Editorial

Learning How to Treat COVID-19 in HSCT Patients

On Manuscript

Early Administration of SARS-CoV-2 Monoclonal Antibody Reduces the Risk of Mortality in Hematologic Malignancy and Hematopoietic Cell Transplant Patients with COVID-19

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Proposed tweet:

Authors @victoriahall26 @benwteh from @NCICancer explore the important & challenging topic of Learning How to Treat COVID-19 in HSCT patients, with updates in novel therapies and review of the use of SARS-CoV-2 monoclonal antibodies.

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Haematopoietic stem cell transplant (HSCT) recipients and patients with haematological malignancy (HM) are at high risk of significant morbidity and mortality from SARS-CoV-2 infection, with an estimated at least 2.5 fold increased risk of death.[1] In HSCT patients, estimated mortality from centres of European Group for Blood and Marrow Transplantation was approximately 25%, and similar for autologous and allogeneic-HSCT patients.[2] Risk factors for severity include older age, higher immunodeficiency scoring index group (based on neutrophils $<0.5 \times 10^9$/l, lymphocytes $<0.2 \times 10^9$/l, age ≥40 years, myeloablative conditioning, graft vs. host disease, use of steroids and HSCT < 30 days) and poor performance status.[2, 3]

The aims of treatment of SARS-CoV-2 infection are based on the pathogenesis of COVID-19, where there is an initial viral phase that may be followed by an inflammatory phase, the latter of which can be the cause of a high mortality rate. In HSCT patients however, there may be a prolonged viral phase, with some patients shedding virus for months and the inflammatory phase may be dysfunctional, weakened and/or delayed due to the underlying HM and its treatment.[4] The current therapies available and recommended as beneficial for the general population for moderate to severe COVID-19 **(Table 1)** have been extrapolated to HSCT patients. To add to the armamentarium against SARS-CoV-2 infection, early treatments for mild COVID-19 **(Table 1)** in this vulnerable population are now available and recommended. To date, data has been lacking regarding the evaluation and use of these treatment strategies, including monoclonal antibodies (MAb), in patients with HM/HSCT. In the current issue of ***Transplant Infectious Disease*** Jabr et al[5] report a retrospective, uncontrolled cohort of 59 HM/HSCT patients with COVID-19 who received either casirivimab-imdevimab or bamlanivimab from November 21, 2020 to September 30, 2021, during the alpha and delta variant SARS-CoV-2 waves in Miami, Florida. Nearly half of

these patients (25/59, 42%) had received cellular therapy; comprising 14/59 (24%) allogeneic HSCT, 9/59 (15%) autologous HSCT, and 2/59 (3%) chimeric antigen receptor T-cell (CAR-T) therapy.[5] There was a relatively even mix of different HM groups, including 22/59 (37%) with lymphoma and 12/59 (20%) with MDS/AML.[5] In those patients (46/59, 78%) who received early treatment of mild COVID-19 as outpatients with either MAb, none required subsequent hospitalization, nor was there documented progression of disease, including no deaths in this group.[5] A smaller proportion of patients did receive these therapies off-label as inpatients (13/59, 22%), and fared worse, with 2 out of 3 deaths in the hospitalized group attributable to COVID-19.[5]

Over the course of the pandemic, there has been an increasing number of mutations in the receptor binding domain (RBD) of the spike protein of SARS-CoV-2, the primary target for vaccine-induced immunity and monoclonal antibody-based therapy.[6] Consequently, the neutralizing ability of therapeutic MAb have significantly reduced, for example, against the Omicron variant sublineage BA.2, both casirivimab-imdevimab and bamlanivimab, examined by Jabr et al, have lost effective neutralizing activity.[5, 6] Sotrovimab is also no longer recommended due to in vitro resistance by BA.2.[6] The antiviral therapies however, seem to be less affected, with similar susceptibilities of Omicron/BA.2 to remdesivir, molnupiravir, and nirmatrelvir to those of the ancestral strain and other variants of concern, and now are considered first line for treatment of mild COVID-19.[6] Remdesivir and Molnupiravir are both nucleoside analogues, whereas nirmatrelvir is a protease inhibitor packaged with ritonavir, a strong cytochrome P450 3A4 inhibitor, to achieve therapeutic levels.[7-9] These antivirals were not examined in this cohort study for mild COVID-19 as they were likely not available or not in routine use during the study period.[5] Although there is no head-to-head trial, in individually assessed large, placebo-controlled randomised trials (RCT) of

