results: Pre-exercise concentrations of D-Dimer were higher in INT travellers compared to DOM travellers ($p < 0.0001$). A main effect for magnitude of change (PRE-POST) for TF ($p = 0.02$) and D-Dimer ($p = 0.002$) was observed, with the magnitude of change for D-Dimer significantly greater in the CONTROL:DOM group compared to SOCK:DOM and SOCK:INT groups ($p < 0.02$).

Conclusion: Greater pre-exercise coagulation activation occurred in runners travelling internationally versus domestically. Compression socks reduced the magnitude of change in D-Dimer only. Therefore, compression socks worn during a marathon have the potential to reduce overall haemostatic activation and blood clot risk.

P325. Popliteal vein entrapment syndrome in a well-trained masters cyclist: a case study

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Aim: Whilst athletes are considered to be the epitome of health and well-being, venous thromboembolisms (VTE) including deep vein thrombosis (DVT) and pulmonary embolism have been demonstrated to occur in well-trained athletes. VTE is frequently misdiagnosed and poorly treated within this population, often resulting in career or life threatening ramifications. Furthermore, VTE risk rises with increasing age (>40 years), potentially affecting master athletes. The aim of this case study was to investigate a VTE in a well-trained master's cyclist.

Method: A 44 year old male cyclist volunteered to participate in a research project investigating the influence of exercise on haemostasis in well-trained athletes (subject cycled >10h per week).

Results: The cyclist had elevated D-Dimer levels both pre- (2251ng/mL) and post-exercise (2653ng/mL) with these results 35- and 30-fold greater than the group of well-trained cyclists mean. Prior to following up with their general practitioner, the cyclist reported constant mild pain in the left mid-calf region with a cold tingling sensation in the left foot. Diagnosis of DVT was confirmed via a DVT squeeze test and Doppler ultrasound, with the clot located in the left popliteal vein.

Conclusion: During the research project the cyclist was exposed to numerous thrombogenic risk factors including travel, dehydration, prolonged sitting and exercise. The development of DVT in the popliteal vein may have resulted from intermittent compression and decompression of the vessel during leg hyper-extension and flexion, and repetitive movements associated with cycling. Additionally, hypertrophy of the gastrocnemius muscle may have impinged the vein. Popliteal vein entrapment syndrome (PVES) is a rare pathophysiological factor for DVT which is underdiagnosed in well-trained cyclists. Therefore when diagnosing VTE within a cycling population, PVES should not be overlooked as a contributing factor.

P329. How should we manage oncology infusion related reactions? A clinical guideline review

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Aim

To identify best practice management of infusion related reactions (IRRs) to oncology treatments.

Method

A systematic review of the literature was conducted across: 1) search engines MEDLINE, CINAHL, TRIP; and 2) Clinical Guidelines library on CKN: including National Guideline Clearinghouse; NICE; NHMRC Australian Clinical Practice Guidelines; New Zealand Guidelines Group and utilising 3) internet engines: Google scholar and uptodate.com, to identify best practice management of infusion related reactions to oncology treatments including the emerging use of monoclonal antibodies.

Result

The search yielded 33 articles which were potentially useful. The author refined this selection by excluding off topic articles to four guidelines, however only two guidelines specifically targeted oncology practice. Of these two only one included managing infusion reactions. Using the AGREE II tool, one guideline - "Management of infusion reactions to systemic anticancer therapy: European Society for Medical Oncology Clinical Practice Guidelines" was appraised.

This single practice guideline clearly identifies the most common drugs used in cancer treatments (chemotherapy, monoclonal antibodies and immunotherapy) which frequently cause IRRs. Information on incidence, signs/symptoms, prophylaxis and reaction management are also provided.

Conclusion

Confidence in the guideline is limited by its basis on expert opinion, rather than empirical evidence. The suggested actions to manage an IRR could be adapted for universal use in oncology treatment reactions, however, more evidence is needed to inform consistent, evidence-based management.

P330. Nurse Led Discharge (NLD) of patients post blood transfusion in an outpatient setting

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Introduction

Historically patient who presented to the Haematology Day Unit at the Calvary Mater for a blood transfusion needed to be reviewed by a resident medical officer (RMO) prior to discharge for a clinical assessment of fluid status and risk of transfusion associated circulatory overload (TACO). This led to delays in discharge, chair blockage and was viewed by the RMO as time consuming and often an unnecessary task.

Aim

To develop a process where suitable patients can be safely discharge by the nurses in the Haematology Day Unit post transfusion.

Method

A retrospective audit was undertaken to determine patients who required any clinical intervention post blood transfusion prior to being discharged.

A set of criteria was determined for those patients who were considered suitable to be included in NLD program through a consultative process with specialist medical and nursing staff. A post transfusion check list has been developed to ensure patient safety for the NDL model. All patients who have meet criteria for NDL are currently flagged on a spread sheet for easy recognition.

