Australia and New Zealand Consensus Position Statement: Use of COVID-19 therapeutics in patients with Haematological malignancies

Introduction

We are currently living with high rates of transmission of SARS-CoV2 in the community. While the high rate of vaccination has resulted in reduced overall hospitalisation and ICU admissions, the risk of severe disease or death from SARS-CoV2 infection (COVID-19) remains unacceptably high for immunocompromised patients with haematological malignancies (1). This is due to impaired humoral and cellular vaccine responses, the underlying disease and/or associated therapy, age and co-morbidities (2).

Before the availability of widespread vaccination, a meta-analysis of patients with haematological malignancies and COVID-19 revealed the risk of death among adult patients was 34%, with patients > 60 years of age having a significantly higher risk of death than those <60 (RR, 1.82; 95%CI, 1.45-2.27; N=1169) (1). While vaccination rates have increased dramatically since these data were collected, numerous studies have reported lower rates of seropositivity following COVID-19 vaccination in patients with haematological malignancies, and lower antibody titres among those who do achieve a response (3-6). Adding to the concerns is the issue of prolonged viral shedding in immunocompromised patients and its associated complications including recurrent illness, challenges in de-isolating patients, and psychosocial implications for patients who remain isolated for prolonged periods of time (4, 7). Effective management requires multidisciplinary care and education of the public, patients and community and hospital clinicians.

This position statement is intended to highlight relevant clinical issues specific to patients with haematological malignancies, but excluding those who are planned for or have received haematopoietic stem cell transplant or CAR T-therapies, whose needs are addressed by the Australia and New Zealand Transplant and Cellular Therapies (ANZTCT) position statements on vaccination and treatment (8, 9) . The relevant literature has been reviewed and selected by the expert authors. The authorship group includes malignant haematology experts in Australia and New Zealand, who have previously collaborated on guidelines on how to manage these diseases during the pandemic and vaccination (2, 10). Input was sought from key stakeholders including the Australasian Society of Infectious Diseases, the Haematology

Society of Australia and New Zealand, Leukaemia foundation, Lymphoma Australia, Myeloma Australia and Leukaemia and Blood Cancer New Zealand. Geographic representation, gender balance and diversity of backgrounds and disciplines were considered where possible. This position statement will be regularly reviewed and updated as further data on COVID-19 therapeutics emerge. Updates will be made on the HSANZ website www.hsanz.org.au.

Vaccine Reponses in Haematology Patients

Widespread vaccination has been crucial in reducing the morbidity, mortality and community impacts of COVID-19 infection. However, seropositivity or seroconversion following the administration of a COVID-19 vaccine; generally defined as SARS-Cov-2 spike IgG levels above a detection threshold or predefined serum antibody concentration; as opposed to the term seroprotection which is a more accurate surrogate for clinical protection; can be significantly reduced in patients with haematological malignancies (3, 11). A systematic review including 7064 patients with haematological malignancies after 2 dose of the COVID-19 vaccine showed that overall the seropositivity rates were 62-66% (11). There was a discrepancy in pooled vaccine responses based on the underlying disease, 51% in chronic lymphocytic leukaemia (CLL), 52-55% in lymphoma, 76-80% in myeloma, 87% in myeloproliferative neoplasms (MPN) including chronic myeloid leukaemia (CML) and 93% in acute leukaemia (11). These results were similar to those found in another systematic review of 2834 patients which reported serological response was seen in 42% with CLL, 52% with lymphoma, 66% with plasma cell dyscrasias, 83% with MPN, and 86% with acute myeloid leukaemia (3).

It is important to note that seroposivity rates also vary with specific treatment and timing of treatment. During active treatment seropositivity rates have been reported as low as 28% compared to 62% when patients are not on active treatment (11). The most vulnerable patient groups are those vaccinated within 12 months of CD-20 antibody therapy who had a seropositivity rate of 19% (compared to 61% when vaccination occurred > 12 months post treatment) (11). Similarly patients who had received targeted therapy such as a Bruton Kinase Inhibitor (BTKi) had a seropositivity rate of 35% (11).

