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POSITION PAPER

Australia and New Zealand Transplant and Cellular Therapies (ANZTCT) position statement: COVID-19 management in patients with haemopoietic stem cell transplant and chimeric antigen receptor T cell

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Abstract

Patients with post-haemopoietic stem cell transplant or chimeric antigen receptor T -cell (CAR-T) therapy face a significant risk of morbidity and mortality from coronavirus disease 2019 because of their immunosuppressed state. As case numbers in Australia and New Zealand continue to rise, guidance on management in this high-risk population is needed. Whilst we have learned much from international colleagues who faced high infection rates early in the pandemic, guidance relevant to local health system structures, medication availability and emerging therapies is essential to equip physicians to manage our patients optimally.

Background

Two years into the coronavirus disease 2019 (COVID-19) pandemic, novel challenges continue to emerge. As the community moves towards high daily case numbers and circulating virus, or so-called 'COVID normal', the risk for adult immunocompromised patients remains high.[1] In the paediatric setting, data are lacking and the risks of morbidity and mortality are likely lower than in the adult setting.

In addition to the physical risk of COVID-19, there are additional psychosocial implications for patients who have received haemopoietic stem cell transplants and chimeric

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antigen receptor T-cell (CAR-T) therapies (TCTs). Many patients report significant anxiety about COVID-19, and it is not always safe to isolate in the early post-TCT period as patients recuperate at home postdischarge.[2] Another challenge in this cohort is prolonged postinfection viral shedding, which can create challenges for access to medical care as well as other household members needing to isolate.

Transplant and cellular therapies are lifesaving interventions and cannot routinely be postponed because of the risk of intervening disease relapse. This has forced great innovation and collaboration internationally by TCT clinicians to ensure access to safe and timely therapy against COVID-19 for patients with TCT.

This position statement is intended to highlight relevant clinical issues unique to patients with TCT and was developed in accordance with the Australia and New Zealand Transplant and Cellular Therapies (ANZTCT) policy for consensus practice/position statement development. The relevant literature has been reviewed and selected by expert authors. The authorship group includes ANZTCT board members who have sought representatives from all TCT centres in Australia and New Zealand and key stakeholders including the Australasian Society of Infectious Diseases, the Haematology Society of Australia and New Zealand, the Australian and New Zealand Bone Marrow Donor Registries, the Leukaemia Foundation and the Leukaemia & Blood Cancer New Zealand. The ANZTCT is committed to equity, diversity and inclusion so geographic representation, sex balance and diversity of backgrounds and disciplines was 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 ANZTCT website at www.anztct.org.au.

Risk mitigation and service strategies for TCT units

Site-specific protocols for COVID-19 mitigation and management have been required to address the evolving challenges. Some strategies employed include the use of telehealth to limit face-to-face contact, hospital and clinic visitor restrictions, surveillance screening of staff, patients and visitors with rapid antigen or polymerase chain reaction (PCR) tests and provision of appropriate personal protective equipment (PPE) to staff and patients. Rotating staff rosters has also been employed at some sites to minimise workforce shortages due to furlough requirements. Ensuring that staff, contractors and visitors are vaccinated is also important.[3]

Adding complexity to risk-mitigation strategies, there are significant logistic challenges related to the management of COVID-19–positive TCT outpatients. Where feasible, positive patients are seen outside of haematology/oncology clinical areas to reduce the risk of transmission to other immunosuppressed patients. Pathways to facilitate ongoing care of such patients vary according to local resources, however, may include pop-up clinics for phlebotomy, transfusion and outpatient COVID-19 treatment or segregated areas within established clinical services. If no other resources are available, patients may be referred to emergency departments with dedicated COVID-19 patient care spaces. Remote care services designed to manage SARS-CoV-2–positive patients in the home are valuable for patients with TCT who have minimal symptoms but require oversight by TCT clinicians.[4]

Symptomatic testing and surveillance strategies have also evolved, with an increasing reliance on rapid antigen tests for case diagnosis. For patients unable to privately access rapid antigen tests, or with significant symptoms despite a negative rapid test, PCR testing is recommended. Ensuring the availability of a dedicated testing space has been a challenge for many sites with the gradual move away from hospital PCR clinics. Testing facilities are also needed for patients requiring repeat PCR or viral culture to confirm clearance of COVID-19 in the event of persistent rapid antigen test positivity.

Patients with COVID-19 requiring admission in the peri-TCT period present a further challenge, due to the need to minimise risk of exposure to other haematology patients. We recommend that patients with TCT who are known or suspected to be positive for COVID-19 be isolated on dedicated COVID-19 wards. To limit exposure risk to other inpatients, where possible, dedicated TCT staff should be assigned for the management and review of COVID-19–positive patients, to ensure that required TCT-related monitoring takes place. Where possible, patients with TCT without COVID-19 should be placed in single rooms to minimise their inpatient exposure risk.