Results

The nurse led discharge model was undertaken for 3 months between March and June 2018. Nineteen patients out of the 49 patients considered were identified to partake in this program. There have currently been no patients who have required readmission to hospital with any transfusion related sources while on this program. The program has also helped to facilitate work flow and discharge of patients in a timely manner.

Conclusion

Patients who fulfil the criteria can safely be discharged post blood transfusion with the NDL model. Limitations of this program to date include timeframe since commencement and the predetermined age cut off has limited the number of eligible patient to be included. A review of the eligibility criteria needs to be attended to determine if we can increase patient numbers without compromising patient safety.

The unit will also need to develop the current patient suitability list from a spreadsheet to become part of our booking and electronic record system.

P331. Outpatient Autologous Transplant: Patient experiences during the first month of stem cell transplant

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Aim

To explore the experiences of patients during the acute phase of an outpatient autologous stem cell transplant.

Methods

People who had received an autologous stem cell transplant were invited to take part in a semi-structured interview to describe their experiences of transplantation. To provide a broad overview of experiences purposive sampling was used to show a range of symptoms to provide a broad overview of symptoms. Twenty of the 25 patients invited to participate in the interview.

Results

Treatment related fatigue was the single most reported significant symptom or side effect experienced. Fatigue was identified as underpinning most of the symptoms reported and its effect on the ability to self-care at home. Fatigue reduced the patient's ability to initiate self-care and maintain activities of daily living.

Conclusion

Specific based programs for people undergoing stem cell transplantation in the outpatient setting may have the potential to promote and instigate early self-care interventions to improve symptoms and Quality of Life.

P332. Implementation of Lymphoma Care Nurses: to provide specialist information, education and support for patients, carers and health professionals across Australia

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Introduction

Lymphoma and Chronic Lymphocytic Leukaemia (CLL) affects more than six thousand Australians every year across Australia. Patients affected are geographically dispersed across Australia and as a result are not always given the opportunity to be referred to a specialist lymphoma service. Nurses caring for lymphoma patients need to be aware of best evidence-based practice in Australia. To improve patient outcomes, Lymphoma Australia has funded specialist lymphoma nurses to promote awareness, to provide education and support for lymphoma patients, carers and health professionals across Australia.

Aim

To ensure all patients, carers and health professionals have access and to be given specialist support from a Lymphoma Care Nurse regardless of their financial situation or where they live within Australia.

Description

In 2016, Lymphoma Australia committed to fund two Lymphoma Care Nurses. The Lymphoma Care Nurse Project was developed to deliver initiatives for patients, specialist education with the latest available evidence informing of best treatments, clinical trials and support available in Australia and across the world. The model that has been developed, provides support Australia wide.

Outcomes

The Lymphoma Care Nurse achievements include, the ongoing development of education, advice and support via hard copy and on-line resources, education events and webinars. The nurses have instigated a national Lymphoma Nurse Hotline and a Lymphoma Nurse Special Interest Group. They support patient advocacy and provide clinical input for Pharmaceutical Benefits Advisory Committee submissions for new treatments. They collaborate with national and global lymphoma related committees, organisations, government and pharmaceutical companies, including attendance at key haematology and oncology events.

Conclusion

Lymphoma Australia is committed to the ongoing funding and to increase the number of Lymphoma Care Nurses to ensure there is national equity for support, access to information and the best available treatments.

P333. Urokinase versus alteplase for the management of occluded central venous access devices: a systematic review

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Aim

Central venous access devices (CVADs) are ideal for the administration of anti-cancer treatments. However, infection and occlusions are common complications that impede treatment. Tissue-type plasminogen activator (t-PA) agents, such as alteplase, and urokinase-type plasminogen activator (u-PA) agents, such as urokinase, are common thrombolytic agents used for occlusion management. Currently, there are no systematic reviews that compare different thrombolytic agents to identify the safest and most effective agent to manage occluded CVADs. The aim was to review randomised control trials (RCT) that compared urokinase versus alteplase for CVAD occlusion management.

Method

Electronic databases including the Cochrane Library, CINAHL and PubMed were searched using the Medical Subject Headings: central venous catheters, central venous access devices, occluded, blocked, urokinase, tissue type plasminogen activator, thrombolytic agent, alteplase. Primary outcomes of restored CVAD patency and secondary outcomes of resolved thrombus and adverse events were assessed.

Results

Searching retrieved 5 studies of which 2 were RCTs and met the inclusion criteria. Both studies favoured the use of alteplase compared to urokinase to restore patency in occluded CVADs after one dose (risk ratio (RR) 1.25; 95% confidence interval (CI) 1.08 to 1.45, p=0.02). One study assessed restored patency after two doses and results favoured the use of alteplase (RR 1.25; 95% CI 0.96 to 1.12, p=0.41). Alteplase was more likely to resolve thrombus compared to the urokinase group after a single dose (RR 2.55; 95% CI 0.97 to 6.75) and after a second dose was administered (RR 1.91; 95% CI 0.97 to 3.77). No adverse events were observed in either study.