Given the vulnerability of the group, studies have focussed specifically on patients with CLL, reporting impaired vaccine responses, regardless of their treatment, with 36.6% of treatment-naive CLL patients failing to seroconvert (defined as <50AU/mL SARS-CoV2 II IgG

antibody to spike protein) (5). Moreover, of CLL patients who were seronegative after 2 COVID-19 vaccine doses, only 23.8% seroconverted after a third dose (12).In CLL patients, titres of anti-spike antibody are low, with 75% of CLL patients failing to achieve neutralising activity against COVID-19 (5). A pooled estimate of seropositivity among those who had received anti-B-cell therapies (anti-CD20 antibodies, BTKis, or venetoclax) was 13% (5).

Patients with plasma cell dyscrasias have suboptimal COVID vaccine responses compared to normal controls (57% versus 81%) (13). Patients with monoclonal gammopathy of uncertain significance do not have significant differences compared with healthy controls however patients with smouldering myeloma and active myeloma do, regardless of treatment (13). Factors associated with vaccine response include, no active treatment (for > 6months) and a complete or partial remission with normal uninvolved immunoglobulin levels (13). Factors associated with suboptimal vaccine responses include grade 3 lymphopenia, active treatment, those who had received over three lines of previous therapy, and those receiving balantamab mafadotin, anti-CD38 or B-cell maturation antigen-targeted therapy (11, 13, 14).

Assessment of vaccine responses in MPN is complicated by the heterogeneity of disease (essential thrombocythemia, polycythaemia vera, CML and myelofibrosis) and by differential effects of treatment. In a study of vaccine responses in patients with haematological malignancies the most profoundly impaired responses were seen with the JAK inhibitor ruxolitinib, and the BTK inhibitor ibrutinib (15). In contrast, the response of CML patients treated with tyrosine kinase inhibitors and MPN patients treated with interferon-α was unaffected (compared to untreated individuals), whereas hydroxycarbamide was associated with reduced antibody titres (approximately 30% of the levels in untreated patients). An adverse impact of JAK inhibitor therapy on immune responses has been shown in several studies and appeared to be most significant in those with myelofibrosis (16, 17).

Serological responses to vaccines directed against seasonal influenza, Diphtheria-Tetanus-Pertussis and Haemophilus influenzae B are impaired in recipients of anti-CD20 therapy, but improve with time elapsed since anti-CD20 therapy, the best responses seen beyond 12 months. For example, seroconversion rates to influenza vaccination within 6 months of anti-CD20 therapy were significantly impaired in comparison to disease controls (relative benefit ratio of 0.22 [95% CI, 0.09-0.56] and 0.44 [95% CI, 0.23-0.84], respectively). However, by 6 to 12 months from anti-CD20 therapy the difference between groups narrowed, and by 12

months after anti-CD20 the response to vaccination was close to that of controls (1, 3). The profound impact of anti-CD20 therapy on serological response to vaccines is relevant when counselling patients, as they may be at elevated risk of developing severe COVID-19 disease even if fully vaccinated.

There may be discordance between cellular (T-cell) responses to vaccination and humoral (serological) responses. In CLL patients, over 80% of patients had SARS-CoV-2-specific T-cell responses in the normal range (5), the immune deficit being primarily humoral. A study evaluating serological and T-cell responses after mRNA vaccination in patients with CLL, B or T cell lymphoma and myeloma showed that T cell responses were detected in 86% of patients, as opposed to an overall seroconversion rate of 64.6% (18). Seventy four percent of the patients who were seronegative demonstrated a T cell response and only 13.1% had absent humoral and cellular responses (18). The correlation between T-cell responses and risk of severe COVID-19 disease is not well established. Despite this potential preserved cellular protection, it has been observed that over 40% of those who are fully vaccinated and hospitalised with COVID-19 are immunocompromised (19, 20). Finally, there is limited data on the durability of vaccine response among those with haematological malignancies who do respond to vaccination.