unvaccinated, high-risk outpatients with mild to moderate COVID-19, remdesivir and nirmatrelvir/ritonavir (paxlovid) had superior reduction in the risk of hospitalization or death compared with molnupiravir (87-89% vs 30%).[7-9] Further evaluation of these antiviral therapies in patients with HM/HSCT are required, including the use of nirmatrelvir/ritonavir given the number of potential drug-drug interactions in cancer patients on medications utilizing the cytochrome P450 (CYP3A4) system. There have also been recent concerns of antiviral rebound in high-risk persons who received the standard 5-day course of paxlovid as early treatment of COVID-19.[10]

Although the observational period of this study ended on September 30, 2021, only 14/59 (24%) of patients were recorded to have received at least one dose of vaccine. This is of interest, given the widespread availability of the mRNA vaccines and the FDA recommendation for a third dose to immunocompromised patients, including HSCT patients, of COVID-19 vaccine since mid-August 2021. In patients who have undergone cellular therapy, a full re-vaccination schedule is suggested to commence at least 3 months from the time of transplant (including CAR-T cell therapy). The patients in this cohort were not close to the time of transplant (median time from autologous or allogenic HSCT to COVID-19 diagnosis 412-609 days), and therefore are recommended to be vaccinated when it is available to them. Due to recognized lowered vaccine immunogenicity and effectiveness in HM/HSCT patients, three doses of SARS-CoV-2 vaccine is now considered the primary course and additional doses the booster(s).[11] The advent of breakthrough infection in this cohort is therefore not surprising, given a sub optimally vaccinated population and known reduced 1 and 2 dose vaccine effectiveness.[12]

Pre-exposure prophylaxis due to the expected high-risk of COVID-19 and reduced humoral immune response to COVID-19 vaccination with the monoclonal antibody combination tixagevimab and cilgavimab (Evusheld) is available and indicated for patients with HM / HSCT.[13] This was likely not available to non-clinical trial patients during the study period by Jabr et al. Evusheld is a recombinant human anti-SARS-CoV-2 MAb given intramuscularly that bind to non-overlapping portions of the SARS-CoV-2 spike protein RBD, preventing the virus from interacting with the human ACE2 receptor.[13] It has a long half-life and has been approved for use for 6 months duration. In a phase III RCT that did include a small proportion of immunocompromised patients, it significantly reduced the risk of symptomatic COVID-19 compared with placebo.[13] Details regarding the number of patients with HM/ HSCT in this trial however are lacking, and this study was performed prior to the Omicron variant. Against omicron/BA.2, tixagevimab/cilgavimab still demonstrates neutralizing activity but has been recommended to be given at double the initial dose based on in vitro data showing significant fold reduction in the neutralization of omicron/BA.1.[6, 13, 14]

The effectiveness of early, outpatient use of MAb therapy in this study by Jabr et al is encouraging, including the lack of protracted COVID-19. In this context, the role of passive immunotherapy has been suggested, including available MAb or high titre convalescent plasma, the latter of which has led to clinical improvement in patients with profound B cell lymphopenia and prolonged COVID-19 symptoms.[15] Antiviral treatment might also be useful in selected patients outside of the recommended timeframe, although should be balanced with the risk of emergence of SARS-CoV-2 escape mutations.[16, 17]

Jabr et al should be commended for their study, which significantly adds to the literature, providing a comprehensive and detailed description of the effectiveness of early outpatient treatment of COVID-19 by the available MAb during the alpha and delta variant SARS-CoV-2 waves in patients with HM/HSCT. In line with prior evidence from the general population, MAb therapy appeared to be less effective against progression of disease in hospitalized patients. Due to cumulative mutations in the spike protein and subsequent reduction in neutralizing activity of MAb therapy, antiviral agents have now become first line in management of mild COVID-19. Ongoing evaluation of these therapies, and newer MAb as they are developed for treatment of mild COVID-19, as well as pre-exposure prophylaxis, and investigational treatments are required. Continual emphasis of optimal vaccination of immunocompromised patients should be encouraged, including their household and close contacts and exercising public health measures.