Conclusion

There is evidence to suggest that alteplase may be a suitable alternative to urokinase for the management of occluded CVADs. Further studies are required to compare the efficacy, safety and cost-effectiveness of both agents.

P334. "Whats your preference"?

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Mrs JS was admitted to St George Hospital Haematology Unit in September 2017 with the diagnosis of Acute Myeloid Leukaemia. She was given induction chemotherapy of 7:3. (Idarubicin & Cytarabine) During the nadir she required many units of platelets and packed red cells and unfortunately became Human Leucocyte Antibody(HLA) positive and required HLA matched platelets from Australian Red Cross.

The Apheresis Service was asked to collect autologous platelets via apheresis prior to consolidation chemotherapy. There were no Spectra Optia® Platelet Collection kits available in Australia. Attempt was made using Spectra Optia® IDL set platelet depletion programme, but after a low yield collection, it was decided to attempt platelet collection using the Spectra Optia® Collect Set which proved very successful.

This poster will describe how 3 successful collections were obtained using the Spectra Optia® collect kit.

P336. Successful identification of patients requiring psychosocial intervention when undergoing HPC and ASCT

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Aim

To identify patients psychosocial needs using validated Distress Screening (DS) tools during HPC (Haematopoietic Progenitor Cell Collection) and ASCT (Autologous Stem Cell Transplant).

Background

The NCCN guidelines recommends screening for psychosocial distress (PD) in the cancer ambulatory care setting in order to improve the patients' quality of life. At our facility much of the HPC/ASCT process is now done in the ambulatory care setting. The change from inpatient to outpatient based management at our facility led to the identification of a service gap in psychosocial support.

Method and Results

All patients presenting to CMN apheresis and BMT service were provided with DS tools from March 2016 to July 2017. A total of 60 patients were planned for HPC collection. 11 patients did not proceed on study; 2 AYA patients, 3 unable to be consented and 6 declined to participate. Study participants (n=49) were evaluated at 3 set timepoints during the HPC collection and ASCT phase of treatment.

Timepoint 1 (T1) 48/49 patients completed tools, T2 27/45, T3 20/35 and 15/34 completed the evaluations with 7 evaluations not sent due to patient death or disease progression.

From these assessments several common themes became apparent with emotional and physical concerns ranking highest. The patient evaluation data confirmed the need for psychosocial support in this population.

Conclusion

From this pilot study we have successfully identified patients requiring PD intervention by screening, assessing, and addressing patient stressors in the area of our acknowledged service gap. As a result of this pilot study we have now incorporated the DS tools at the initial workup for all HPC patients.

P338. Post dural puncture headache following lumbar puncture and intrathecal chemotherapy, how long should patients remain recumbent - a systematic review.

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Aim

Lumbar puncture (LP) is associated with patient-reported post-dural puncture headache (PDPH). There is no consensus on duration for patients to remain recumbent post intrathecal (IT) chemotherapy via LP to prevent PDPH. Our aim was to conduct a systematic review on the duration of lying supine on prevalence of PDPH.

Method

This systematic review included randomised control trials and cohort studies comparing the effect of a patient lying recumbent for one hour versus greater than one hour following LP. The primary outcome was patient-reported PDPH. The secondary outcome was severity.

Result

No studies compared duration of lying supine following IT administration of chemotherapy via LP and relationship to PDPH. Therefore, criteria were modified. Two papers in neurological populations were included reviewing time recumbent following LP and prevalence of PDPH. LP performed for diagnostic purposes. No difference in number of patients reporting PDPH following LP in either the ≤ 1 hour recumbent group or the > 1 hour recumbent group (Risk Ratio 1.07; Confidence Interval [CI] 95%, 0.60-1.93; $P=0.81$, > 1 hour 17/67; 25% vs ≥ 2 hours 16/68; 24%). Reduction in severity of PDPH was demonstrated in the ≤ 1 hour recumbent group (Mean Difference -0.64; CI 95%, -1.16- -0.12, $P=0.02$).

Conclusion

There is no evidence available determining the time required to remain recumbent after IT chemotherapy via LP. The literature highlights there is no difference in reporting of PDPH by neurological patients remaining recumbent for ≤ 1 hour versus > 1 hour following LP. Therefore, this review has demonstrated the need for further research including randomised controlled trials to examine the time required to lie supine following administration of IT chemotherapy via LP.

P339. Straight to the heart: a glimpse of CLABSI in our haematology unit - a single centre experience

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Aim

The aim of this clinical audit is to identify the patterns of proven central line associated bloodstream infections (CLABSI) in acute leukaemia and stem cell transplant (SCT) patients, by looking at the incidence of BSI on a haematology ward.