Because TCTs are only available at major urban centres, many patients receiving these therapies are required to relocate from regional and rural areas during their treatment. Organisations such as the Leukaemia Foundation in Australia assist in provision of accommodation for these patients, often to facilities with communal kitchen and/or bathroom facilities. The best way to isolate COVID-19–infected patients with TCT in this setting, or indeed to protect them from infected cohabitants requires attention, and solutions will need to be locally specific depending on resource availability.

Prevention

Vaccination

The ANZTCT has recently published a COVID-19 vaccination position statement that outlines Australian and

New Zealand expert consensus on vaccination of patients with TCT, but advice in this area is likely to change with infection rates, emerging variants and contemporaneous evidence of immune response durability.[5,6] There is evidence of poor serological vaccination responses amongst TCT recipients,[7,8] although T-cell responses appear to be reasonable. When to start vaccination to achieve optimal protective humoral and cellular immune responses is yet to be determined in this population; however, current recommendations are to vaccinate between 3 and 6 months post-TCT. If patients receive tixagevimab and cilgavimab (Evusheld) post-TCT, it may be optimal to revaccinate at 6 months post-TCT, when immune response is more likely to be achieved. Importantly, all patients with TCT require a full revaccination course following transplant or CAR-T therapy, regardless of their pretreatment vaccination status. There are also limited data on the response durability or the impact of post-TCT immunosuppression and/or graft-versus-host disease on vaccine response.

Serological testing in this patient population is of limited utility. Even in the presence of seroconversion, whether this confers ability to mount an adequate immune response in the setting of antigenic challenge is unknown. Furthermore, serial testing would be needed as hypogammaglobulinaemia can develop over time in this clinical cohort.

Preexposure prophylaxis

Tixagevimab/cilgavimab is a dual monoclonal antibody therapy that binds to the SARS-CoV-2 spike protein to prevent viral entry into host cells.[9] Tixagevimab/cilgavimab may offer up to 6 months of protection following two intramuscular doses, which can be given simultaneously at two different intramuscular sites.[9] This agent is recommended for immunocompromised patients at highest risk of poor response to vaccination.[10] There is evidence suggesting it retains effectiveness against the emerging Omicron BA.4/5 strains in addition to the dominant Omicron BA.2 variant.[11] It is recommended that tixagevimab/cilgavimab administration is delayed by at least 2 weeks following COVID-19 vaccination. Tixagevimab/cilgavimab could be considered prior to TCT, based on vaccination history and disease risk, but ideally should be given as soon possible post-TCT in clinically stable patients with adequate count recovery, or with platelet support for safe intramuscular injection. Identifying an appropriate facility for the rapid delivery of this treatment requires consideration of both patient exposure risks versus resource-constrained haematology/oncology ambulatory care units.

Treatments

The ANZTCT 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.[12,13] It is important to acknowledge that treatment strategies will continue to evolve with the emergence of new variants. Whilst the current case numbers prevent routine sequencing outside of surveillance programmes, sequencing may be of use in the future to facilitate variant-specific therapy.

The authors acknowledge that the data supporting the treatments discussed below are in some cases extrapolated from data in immunocompetent hosts and do not apply to younger children.

Mild to moderate COVID-19

Anti-SARS-CoV-2 monoclonal antibodies

Sotrovimab is a recombinant human IgG1-kappa monoclonal antibody that binds extracellular COVID-19, facilitating both antibody-dependent cell-mediated cytotoxicity and antibody-dependent cellular phagocytosis.[14] Based on local experience, it has been widely used and well tolerated in patients with TCT infected with COVID-19 during the Omicron wave. 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 monoclonal antibodies depends on the underlying strain of SARS-CoV-2 and currently casirivimab/imdevimab is thought to be less effective against the Omicron strain, and it is unlikely that sotrovimab is effective against the B.1.1.529/BA.2 strains.[15,16]

Other agents to consider in patients with TCT who have mild to moderate disease

Both local and international guidelines on COVID-19 treatment often group TCT patients with immunocompromised or high-risk patients, despite evidence of low vaccine responses and particularly high mortality rates in recipients of TCT.[1,7,8,17] In addition to monoclonal antibody therapy, other agents that can be considered in patients with TCT who have mild to moderate disease include remdesivir, inhaled budesonide, nirmatrelvir

with ritonanir (Paxlovid) and molnupiravir. Of note, molnupiravir has been associated with increased SARS-CoV-2 mutagenesis,[18] which is of particular concern in a population of patients at risk of prolonged viral shedding. Caution is recommended with the use of molnupiravir in patients with TCT for this reason. Nirmatrelvir with ritonavir (Paxlovid) is contraindicated in patients using calcineurin inhibitors or sirolimus due to major drug interactions through the CYP450 pathway, as well as patients with significant renal or liver impairment. Ritonavir interacts with many agents, so a thorough medication review should be undertaken if this agent is considered. Sarilumab and tocilizumab are interleukin 6 inhibitors, which have shown some benefit in reducing the immune response to infection.