Risk mitigation strategies

This group has previously published consensus position statements on risk mitigation strategies, underlying disease management and vaccination of patients with haematological malignancies during the COVID-19 pandemic (2, 10). Advice in this area is likely to change with infection rates, emerging variants, and contemporaneous evidence of immune response durability. If possible, haematology patients should be vaccinated at least 2 weeks before immunosuppressive treatment (2) . However, urgent treatment must not be delayed in order to facilitate COVID-19 vaccination. Patients should be counselled regarding their risks of COVID-19 disease including at initiation of treatment. We recommend that patients are provided with clear instructions regarding what to do if diagnosed with COVID-19 in the community.

<u>Pre-exposure prophylaxis</u>

Patients at the highest risk of severe COVID-19 disease are those unable to generate an immune response to vaccination. For these individuals, passive immunotherapy with long-acting monoclonal antibodies can provide much needed additional protection.

A long-acting dual monoclonal antibody, tixagevimab and cilgavimab, (Evusheld®) binds to the SARS-CoV2 spike protein at 2 sites, to prevent viral entry into host cells. It is reported to reduce the risk of developing symptomatic COVID-19 infection by 77% (95% confidence interval 46.0,90.0) versus placebo (P<0.001) when tested in patients who were not vaccinated against COVID-19 and who were at increased risk of severe disease because of comorbidities including immune compromise, obesity and COPD (21). Tixagevimab/cilgavimab may offer up to 6 months protection following two intramuscular doses, which can be given simultaneously at two different intramuscular sites (22). This agent is recommended for immunocompromised patients who cannot be vaccinated or are at high risk of a poor response to vaccination (23). It is recommended that tixagevimab/cilgavimab administration is delayed by at least 2 weeks following COVID-19 vaccination.

While anticipated lack of an anti-spike protein vaccine response (which correlates with lack of anti-SARS-CoV-2 neutralisation activity) can be used to prioritise individuals for receipt of Tixagevimab/cilgavimab, this is not widely available (5). Tixagevimab/cilgavimab could be considered for patients who are least likely to respond to vaccination. Patients who have received haematopoietic stem cell transplantation and CAR-T therapy should be prioritised however this group's needs are addressed in the ANZTCT guidelines (8). The following groups with haematological malignancies who should be considered for Tixagevimab/cilgavimab (in order of least to more likely to respond to vaccination):

- Patients on BTKi, BCL2 inhibitors and JaK2 inhibitors and patients who have received anti CD20 therapy in the last 12 months.
- Patients who have received anti CD38, anti-antibody drug conjugates and bispecific agents in the past 6 months.
- Patients with CLL, other lymphoid malignancies and multiple myeloma who are considered clinically unlikely to respond to vaccination.
- Patients with acute leukaemia or myeloid disorders who are considered clinically unlikely to respond to vaccination.

Tixagevimab/cilgavimab can also be considered before initiation of therapy based on vaccination history, disease risk, B-cell depleting potential of the underlying treatment, and the likelihood of response to future vaccination. If patients receive passive immunotherapy with tixagevimab and cilgavimab during therapy or before potential B-cell depleting therapy, it may be optimal to re-dose with tixagevimab and cilgavimab at 6 months and/or offer additional vaccination doses 6-12 months after B-cell depletion, when an immune response is more likely to be achieved (11).

At this time the neutralising activity of tixagevimab/cilgavimab appears to be reduced with newer variants of SARS-CoV-2 and increased dosing maybe required (24).

During community COVID-19 spread, selection of an appropriate facility for the delivery of this treatment may require consideration of both patient exposure risk and resource constraint. Haematology units need to consider implementation strategies to ensure patients are informed of their eligibility and to facilitate equitable access.