Method

We felt our unit had an increase in CLABSI rate and undertook this audit to quantify and understand the source of CLABSI. We retrospectively reviewed medical files for all patients with a long term central venous access device (CVAD), who received treatment for acute leukaemia and/or underwent an allogeneic stem cell transplant at our institution over a 90-day period. CVAD insertion and removal date, blood culture source and positivity were collected. A CLABSI was determined using CDC and VICNISS definitions.

Result

79 patients were included. Patients without a CVAD were excluded as were blood cultures positive for commensal or mucosal barrier injury organisms. 12 individual CLABSI over a period of 4726 line-days yields a CLABSI rate of 2.53 ‰. Of the identified CLABSI, 33.3% (n=4) were within 2 days of admission to the inpatient ward and so attributable to outpatient whilst 66.7% (n=8) were attributable to the inpatient ward.

Conclusion

CLABSI rates on the inpatient ward were high comparing to ICU (1.6‰), which highlights an area for improvement for the ward staff. Identifying the source of CLABSI is useful to assist with targeting educational approaches and policy shifts where there is potential for greater effectiveness in patient outcomes and cost-savings for the hospital.

P340. Haematology/bone marrow transplant/oncology moved one floor down....but were we up for the challenge?

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Aim: To explore and describe the nursing educational challenges when a bone marrow transplant unit merges with a mixed medical ward.

Background: After extensive fundraising and capital works planning, the Haematology/Bone Marrow transplant (HBMT)/Oncology ward at St Vincent's Hospital, Sydney closed temporarily in October 2017. During the renovations our HBMT/oncology patients were co-located on a mixed medical ward. Combined with high staff attrition rates, this posed enormous educational and workforce challenges to ensure patient safety. Transplant numbers were not reduced during this period, it was business as usual.

Method:

The process involved:

- Confirming nursing workforce and skill mix in the new combined ward.

- Obtaining baseline mandatory training data from online data base (HETI) and associated ward competencies. Collating completion rates.

- Accessing online mandatory training data to access completion rates on Antineoplastic Drug Administration Course (ADAC) Module 1 and Module 6, attendance at the cytotoxic workshop and numbers of cytotoxic accredited nurses.

- Conducting a ward based needs analysis survey on their education needs.

Outcomes:

The survey identified priority areas of need:

- Understanding safety issues relating to cytotoxic drugs,

- Ensuring staff have the opportunity to gain ADAC accreditation to ensure safe and competent administration of cytotoxic drugs,

- Improve knowledge relating to diagnosis, treatments and nursing care for HBMT/oncology patients,

- Cancer Institute NSW EviQ education and training for staff to easily access commonly used chemotherapy protocols,

- Bedside teaching to recognise and manage side effect of cytotoxic treatments

- Improve visibility and access to nurse educators, nurse clinical leads and clinical nurse consultants.

Conclusion:

Integrating HBMT/oncology patients has provided considerable challenges that have been overcome with education and support. Involving staff through a needs analysis has engaged staff in a process they were initially sceptical about. Maintaining patient and staff safety throughout the process.

P342. Processes for the introduction and expansion of an acute haematology service at Epworth Freemasons

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Background

Epworth Health Care is the only private provider of comprehensive cancer services offering treatment across a range of oncological and haematological malignancies in Victoria. Epworth Freemasons identified an opportunity to expand its cancer services by introducing treatment for patients affected by haematological malignancies and related blood disorders; the service was introduced in 2015. The aim of this presentation is to outline the processes instituted to grow a high quality acute haematology service at Epworth Freemasons.

Methods

The approach was multifocal targeting initiatives to lay the foundation for robust service delivery and ranged from establishing governance structures to preparation of the workforce. Procurement of specialised equipment and purpose built facilities to maximise the patient experience and delivery of specialised chemotherapy regimens was required. We undertook an evaluation of existing services to inform operational and workforce recommendations and initiatives. Implementation included changes/expansion of the nursing workforce/model of care, pharmacy and pathology services and development of supporting units across the campus.

Results

The service has expanded threefold since 2015. A day medical unit was established including a bone marrow biopsy service. The day oncology unit services outpatient treatment delivery and the day medical unit delivers supportive care. Nursing and multidisciplinary teams have a deeper and more extensive understanding and awareness of how to care for this patient population.

Discussion

We have successfully reached our objectives in delivering an acute haematology service through a planned and targeted approach. The unit has begun successful expansion into caring for patients with AML with promise of future growth including the expansion of the availability and delivery of clinical trial treatment for haematology.