Table 1. Current treatment options for COVID-19 in HSCT/HM patients

Severity of illness	Recommendations	Comments for HSCT/HM patients
None • *Pre-exposure prophylaxis*	Long-acting anti-SARS-CoV-2 MAbs (tixagevimab/cilgavimab, EVUSHELD™) in those at risk for severe COVID-19 and not expected to mount an adequate humoral immune response to COVID-19 vaccination[13] • Expected duration of protection 6 months • May be re-dosed after 6 months • In individuals who have received a COVID-19 vaccine, should be administered at least two weeks after vaccination	Recommended for HSCT or CAR-T within 2 years of transplant, or on immunosuppressive medications ie for active GvHD[13] • Not a substitute for vaccination in individuals for whom COVID-19 vaccination is recommended (can be given to those patients within 90 days post-transplant) • Proceed with caution in those on anticoagulant therapy or thrombocytopenia
Mild • *No new or additional requirement for supplemental oxygen therapy from baseline status*	Antiviral therapy • Remdesivir, 3 days[8] • Ritonavir/nirmatrelvir[9] • Molnupiravir[7] Anti-spike monoclonal Ab therapy • Depending on availability and current guidelines for efficacy against dominant circulating variant High-titre convalescent plasma • If above therapies not available and within 72 hours of symptom onset[18]	Caution for drug-drug interactions with ritonavir/nirmatrelvir in patients on concomitant medications utilizing the cytochrome P450 (CYP3A4) system – seek expert Infectious Diseases and Pharmacy consultation. Baseline liver and renal function should be assessed in patients prior to commencement of antiviral therapy.
Moderate • *Hospitalized, receiving low flow oxygen therapy, with clinical or radiological evidence of lower*	Antiviral therapy • Remdesivir, 5 days[19] Anti-inflammatory • Dexamethasone 6mg daily for 10 days[20] • Consider baricitinib as an alternative if corticosteroids are contraindicated[21]	Remdesivir has shown benefit to faster rates of recovery in patients with cancer, most pronounced in those with low flow oxygen requirements and within 10 days of symptoms.[19] There was a detrimental effect when dexamethasone was used in those not requiring oxygen during the earlier viral phase of COVID-19.

respiratory tract infection	Adjunctive anti-inflammatory if CRP ≥ 75 mg/dl or other available inflammation parameters or score and have evidence of progression despite 24-48 hours of dexamethasone and within 14 days of COVID-19 diagnosis • Anti-IL-6 monoclonal therapy ie tocilizumab[22] OR • JAK 1/2 inhibitor ie baracitinib[23]	The effects of immunomodulatory therapies targeting COVID-19 in HSCT/HM patients whom are already immunosuppressed is poorly understood given the small numbers of these patients represented in trials; the risks and benefits for the individual patient require consideration.
Critical • *Ventilatory or circulatory support, including high flow nasal oxygen, non-invasive ventilation, invasive mechanical ventilation or extra-corporeal membrane oxygenation*	Antiviral therapy • Remdesivir, 5 days may be considered in those patients requiring high flow oxygen but is *not indicated* for patients requiring invasive mechanical ventilation[19] Anti-inflammatory • Dexamethasone 6mg daily for 10 days[20] • Consider baricitinib as an alternative if corticosteroids are contraindicated[21] Adjunctive anti-inflammatory if CRP ≥ 75 mg/dl or other available inflammation parameters or score and have evidence of progression despite 24-48 hours of dexamethasone and within 14 days of COVID-19 diagnosis • Anti-IL-6 monoclonal therapy ie tocilizumab[22] OR • JAK 1/2 inhibitor ie baracitinib[23]	For immunosuppressed patients with acute respiratory failure and COVID-19, it is also important for the clinician to consider other infectious co-pathogens including invasive fungal infection and thromboembolic risk.

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