Treatment

This group supports treatment guidelines by the National COVID-19 Clinical Evidence Taskforce, and the New Zealand Ministry of Health and Cancer Agency Te Aho o Te Kahu COVID-19 Guidelines (25, 26) . The authors acknowledge that at the time of writing, availability of monoclonal antibodies is limited, and that emerging SARS-CoV-2 variants may render some products unsuitable. Furthermore, the data supporting the treatments discussed below does not include younger children.

<u>Mild to Moderate COVID-19</u>

Anti-SARS-CoV-2 Monoclonal antibodies

Sotrovimab is a recombinant human IgG1-kappa monoclonal antibody, which binds extracellular COVID-19 and facilitates antibody dependent cell-mediated cytotoxicity and antibody dependent cellular phagocytosis. It can reduce the risk of disease progression as measured by all cause hospital admissions and all cause death in high-risk patients (relative risk reduction, 85%; 97.24% confidence interval [CI], 44 to 96; P=0.00), it was also found to reduced ED presentations and ICU admissions (27). There is no contraindication to the use of sotrovimab in those with significant renal or hepatic impairment. The terminal half-life of

sotrovimab is less than 2 months, limiting it to treatment rather than prophylaxis, and vaccination should be deferred until 3 months following sotrovimab infusion to maximise vaccination responses. Importantly, efficacy has only been shown when administered within 5 days of symptom onset, in patients with mild to moderate disease. Several other anti-SARS-CoV-2 monoclonal antibodies are available for mild to critical COVID-19 infection, including casirivimab and imdevimab. Of note, the activity of this agent depends on the underlying variant of SARS-CoV-2, and it is unlikely that sotrovimab is effective against the B.1.1.529/BA.2 strains (28, 29).

Antiviral agents

Nirmatrelvir plus ritonavir (Paxlovid): Nirmatrelvir is a protease inhibitor, and ritonavir, when used in combination, inhibits its CYP3A metabolism. Paxlovid is indicated in patients with mild COVID-19 disease and no oxygen requirement who are within 5 days of symptom onset. The treatment course is nirmatrelvir 300mg (2 x 150mg) plus ritonavir (100mg) po bd for 5 days. It is contraindicated in severe liver disease and in those with severe renal impairment (eGFR < 30 mL/min/1.73 m2). Dose reduction (nirmatrelvir 150mg + ritonavir 100mg) is recommended in patients with eGFR 30-60 mL/min/1.73 m2. There are multiple drug interactions to be aware of with the use of Paxlovid. The ritonavir component is a strong CYP3A inhibitor, and can increase concentration and toxicity risk of many cancer therapies including BTK inhibitors, venetoclax, brentuximab, vincristine, ruxolitinib and prednisone. Of particular concern is the increased concentration of venetoclax; this combination should be avoided during the venetoclax dose escalation phase of venetoclax due to the elevated risk of tumour lysis syndrome. Supportive agents including azole antifungals such as voriconazole and immunosuppressants such as ciclosporin are also affected by ritonavir, and are likely to require dose modification and/or close therapeutic drug monitoring.

Molnupiravir (Lagevrio): is a ribonucleoside analog that inhibits SARS- CoV-2 replication. It should be administered within 5 days of illness onset in those with mild symptoms and no oxygen requirement. Molnupiravir 800mg (4x200mg) po bd is administered as a 5 day course of treatment with no requirement for dose adjustment for age or renal or hepatic impairment. It is contraindicated in pregnancy (category D). Molnupiravir is associated with an increased SARS-CoV2 mutagenesis (30). which could be a concern for immunosuppressed

patients at risk of prolonged viral shedding. However, it has fewer drug interactions than nirmatrelvir plus ritonavir.

Steroids: Inhaled budesonide and systemic dexamethasone are adjunctive treatments, the latter indicated in patients who have developed an oxygen requirement. Prolonged and high steroid use in patients with haematological malignancies should be supported with PJP, antiviral and antifungal prophylaxis as clinically indicated.

