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REVIEW: CORONAVIRUS DISEASE (COVID-19) IN PATIENTS WITH HEMATOLOGIC MALIGNANCY

Introduction

The Coronavirus disease that emerged globally in 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was first identified in December 2019, with rapid worldwide spread leading to a pandemic soon after. Three years later, although the virus now holds a diminished role in the public agenda, COVID-19 remains a real and present danger for patients with hematologic malignancy (HM).^{1,2} This paper provides an overview of the risks of COVID-19 in patients with HM, the effectiveness of vaccination, and management strategies in these vulnerable patients.

Outcomes of COVID-19 in Patients with Hematologic Malignancy

Patients with HM have impaired immune function due to the malignancy itself and as a consequence of HM treatments.

Immune dysfunction can affect all aspects of the immune system including disruptions to mucous membranes and other protective barriers; impaired innate immunity with reduced and/or dysfunctional granulocytes; and diminished adaptive immunity including low baseline antibody levels, delayed and/or reduced seroresponse, and impaired T cell response.³⁻⁶ These deficiencies result in increased vulnerability to infection, increased severity of illness and, in the case of COVID-19, prolonged viral clearance.⁷⁻¹⁰ B-cell depletion therapy, in particular, can greatly diminish seroresponse to vaccines and infection, and significantly increases the risk of severe COVID-19.³⁻⁵

At the outset of the pandemic, reports from Wuhan, China had already noted a more severe COVID-19 disease course and a higher case fatality rate in patients with HM infected with SARS-CoV-2.² In the numerous global reports that

followed, hospitalization rates were reported to be between 56% to 74%, intensive care unit (ICU) admission rates ranged from 10% to 24%, and case fatality rates ranged from 14% to 52% during the early waves of the virus.¹¹ A meta-analysis conducted during the early phase of the pandemic estimated a 34% risk of death in hospitalized patients with HM.¹ It is possible that selection bias augmented early estimates of COVID-19 mortality in patients with HM as initial reports were heavily skewed to hospitalized patients; however, with the passage of time it has become certain that patients with HM are at higher risk of serious morbidity, as well as mortality, than patients without cancer, and are even at higher risk than patients with solid tumors.¹¹ Predictors of worse outcomes in patients with HM include older age; specific subtypes of HM (higher risk for lymphoid malignancies and acute myeloid leukemia [AML]); higher comorbidity burden; having active malignancy; and receiving particular treatments (e.g., cellular therapy).¹²⁻¹⁴ During the last two years of the pandemic, the SARS-CoV-2 virus has continued to evolve leading to surges of new variants of concern (VOC) with increased transmissibility and immune escape. Despite this viral evolution, COVID-19 outcomes have improved over time,^{15,16} a trend that has also been observed among those with HM infected with SARS-CoV-2.^{17,18} For example, a recent study reporting on >1,500 patients with HM in the EPICOVIDEHA registry demonstrated reduced hospitalization rate (53% vs 73%), decreased ICU admission rate (10% vs 18%), and lower mortality (9% vs 31%) when compared to earlier in the pandemic.¹⁸ These improved outcomes are likely the result of several factors, including the natural evolution of SARS-CoV-2 leading to reduced virulence, immunologic protection from vaccination or past infection, and improved COVID-19-directed treatments. However, the relative contribution of each of these factors is difficult to tease out. Nevertheless, even in the contemporary era of COVID-19, it is widely recognized that patients with HM remain at increased risk of poor outcomes.¹¹

Prevention of SARS-CoV-2 Infection

Vaccination

One of the impressive success stories of the COVID-19 pandemic is the speed with which effective vaccinations were developed. Vaccines against SARS-CoV-2 became available in Canada in late 2020. Randomized controlled trials (RCTs) have demonstrated that all of the vaccines approved for use in Canada are highly efficacious in preventing severe COVID-19 infection,¹⁹⁻²¹ and real-world studies have confirmed that the vaccines are effective in preventing hospitalization and death.²² However, patients with cancer were excluded from vaccine RCTs and are under-represented in many population studies. Fortunately, large retrospective studies have recently been completed

which demonstrate that patients with HM also benefit from COVID-19 vaccination, although not to the same extent as patients without cancer, or even to the same extent as those with solid tumors.^{23,24}

Due to the technical challenges involved with assessing T cell response post-vaccination, most clinical studies have reported vaccine-mediated humoral response. It has been observed that breakthrough COVID-19 infections correlate with lower levels of anti-spike IgG and neutralizing antibodies, suggesting the importance of serologic response in protective immunity against COVID-19.²⁵ Patients with HM, particularly those with lymphoid malignancy and/or receiving B-cell depletion therapy, have impaired vaccine-mediated antibody responses, contributing to the vulnerability of this patient population.²⁶ Some of the lowest seroresponses have been observed in patients with chronic lymphocytic leukemia (CLL), irrespective of therapy. This has occurred among patients with prior or ongoing exposure to anti-CD20 therapy; in those receiving Bruton's tyrosine kinase inhibitors (BTKi's); and among recent cellular therapy recipients, including chimeric antigen receptor T-cell (CAR-T) therapy and stem cell transplant.²⁷⁻²⁹