P343. Implementation challenges and successes of a geriatric screening/assessment program in a secondary cancer service: A New Zealand case-report

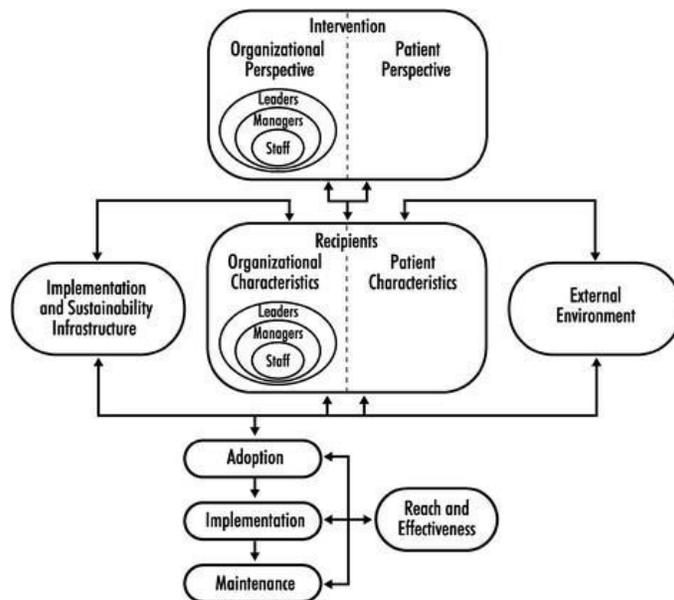
Stolz Basket P¹

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Background: Many patients diagnosed with haematological malignancies are ≤ 70 years of age. Comprehensive geriatric assessment (GCA) is integral to best practice in geriatric cancer care. No studies described system-level challenges/facilitators to design/implementation of a CGA program for malignant haematology in the secondary care setting. This case report explores the viewpoints of the program lead before/during implementation of a Clinical Nurse Specialist (CNS) led CGA program as a quality improvement initiative in a New Zealand.

Methods: Aligned to the Practical Robust Implementation and Sustainability (PRISM) model, a CNS-led quality improvement initiative aiming at implementing CGA for haematology patients ≤ 70 years old and newly diagnosed with a malignancy was developed 2017 -18. Barriers/facilitators related to organisational/patient at the intervention/recipient levels, as well as factors pertaining to infrastructure and environment are qualitatively assessed and described (Fig.1).

Fig.1 PRISM Model (Feldstein & Glasgow, 2012)



Results: Whilst patient characteristics and perspectives on nurse-led CGA interventions might not differ across settings, secondary care level organisations characteristics and interdependent perspectives pose barriers to implementation due to lack of funding, available structural support and clinician expertise/experience within the multidisciplinary team (MDT). For example, the lack of administrative support impacts on establishing a reliable process to intervention appointment planning. Lack of prior exposure to advanced practice nurse-led care initiative in secondary care MDTs impacts on understanding of role scope/competencies prior to intervention implementation.

Conclusions: Addressing barriers at multiple system levels by site-specific design and changes in delivery of CGA interventions to older people with a haematological malignancy has both benefits and problematic consequences. Other smaller secondary level cancer care organisations can use our case-report results to understand the complexity of implementation of a CGA program within their services.

P344. Does a clinical sepsis pathway improve outcomes in cancer patients? A systematic review

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Aim

Sepsis is prevalent in Cancer patients. The associated mortality rates due to severe sepsis and septic shock range from 25 to 70%. Early identification and the introduction of a clinical sepsis pathway is instrumental in improving patient outcomes. Pathways include administration of intravenous (IV) antibiotics within 60 minutes, blood cultures and lactate levels prior to IV antibiotics. The aim was to critique current evidence of sepsis pathways and its effect on patient outcomes.

Method

Journal articles that compared standard care with a clinical sepsis pathway were included in this review. Our primary outcomes was IV antibiotics within 60mins of fever. Secondary outcomes were length of stay and mortality.

Result

Three papers met the selection criteria. Patients on a sepsis pathway are: (i) 1.5 more likely to receive IV antibiotics within 60mins (Risk Ratio (RR) 1.47; Confidence interval (CI) 95% 0.93, 2.31; P = 0.10); (ii) more likely to stay in hospital by 2 days (Mean difference 1.78; CI 95% - 1.82,5.37; P = 0.33); and (iii) less likely to die (RR 0.75; CI 95% 0.56,1.01; P = 0.06).

Conclusion

A clinical sepsis pathway improves time to IV antibiotics within 60mins and rates of mortality. This review showed no improvement in length of stay. This systematic review has highlighted the need for further studies to investigate the efficacy of a clinical sepsis pathway.

P345. Development and Implementation of a Subcutaneous Immunoglobulin Program in the Day Oncology setting at Northern Health

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Aim

To develop and implement a program to transition patients from receiving Intravenous Immunoglobulin (IVIG) to Subcutaneous Immunoglobulin (SCIG) in a Day Oncology setting at Northern Health.

Method

The National Blood Authority offered funding for public hospitals to provide a program for patients, who meet the criteria, to switch from IVIG to SCIG. Approval was sought from the organisation to fund a SCIG Program Coordinator at 1 day a week, to provide a dedicated support to patients as they transition from IVIG to SCIG.