Moderate to Severe disease

Patients with haematological malignancies and moderate to severe disease due to COVID-19 infection should receive multi-disciplinary care from experts in intensive care, infectious disease and respiratory medicine in collaboration with the treating haematologist. In addition to standard COVID-19 management strategies such as anticoagulation, prone nursing and oxygen supplementation, the haematologist can assist in providing guidance regarding the level and duration of immunosuppression of the patient depending on their treatment and underlying disease and can oversee therapeutic drug monitoring for example in patients on antifungal prophylaxis and viral reactivation risks and can suggest escalation of care or adjuncts specific to the needs of patients with haematological malignancies such as intravenous immunoglobulin (IVIG) for patients with hypogammaglobulinaemia or granulocyte colony stimulating factor for neutropenic patients.

Monitoring of Patients with COVID-19

We recommend that patients with COVID-19 receive standard of care monitoring via their local hospital COVID-19 pathway, as well as regular review, by Telehealth where appropriate, by a haematologist or clinician experienced in managing immunocompromised patients, to advocate in the event of deterioration, to monitor disease resolution, and to ensure that disease-related follow up is not overlooked. If patients are on ongoing treatment for their underlying haematological malignancy close follow up to screen for recurrence of symptoms that my necessitate re-testing and retreatment is needed.

Prolonged viral infection, issues with de-isolation and viral reactivation

Immunocompromised individuals can also have prolonged COVID-19 infection and viral shedding (31-33) which in part may relate to the development of T-cell exhaustion (2).

Consequently, this can cause difficulty in de-isolating patients following infection, as well as delayed manifestations of COVID-19. Anecdotally there have been several cases of patients experiencing re-infection or failure to clear infection within the first few months of infection. There is mixed guidance regarding surveillance testing and re-treatment. Increasingly, use of PCR cycle threshold (Ct) and viral cultures may be used to guide management and de-isolation of patients with persistent PCR positivity (34, 35). Cycle threshold on PCR testing correlates inversely with viral load, and is a surrogate marker proposed for clearance testing. Assays vary in sensitivity making identification of a universal Ct cut-off difficult, however higher Ct values are thought to be associated with a low risk of infectivity. Haematologists should liaise with local infection control, microbiology and infectious diseases teams to interpret local values. Viral culture is also useful if positive, however test accuracy is dependent on specimen quality so negative results should be interpreted with caution, and in conjunction with Ct values. Correlation between high Ct and negative viral culture has been established. Viral culture may not be readily available at all centres. If viral culture is not available, then high Ct, symptom resolution and negative rapid antigen test could be relied on to determine safety to deisolate. Importantly symptom recurrence following resolution of symptoms should prompt re-testing. COVID positive patients who remain SARS-CoV-2 culture positive, have low Ct values or who have declining Ct values after a course of treatment should be evaluated for additional or continuing antiviral therapies in consultation with their haematologist and a medical virologist Infectious diseases/ microbiology specialist with expertise in managing COVID-19. No recommendation to deisolate can be made whilst there is evidence of ongoing replication-competent viral shedding however additional psychosocial support should be offered if this resource is available given the impacts of prolonged isolation in this patient population (7). In a persistently positive patient who remains SARS-CoV-2 culture positive or who has falling Ct values following treatment, the decision to release from isolation should be made by the treating clinician and local infectious diseases/infection prevention teams.

Mitigating Treatment Delays Due to COVID-19 positivity

Patients initiating chemo- or immune-therapy for a haematological malignancy in a hospital setting should be screened for COVID-19 by PCR or rapid antigen testing. If possible, we recommend delay of therapy until PCR negative and asymptomatic. Optimal delay between infection and treatment is unknown and proceeding with treatment may need to be weighed

against the severity of symptoms and the urgency of treatment. If patients are a close contact prior to treatment, we recommend a 14 day deferral period if possible, given the infection latency period. We recommend that patients who become positive following initiation of therapy should be treated as described above with COVID appropriate treatment and the decision to proceed with therapy be based on clinical urgency and need.