Real-world studies have demonstrated that patients with cancer experience more rapid antibody waning than the general population following primary vaccination series,^{24,30} suggesting that earlier and greater booster doses may be required for ongoing protection from COVID-19. Recent clinical data from patients with cancer demonstrated that booster doses could seroconvert some patients who were previously negative, even among patients with lymphoid malignancies such as CLL. However, patients who received anti-CD20 therapy within one year of vaccination do not appear to derive the same benefit.^{27,31,32} For instance, a recent study by Shen et al evaluated seroconversion rates in patients with CLL and monoclonal B-cell lymphocytosis (MBL) following multiple (up to 8) COVID-19 vaccine doses; virtually all patients who were previously seronegative ultimately converted to seropositive.³³ Collectively, existing data support the use of repeated vaccine boosters to improve SARS-CoV-2 antibody levels among patients with HM.^{27,34} Moreover, despite poor humoral response to vaccination, up to 80% of patients treated with anti-CD20 therapy mounted a cellular T cell response; this may translate to some degree of protection even in the absence of antibody response.³⁵

Few clinical studies have addressed COVID-19 vaccine clinical effectiveness specifically in patients with HM. In a U.K. retrospective study conducted prior to the emergence of the Omicron variant, patients with cancer had 66% vaccine effectiveness for breakthrough infection; HM patients demonstrated reduced effectiveness.²⁴ In a matched comparative analysis using a population-based dataset from Ontario, including Omicron infections, patients with HM

had a higher risk of breakthrough infections and COVID-19-related poor outcomes versus noncancer controls and patients with solid cancers.²³ Booster vaccination reduced this risk, except for those who received anti-CD20 therapy in the year prior.³⁶

Nevertheless, although the relative risk of COVID-19 severe outcomes in patients with HM remains elevated, the absolute risk of death is much lower as compared with the pre-vaccination era³⁶; and vaccination remains the most important line of defense against COVID-19 for all patients, including those with HM. Strategies to improve immune responses include repeated vaccinations, maximizing vaccination prior to BCDT where possible, and revaccination three months following stem cell transplantation or CAR-T therapy.²⁵ Another important strategy is to optimize COVID-19 immunity among family members and caregivers of patients with HM via complete and up-to-date COVID-19 vaccination.

Pre-exposure Prophylaxis

Earlier in the pandemic, tailored antibodies directed against the SARS-CoV-2 spike protein were demonstrated to be a promising therapy to prevent severe COVID-19 in immunocompromised patients. Based on the PROVENT trial, the combination therapy tixagevimab/cilgavimab was approved as pre-exposure prophylaxis in patients with HM receiving immunosuppressive therapy such as anti-CD20 therapy and BTKi, as well as in transplant or CAR-T recipients.³⁷ Unfortunately, viral evolution has resulted in mutations in the SARS-CoV-2 spike protein, allowing immune escape from all commercially available monoclonal antibodies including tixagevimab-cilgavimab, and its use is no longer recommended.³⁸ However, research to develop monoclonal antibodies directed against more highly conserved portions of the virus is ongoing, and it is possible that monoclonal antibodies may prove to be useful again in the future.³⁹

Management

In addition to vaccines, new or newly re-purposed medical therapies have been developed to reduce the morbidity and mortality of COVID-19 in the outpatient and inpatient settings. Here-in, we provide a brief overview of COVID-19 management, current at the time of publication. With more than 3,000 trials of COVID-19 treatment registered,⁴⁰ the field of COVID-19 therapeutics is rapidly evolving, and we encourage readers to refer to rigorous, evidence-based guidelines available on this topic; in particular, the World Health Organization maintains a living, open-access guideline of COVID-19 therapeutics (<https://app.magicapp.org/#/guidelines>).⁴¹

Outpatient treatments

The first therapy approved by Health Canada for the treatment of COVID-19 was remdesivir, an intravenous

(IV) therapy. Remdesivir was approved by Health Canada on July 27, 2020, for treatment of SARS-CoV-2 pneumonia causing hypoxia. However, based on the PINETREE trial in non-hospitalized, unvaccinated patients at high risk for disease progression (5.3% had a cancer diagnosis), remdesivir's treatment indication was expanded to include non-hypoxic out-patients at risk of progression to severe COVID-19 in April, 2022. The PINETREE trial reported an 87% relative risk reduction (RRR) in hospitalization or death vs placebo when remdesivir was administered within seven days of symptoms onset.⁴² Despite demonstrated efficacy, the three-day IV regimen poses logistical challenges for the outpatient population. As well, evidence of benefit in vaccinated individuals, or in those with natural immunity, is sparse and the benefits are likely lower in this setting. Nevertheless, real-world evidence suggests that remdesivir use is associated with decreased mortality in patients with HM.⁴³