Subcutaneous Immunoglobulin (SCIG) administration offers patients the opportunity to self-administer at home and reduce hospital visits.

Benefits to the organisation include, creating more capacity in Day Oncology Unit and providing opportunity to be a leader in the field of managing patients with immunodeficiency

In the initial phase an RN was recruited to coordinate the implementation of the SCIG program and to ensure a smooth transition for patients within the Day Oncology setting.

A working group was established with major stakeholders and the program guidelines were developed. The guidelines included patient engagement and recruitment, ordering and dispensing of products and education to Day Oncology staff.

An Education Booklet was designed for patients with information on the program and the benefits of self-administration at home, competency assessment form, and all information on safe handling, transportation and storage of the product. Contact details with name and phone number of the SCIG nurse was also included.

Results

The program development and guidelines were completed in the first 4 months of the appointment of the SCIG Coordinator. At the conclusion of June 2018, 5 patients have been successfully recruited to the program.

Conclusion

Northern Health has successfully established a SCIG program for patients with positive results. The transition has allowed patients to be able to take control in the decision making of their treatment regime.

P349. Effect of storage duration of cryopreserved haematopoietic progenitor cells on haematopoietic recovery

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Aim: The aim of this study was to assess the effect of storage duration of cryopreserved haematopoietic progenitor cells on haematopoietic recovery in multiple myeloma patients who had two autografts.

Method: Thirty nine patients with multiple myeloma were mobilised for autologous transplants between Jan 1996 to Dec 2016. Six patients who were either mobilised elsewhere or had second transplant at another centre were excluded from this study. CD34 cells were collected in single mobilisation using chemotherapy and GCSF until the end of PBSC collection.

Fresh stem cell harvests were stored at 2-8°C and were processed within 24 hours of collection. Frozen cells were cryopreserved using controlled rate freezer containing 10% DMSO as cryoprotectant solution. Products were cryopreserved into even number of bags with sufficient CD34 cells for two transplants. Cells were then stored in vapour phase of LN₂ storage tanks until required for the transplant.

FBC were performed until patient engrafted for absolute neutrophil counts (ANC) $\geq 0.5 \times 10^9/L$ three consecutive days and platelet counts $\geq 20 \times 10^9/L$ for three consecutive days unsupported.

Results: There was no significant difference between first and second transplant in terms of number of CD34 cells infused and time to neutrophil and platelet engraftment as demonstrated in table below.

Characteristics	First AHCT Mean (range)	Second AHCT Mean (range)	P value
CD34 cell dose $\times 10^6/Kg$	4.8 (2-11.4)	4.5 (2.04-9.1)	0.16
Storage duration (days)	79 (22-562)	1473 (118-4430)	-
Age (years)	55.2 (41-66)	59.1 (43.4-69.3)	-
Days to ANC $\geq 0.5 \times 10^9/L$	10.6 (8-15)	10.5 (9-13)	0.71
Days to Platelet $\geq 20 \times 10^9/L$	15.4 (11-19)*	16.8 (9-34)	0.07

*Two patients platelet counts never below $20 \times 10^9/L$

Regression analysis found no significant effect of storage duration between transplants, storage duration from time of harvesting or age at time of transplant or harvest on time to neutrophil or platelet engraftment.

Conclusion: Our results demonstrate that long term storage of HPC does not have any significant impact on haematopoietic recovery of ANC to $0.5 \times 10^9/L$ and platelet counts to $20 \times 10^9/L$.

P350. Evaluation of poor CD3+ viability and recovery post cryopreservation of allogeneic haematopoietic progenitor cell (HPC) and T Cell (TC) donations.

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Aim: To determine the cause of an observed and recurrent loss of CD3+ cells in allogeneic haematopoietic progenitor cell (HPC) and T Cell (TC) donations after cryopreservation, with a non-proportional reduction in CD34+ viability.

Method: A retrospective analysis of 41 allogeneic donor products collected by apheresis was performed. The pre/post thaw viability and CD3+ dose recovery (%) was assessed using single platform flow cytometry and 7AAD (7-amino-actinomycin D). The statistical analysis of multiple variables including, time from collect until cryopreservation (hours), type of collect (HPC(A) vs.TC(A)) and total nucleated cell (TNC) was performed to determine cause for poor post thaw CD3+ recovery.

Results: The average CD3+ viability prior to cryopreservation for all 41 products was 99% and 72% post thaw (mean difference of 27%) ($p < 0.001$). The mean CD3+ post thaw dose recovery was 59%. The mean post thaw recovery for the HPC(A) products ($n=35$) was 57% and 67% for TC(A) products ($n=6$). This was not statistically significant ($p = 0.363$). Of the 35 HPC(A) grafts processed, 10 processed immediately (storage < 3 hr) had a mean CD3+ cell recovery of 78% compared to a mean of 50% for the 25 grafts stored >18 hrs ($p < 0.001$). There was no corresponding effect on CD34+ recovery with increased storage ($p = 0.354$). No correlation between TNC and CD3+ post thaw recovery observed.