Considerations for patients with TCT and severe COVID-19

In patients requiring treatment for severe or critical COVID-19, optimal management requires a multidisciplinary approach. This should include a TCT haematologist to monitor and manage TCT complications such as therapeutic drug monitoring, graft-versus-host disease, viral reactivation, cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome and hypogammaglobulinaemia. This is in addition to standard COVID-19 management strategies such as anticoagulation, prone nursing and oxygen supplementation. A summary of COVID therapeutics and their potential adverse effects in patients with TCT is shown in Table 1.

Convalescent plasma

The benefit of convalescent plasma for immunosuppressed patients with COVID-19 is uncertain as data from this group are lacking, and there is potential for harm.[20,21] Convalescent plasma containing high-titre neutralising antibodies against SARS-CoV-2 is recommended either within a clinical trial, or if suitable monoclonal antibody therapies are unavailable.

Monitoring of TCT patients with COVID-19

Rates of severe and critical COVID-19 are high in patients with TCT, with international reports of 30-day mortality of 32% in haemopoietic stem cell transplant recipients during the initial COVID-19 wave.[22] Mortality amongst CAR-T cell recipients is reportedly as high as 41%.[17] We recommend informed consent regarding these risks when TCT treatment is proposed, and facilitation of access to COVID-19 therapeutics if patients are infected. We recommend that TCT patients with COVID-19 receive standard of care monitoring through their local hospital COVID-19 pathway, as well as regular review, by telehealth where appropriate, by a TCT clinician to advocate in the event of deterioration, monitor disease resolution and ensure that TCT-related follow-up is not overlooked. We recommend that TCT recipients are provided with clear instructions regarding what to do if they are diagnosed with COVID-19 in the community. The risk of prolonged viral infection in patients with TCT is well documented, and prolonged infection has been associated with viral evolution and development of resistance mutations.[16]

Deisolation of TCT patients with TCT and COVID-19

One challenge in patients post-TCT is persistent viral RNA shedding and resultant difficulty in establishing safety for deisolation. In addition to resolution of symptoms, the exclusion of replication-competent viral shedding must be established in order for patients to deisolate. While there is some variability internationally on specific deisolation criteria for immunosuppressed patients, there is increasing use of PCR cycle threshold (Ct) and viral culture to inform deisolation eligibility in patients with persistent PCR positivity.[23,24] Cycle threshold on PCR testing correlates inversely with viral load, and is one surrogate marker proposed for clearance testing. Assays vary in sensitivity making identification of a universal Ct cutoff difficult; however, higher Ct values are thought to indicate a low risk of infectivity. TCT units should liaise with local infection control, microbiology and infectious diseases teams to identify local laboratory cutoffs. 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.[25] It is important to acknowledge that significant variability in the availability of Ct and viral culture has been reported across Australian TCT centres. If viral culture is not available, then high Ct, symptom resolution and negative rapid antigen test must be relied on to determine safety to deisolate. Importantly, symptom recurrence in patients with TCT following the resolution of symptoms should prompt retesting.

For patients who remain viral culture positive or with high Ct values beyond 20 days, ongoing isolation may cause significant psychosocial pressure for both the patients and their household members. No recommendation to deisolate can be made whilst there is evidence of ongoing replication-competent viral shedding; however, additional

Table 1 COVID-19 therapeutics and potential challenges in patients with TCT[19]

Therapeutic agent	Indication	Used in patients requiring oxygen	Use in ventilated patients	Potential CYP 450 interaction	Relevant adverse effects
Tixagevimab/cilgavimab	• Sars-CoV-2 prophylaxis	No	No	No	
Casirivimab plus imdevimab: anti-spike protein monoclonal antibodies	• Non-Omicron infection • Mild disease	Yes	No		Pruritis, urticaria, erythema, dizziness lymphadenopathy post subcutaneous injection
Remdesivir: RNA polymerase inhibitor	• Mild-moderate disease • Within 7 days of symptom onset	Yes	No	Yes	Rash, headache transamimtis
Molnupiravir: ribonucleoside analogue	• Mild disease • Within 5 days of symptoms onset	No	No		Dizziness
Nirmatrelvir with ritonavir: protease inhibitors	• Mild-moderate disease • Unvaccinated • Within 5 days of symptoms onset	No	No	Yes Contraindicated with calcineurin inhibitor use	
Sarilumab: IL-6 inhibitor	• Moderate to severe disease	Yes	Yes		Neutropenia, leukopenia
Tocilizumab: IL-b inhibitor	• Moderate to severe disease • Evidence of systemic inflammation	Yes	Yes		
Dexamethasone	• Severe disease	Yes	Yes	Yes	
Baricitinib: JAK1 inhibitor	• Moderate to severe disease			Yes	Rare cytopenias