Ritonavir-boosted nirmatrelvir is an oral protease inhibitor that inhibits the SARS-CoV-2 protease critical for viral replication. It was approved by Health Canada on January 17, 2022, for the treatment of patients with mild-to-moderate COVID-19 based on the EPIC-HR trial in high-risk, unvaccinated individuals. The trial reported reduced COVID-19 hospitalizations/death from 6.4% to 0.8% vs placebo.⁴⁴ Although prospective data on the effectiveness of nirmatrelvir/ritonavir is lacking among vaccinated or naturally immunized individuals, due to its ease of use it has rapidly become first-line therapy for out-patients at risk of severe COVID-19. At the time of this writing, a 5 day course of nirmatrelvir/ritonavir is indicated as first-line treatment for symptomatic outpatients with mild-to-moderate COVID-19 presenting within 5 days of symptom onset. Of note, its use is complicated by drug-drug interactions due to ritonavir-mediated CYP3A4 inhibition. Numerous drugs used to treat HM have important interactions with ritonavir requiring either dose adjustments or avoidance. Detailed information on drug interactions with nirmatrelvir/ritonavir is available via open-access resources including the Liverpool COVID-19 Drug Interaction Checker (<https://www.covid19-druginteractions.org/checker>)⁴⁵ and the University Health Network drug-drug oncology interaction checker (<https://www.antimicrobialstewardship.com/paxlovid-ddi-oncology>).⁴⁶ Nirmatrelvir-ritonavir requires dosing modifications in cases of renal impairment, as well as avoidance in patients with severe hepatic impairment (<https://doi.org/10.47326/ocsat.2022.03.58.3.0>).

Three SARS-CoV-2 neutralizing antibody therapies have been authorized by Health Canada for reducing the risk of severe COVID-19 in non-hospitalized, high risk patients: bamlanivimab, casirivimab plus imdevimab, and sotrovimab. However, similar to prophylactic monoclonal antibody treatment, these monoclonal antibodies are no longer

recommended as dominant circulating strains of SARS-CoV-2 in Canada have reduced susceptibility to these agents.⁴⁷

In summary, nirmatrelvir-ritonavir (oral) and remdesivir (IV) are the two treatment options currently recommended for ambulatory patients with mild-to-moderate COVID-19 in Canada (**Figure 1**).^{48,49} Both of these agents require initiation shortly after symptom onset in order to be effective. Oncologists and hematologists can play a key role in counselling patients with HM regarding how to recognize the symptoms of COVID-19 and the importance of prompt testing to facilitate early COVID-19 treatment. New therapeutic strategies are currently under active evaluation, including oral analogues of remdesivir⁵⁰ and a single dose of subcutaneous pegylated interferon lambda,⁵¹ and may become available in the future.

Inpatient treatments

A number of important inpatient therapies have been developed for those with severe-to-critical COVID-19 (**Figure 1**). Patients with mild-to-moderate COVID-19, hospitalized for non-COVID-19 indications, should be treated in the same manner as outpatients with COVID-19, with either a three-day course of IV remdesivir or a five-day course of nirmatrelvir/ritonavir. Patients admitted with severe COVID-19 requiring supplemental oxygen but not requiring invasive ventilation may benefit from a

five- to ten-day course of IV remdesivir.⁵² A recent meta-analysis of this population suggests a slight mortality reduction and decreased need for mechanical ventilation.⁵³ A ten-day course of dexamethasone 6 mg is recommended for the treatment of COVID-19 in hospitalized patients who require non-invasive or high-flow supplemental oxygen, given the mortality benefit demonstrated in the RECOVERY trial.⁵⁴

For patients with critical COVID-19, particularly those with elevated inflammatory markers, the addition of the anti-interleukin 6 (IL-6) monoclonal antibody tocilizumab or Janus kinase (JAK) inhibitor baricitinib should be considered.⁵⁵ None of the trials of the above-mentioned COVID-19 therapeutics included patients with HMs; nonetheless, most experts recommend that these patients be treated similarly to those without HMs with severe COVID-19, with the caveat that treating clinicians should be mindful of the further immunosuppressive effects of these therapies and the potential implications for infectious complications.