Conclusion: Of the variables analysed, it was observed that time from collection until cryopreservation had the greatest impact on viability and recovery of CD3+ cells in allogeneic products post thaw. Travelled grafts were subject to the greatest loss in CD3+ cells post cryopreservation. Although statistically there was no significant difference in the CD3+ cell recoveries between HPC(A) and TC(A) collections, one limitation of this study was the limited number of TC(A) products analysed. Data will continue to be collected and analysed.

P351. First use of CMV-specific T-cells to confer adoptive immunity in a Western Australian haematopoietic stem cell transplant recipient

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Since the dawn of allogeneic haematopoietic stem cell transplantation (HSCT), post-transplant cytomegalovirus (CMV) infection has been a major source of morbidity and mortality for recipients. This remains the case despite significant improvements in early post-transplant infection rates due to the development of effective strategies for monitoring CMV viraemia and timely initiation of pre-emptive treatment. In particular, late infection in the period following the first 100 days post-HSCT continues to pose a significant threat to HSCT recipients due to direct and indirect effects. Resistance to antiviral therapy presents significant clinical challenges in this context due to limited effectiveness of current alternatives such as CMV-hyperimmune IVIG and therapeutic tension from reducing immune suppression, increasing the likelihood of provoking or exacerbating graft versus host disease (GVHD). Adoptive immunity by infusion of ex-vivo cultured CMV-specific T-cells presents a promising new treatment strategy in the setting of drug-resistant CMV infection in HSCT recipients. We present a brief review of the literature of virus-specific T-cell therapy in transplantation and report the Fiona Stanley Hospital bone marrow transplant program's first experience with the use of adoptive CMV-specific T-cell therapy in a case of multiple drug-resistant CMV infection 1 year post-transplant.

P352. Both short-term and long-term cryogenic storage of HPC result in similar thawed viable CD34 recoveries and post infusion haematological recoveries

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Introduction

Most apheresis haematopoietic progenitor cells (HPC-A) are collected for imminent stem cell transplants. Sometimes CD34 doses exceeding more than one transplant are collected from excellent mobilisers. Half of the product may be stored for another transplant according to disease indications.

Aim

To assess the effect of long-term cryogenic storage of HPC-A on haematological recoveries and viable CD34 recovery.

Method

24 HPC-A products at Westmead Hospital BMT Lab were equally split between an imminent and a later transplant. Time to haematological recoveries (absolute neutrophil count (ANC) > 0.5x10⁹/L and platelet > 20x10⁹/L) after both transplants were compared. All patients were autologous donors for multiple myeloma. Post-thaw viable CD34 counts were analysed by flow cytometry using ISHAGE gating with analysis performed before the second transplant only if product has been in storage for >5 years. For statistical comparisons, two-tailed paired Student's t-test was used.

Results

ANC and platelet recovery times were similar between both transplants (n = 24)

Median (range)	First transplant	Second transplant	p-value
Cryogenic storage time (weeks)	4 (2-15)	192 (7-555)	<0.0001
Days to ANC > 0.5x10 ⁹ /L	11 (9-19)	10 (7-18)	0.1171
Days to platelet > 20x10 ⁹ /L	11 (0-18)	11 (0-18)	0.7376

No serious adverse reactions were observed.

WBC and CD34 recoveries were similar between first and second pilot-vial thaws (n = 14).

Median (range)	First thaw	Second thaw	p-value
Storage time at thaw	7 (4-9) days	6.3 (1.9-10.5) yrs	<0.0001
vCD34 % recovery	71% (35%-95%)	72% (36%-99%)	0.7286

Conclusion

There was no observed difference in either haematological recoveries post-transplant or vCD34 counts post-thaw between short-term and long-term cryogenic storage. Therefore HPC-A products cryogenically stored for up to 10 years are still safe and efficacious for stem cell transplants. It is now required each lab perform their own stability testing program as part of FACT accreditation.

P353. Snapshot of Calvary Mater Newcastle autologous haematopoietic cell transplant unit 2011-2018

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Aim

To conduct an unbiased audit of haematopoietic cell (HPC) collection and transplant information gathered from 2011-2018 in order to observe for trends that can be adjusted for and areas of improvement that will greater benefit our patients.

Method

Recorded data from all 292 patients that attended the Calvary Mater Newcastle Hospital for HPC harvest by apheresis (HPC-A) from January 2011 until April 2018 was collated into a single database. Median values were found for age, weight, cell numbers and collection volumes broken down by year and disease category (multiple myeloma, non-Hodgkin's lymphoma, Hodgkin's lymphoma, solid tumour and others, including Waldenstrom's and amyloidosis). Harvest yield was calculated as total volume of harvest to obtain total CD34⁺/μL, ideally a total volume of <500ml with CD34⁺>2000cells/μL. Median survival post-transplant was assessed overall and by disease.