COVID-19, coronavirus disease 2019; CYP450, cytochrome P450; IL, interleukin; TCT, chimeric antigen receptor T-cell therapy.

psychosocial support should be offered if this resource is available. 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 COVID-related obstacles in TCT

TCT donors should be screened prior to cell product collection as per the Australian Bone Marrow Donor Registry guidelines. We recommend screening for COVID-19 using PCR within 24 to 72 h of collection initiation. We recommend cryopreservation of cellular product where possible to avoid delays due to donors testing positive. There is a latency from infection to shedding so where fresh product infusion is planned, an isolation period of 7 days as well as PCR testing prior to mobilisation should be considered. Donors should also be encouraged to take precautions to reduce the risk of contracting COVID-19 in the weeks leading up to donation. If donors of fresh product test positive for COVID-19, we recommend a 7-day deferral period after full recovery or 7 days after the most recent positive result, for asymptomatic infections. If a donor becomes positive following mobilisation but prior to collection, we recommend consultation with the donors' transplant physician with regards to safety to proceed with collection. We recommend a 14-day donor deferral after close contact. In the setting of urgent allogenic stem cell transplantation, earlier donations should be considered on a case-by-case basis.[26]

Within 72 h prior to initiation of conditioning or lymphodepleting therapy, patients should undergo PCR screening for COVID-19. If positive, treatment delay is recommended until the patient is PCR negative and asymptomatic. Optimal delay between infection and TCT is unknown; however, transplant has been performed as early as 44 days following infection and this may need to be weighed against the severity of symptoms and the urgency of proceeding to transplant.[27] If patients are a close contact prior to TCT, we recommend a 14-day deferral if possible. We recommend that patients who become positive following conditioning or lymphodepleting therapy should proceed with infusion of cell products in conjunction with COVID-19 appropriate treatment and monitoring as outlined above, acknowledging the paucity of evidence to guide patient management in this situation.

Long COVID

The long-term impact of COVID-19 on patients with TCT is yet to be established, particularly in terms of quality of life and potential interaction with graft-versus-host disease. We recommend where possible, considering multidisciplinary approaches in managing patients with TCT who have long COVID, in collaboration with respiratory and rehabilitation physicians. Local models for screening, assessment and management of long COVID are emerging.

Summary of recommendations

Prevention strategies

- Telehealth utilisation, visitor restrictions, PPE use, surveillance programmes
- Vaccination of recipient and donor prior to TCT where possible, and revaccination of recipient from 3 to 6 months post-TCT, according to local guidelines (at least three primary doses and booster/s), regardless of tixagevimab/cilgavimab use
- Dedicated testing/management area, emergency department TCT pathway, dedicated TCT COVID-19 case clinician, patient education, clear remote management pathways
- Administration of tixagevimab/cilgavimab post-TCT, unless contraindicated.

Treatment approach

- Early treatment is essential in TCT patients, consulting infectious diseases, respiratory and/or intensive care specialists, and in accordance with local guidelines from the National COVID-19 Clinical Evidence Taskforce and New Zealand Ministry of Health and Cancer Agency Te Aho o Te Kahu COVID-19 guidelines.

Postinfection monitoring and deisolation

- Patients may deisolate after two negative SARS-CoV-2 PCR or rapid antigen tests
- In patients with persistent positivity beyond 20 days, viral culture, PCR Ct and/or symptom resolution may guide deisolation, in discussion with infectious diseases
- Symptom recurrence following resolution should prompt retesting
- Patients with long COVID should ideally be managed by a multidisciplinary team including respiratory and rehabilitation physicians.

Mitigating COVID-related obstacles during TCT

- Cell therapy products should be cryopreserved when possible, to avoid critical delays
- If fresh cellular product use is essential, donor isolation for 4 to 7 days prior to collection, with PCR at collection, is recommended
- For donors who are positive or close COVID-19 contacts, follow Australian Bone Marrow Donor Registry guidance
- All donors should be screened by PCR within 24 to 72 h of collection and recipients within 72 h prior to conditioning or lymphodepletion
- Patients who are close contacts prior to TCT should ideally be deferred for 14 days
- The optimal delay between patient infection and proceeding to TCT is unknown
- Once conditioning or lymphodepletion has commenced, TCT should proceed in patients with interval COVID-19 positivity with appropriate COVID-19 treatment.

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