Although case series have reported convalescent plasma effectiveness in patients with HM, its routine use is controversial as large clinical trials have failed to demonstrate efficacy and its use is operationally challenging.¹¹

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COVID-19 outcomes in patients with blood cancer



SARS-CoV-2 vaccination is effective in patients with blood cancer

While COVID-19 morbidity and mortality is decreasing, it remains 2-fold higher in patients with blood cancer compared to no cancer and solid cancer

Immunologic response:
 Humoral response 40-77%
 Cellular response 53-79%

Vaccine effectiveness:
 Infection: 52.9% for blood cancer (65.5% all cancer)
 Hospitalization: 84.5% (all cancer)
 Mortality: 93.5% (all cancer)

Predictors of worse outcomes:
 age ≥60-75, comorbidity burden, active cancer, subtype (lymphoma, CLL, myeloma, AML)

High risk for blunted vaccine response:
 Lymphoma/CLL, BTKi, anti-CD20 treatment, ASCT, CAR-T



Patient with hematologic malignancy with SARS-CoV-2 infection

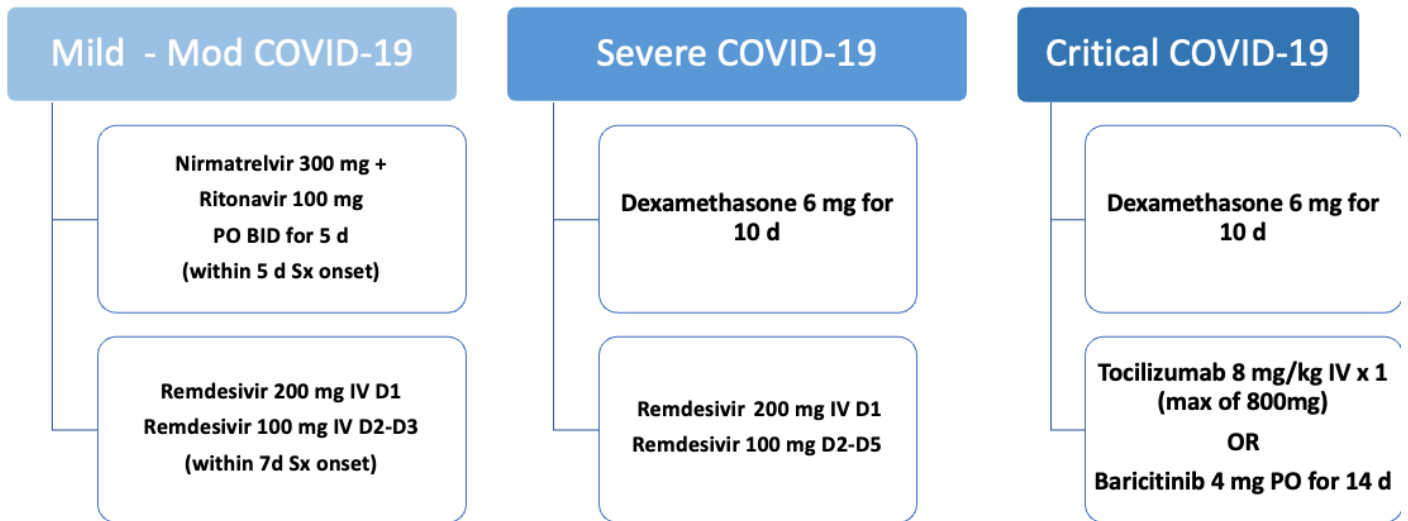


Figure 1. Overview of COVID-19 outcomes, vaccine efficacy and treatment strategies for patients with hematologic malignancy; courtesy of Inna Gong, MD and Lisa Hicks, MD

For non-critically ill, hospitalized patients, therapeutic intensity anticoagulation with heparin or low molecular weight heparin (LMWH) is suggested over prophylactic intensity, based on evidence from three RCTs.⁵⁶ For critically ill patients, prophylactic intensity anticoagulation is recommended.⁵⁶

Conclusion

Clinicians caring for patients with HM have an important role to play as the COVID-19 pandemic stretches into its fourth year. Despite major scientific advances, patients with HM remain uniquely vulnerable to hospitalization, morbidity and mortality from COVID-19. Vaccination is the most important defence against COVID-19, even among patients with HM who may have an attenuated or initially absent vaccine response. The benefits of vaccination for patients with HM have been shown in real-world population-based studies, and encouraging patients

with HM, their household contacts, and their caregivers (including healthcare workers) to stay current with vaccination is an important part of contemporary HM care. Teaching patients how to recognize COVID-19 infection, as well as the importance of early testing to facilitate outpatient anti-viral treatment, is also critical. Finally, one of the most important things that oncologists can undertake to reduce COVID-19 morbidity and mortality is advocacy. As COVID-19 retreats from the front pages of newspapers it is incumbent upon experts in HM to remind healthcare, civic and government leaders that COVID-19 remains a threat for our patients.

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