Results

Of the 292 patients that underwent HPC-A in our hospital, 62% were male, 49% had Multiple Myeloma and the median age was 59 years (range 14-71). Overall 78% of patients went on to receive at least one reinfusion, and this has been a steady upwards trend from ~40% of patients in 2011 to ~69% patients harvested in 2017. Median survival post-transplant is 49 months, with some variability between diseases. Overall, there have been 64 patient deaths, of which 13 occurred pre-transplant.

The most important finding has been the drop in the yield of patient harvests, possibly related to harvest timing issues. This trend was restricted to collections from 257 patients with either Multiple Myeloma or Non-Hodgkin's Lymphoma.

Conclusion

Having all our spreadsheets in one workbook has given us a wealth of information that is yet to be fully tapped. But certainly, a more in-depth investigation into the cause of the drop in yield from particular groups of patient collections is warranted to improve overall patient care.

P354. Long Term Storage Effects of Cryopreserved Haematopoietic Progenitor Products (HPCs)

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Aim/Background

HPC products are cryopreserved for storage for prolonged periods between collection and infusion. Routine cryopreservation procedures use 10% DMSO cryoprotectant. Current storage policy of HPC is seven (7) years on NSW Health Bone Marrow Transplant (BMT) Network recommendations. This is to verify that cryopreserved HPC retains statistically significant viability compared to its original cryopreserved sample. Available HPC samples in long-term storage were tested. This validation was performed on samples that had post thaw viability performed via viable CD34+ cell enumeration. Viable CD34+ cell counts for historical samples were only available since November 2003. Previously CFU-GM culture assay methods were used.

Methods

HPC samples were tested on patients with excess cryovials. Following cryopreserved storage at below -150 0C in liquid nitrogen vapour phase, cryovials from patient samples were thawed at 37 0C and tested for CD34+ cell enumeration. The effect of long term storage (106 – 139 months) on the viable CD34+ cell dose of peripheral blood products from five patients (7 HPC collections) was tested. Cell dose, CD34+ cells (x 10⁶) per kg of patient's body weight at collection, was calculated and compared to that obtained after cryopreservation. Statistical analysis was performed to compared results

Results

The Pearson correlation test for CD34+ cell enumeration between the samples tested at time of cryopreservation and after storage was statistically significant. The Student's t-Test result is not statistically significant and thus no significant difference exists between the mean of two sample pairs. This indicates no significant difference in values tested.

Conclusion

Results indicate storage ranging from 106 to 139 months without any significant loss, as no significant difference exists in viable CD34+ cells after storage from samples tested at time of cryopreservation. Thus HPC viability does not deteriorate significantly up to 11.5 years thus greater than the period recommended by the NSW BMT Network storage period in the LN2 vapour phase.....

P355. Bone marrow processing on the Spectra Optia: A comparative study to the traditional marrow processing on the Cobe 2991 machine

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Aim

To evaluate the Spectra Optia for BM processing and to compare the results to the Cobe 2991 to determine if the new bone marrow processing procedure on the Spectra Optia is suitable for volume reduction and RBC depletion of bone marrow harvests before transplantation.

Method

Fifteen allogeneic marrows were processed on the Spectra Optia (n= 7 for adults and n= 8 for paediatric BMT patients). Statistical analyses was used for unpaired t-test to determine if there was a significant difference (p-value < 0.05) amongst the key parameters between the two machines.

Results

Table 1: Comparison of Spectra Optia to Cobe 2991:

Median (range)	Spectra Optia (n = 15)	Cobe 2991 (n = 38)	p-value
Volume Reduction %	91 (89 – 94)	88 (73 – 94)	0.0066
TNC Recovery %	59 (33 – 82)	76 (47 – 99)	<0.0001
MNC recovery %	83 (73 – 96)	83 (50 – 97)	Guttridge et al 2016 (n = 30)
RBC Reduction %	98 (98 – 99)	87 (67 – 98)	<0.0001
Viable CD34 Recovery %	90 (67 – 120)	91 (59 – 103)	NS

Conclusion

The Spectra Optia shows superior RBC volume reduction compared to the Cobe 2991. This is critical in the clinical setting and patient outcome of major ABO mismatch transplants where the laboratory has a defined release criteria of ≤ 0.5 mls/kg of RBCs per recipient weight. The superiority in volume reduction is also observed and reduces the volume for infusion or for further processing. There was no significant difference in the CD34 recovery percentage. Our laboratory's evaluation of the Spectra Optia demonstrates a replacement for the Cobe 2991. The laboratory's processing time of marrow is greatly reduced and it is easier for staff training with full automation.