Long COVID

The long term impact of COVID on patients with haematological malignancies is yet to be established, particularly in terms of quality of life. We recommend where possible, considering multidisciplinary approaches, in collaboration with respiratory and rehabilitation physicians. Local models for screening, assessment and management of long COVID are emerging.

Summary of Recommendations

Prevention

- Patients should be counselled regarding their increased risk of severe COVID-19 infection in the setting of sub-optimal vaccine responses
- Patients should be ideally fully vaccinated 2 weeks prior to treatment as per local guidance but crucial therapy such as induction therapy for acute leukaemia must not be delayed
- Patients should be counselled regarding their risks of COVID-19 including at initiation of treatment
- Provide clear patient education regarding actions to take in the event of community COVID-19 diagnosis
- Patients with anticipated suboptimal vaccine response based on disease or treatment should be offered pre-exposure prophylaxis with tixagevimab and cilgavimab:
    - Patients on BTKi, BCL2 inhibitors and JaK2 inhibitors and patients who have received anti CD20 therapy in the last 12 months.
    - Patients who have received anti CD38, anti-antibody drug conjugates and bispecific agents in the past 6 months.

    - Patients with CLL, other lymphoid malignancies and multiple myeloma who are considered clinically unlikely to respond to vaccination.
    - Patients with acute leukaemia or myeloid disorders who are considered clinically unlikely to respond to vaccination.
- Patients who receive tixagevimab and cilgavimab in an attempt to protect patients during a period of treatment or during a period of B-cell depletion should be provided with a vaccination plan (e.g. additional doses and timing) following completion of therapy.

Treatment

- Patients with mild to moderate COVID-19 should be offered antiviral treatment as early as possible.
- Remote care services to manage COVID-19 positive patients in the home and the hospital setting require oversight by a haematologist or clinician experienced in managing immunocompromised patients
- COVID-19 infection should be managed in accordance with best practice at the time of diagnosis, as advised by Infectious Diseases, Respiratory and Intensive Care specialists, and in line with current guidelines from the National COVID-19 Clinical Evidence Taskforce and the New Zealand Ministry of Health and Cancer Agency Te Aho o Te Kahu COVID-19 Guidelines.
- Site-specific treatment pathways in patients with haematological malignancies with COVID-19 are encouraged to ensure supply and facilitate timely administration of treatments
- Caution is recommended regarding potential drug interactions and renal and liver impairment when using nirmatrelvir plus ritonavir

Post-infection monitoring and de-isolation

- Guidelines in this area are rapidly evolving, and confirmation with local regulations is recommended
- Consider the use of PCR cycle threshold (Ct) and viral cultures to guide management and de-isolation of patients with persistent PCR positivity

- Patients with persistent positivity; where viral culture is not available, Ct value and symptom resolution could guide deisolation
- In persistently positive patients, discussion with local Infectious Disease specialist is recommended, and extended psychosocial supports should be offered where possible
- Symptom recurrence following resolution of symptoms should prompt re-testing
- Patients with long COVID where possible should be managed with the support of a multidisciplinary team including respiratory and rehabilitation physicians

Mitigating COVID related treatment delays

- Patients initiating chemo- or immune-therapy for a haematological malignancy in a hospital setting should be screened for COVID-19 by PCR or rapid antigen testing
- If positive we recommend delay of therapy until PCR negative and asymptomatic if possible.
- If patients are a close contact prior to treatment, we recommend a 14 day deferral period if possible given the infection latency period
- Optimal delay between patient infection and proceeding to treatment is unknown but this needs to balance the urgency of treatment and severity of symptoms

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Lane, S.

Dickinson, M.
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Ho, P. J.
Cochrane, T.
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Berkahn, L.
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Armytage, T.
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Tam, C
Hamad, N

Endorsements (pending)

- HSANZ
- ALA
- Myeloma Australia MSAG
- ASIC
- Leukaemia Foundation
- Lymphoma Australia