COVID-19 Patients with Hematologic Malignancies

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Patients with hematological malignancies have an increased risk of serious outcomes following COVID-19 infection, suggesting broader protection is needed beyond vaccination. Monoclonal antibodies such as sotrovimab, casirivimab–imdevimab, and bamlanivimab have provided valuable options for the treatment of COVID-19 disease. More recently, monoclonal antibodies have been examined for the prevention of COVID-19 infection.

COVID-19 coronavirus hematology malignancy

1. Introduction

Since the COVID-19 pandemic was first reported in China in December 2019, cases have exploded globally, with a total of 3.3 million cases and 36,630 deaths reported in Canada as of 2 March 2022 [1]. Although people of all ages are at risk of infection, the probability of more serious disease is greater in people with chronic medical conditions, who are 60 years or older, or who are living in nursing homes or long-term care facilities [2]. People who are immunocompromised are one such group with an increased risk of serious outcomes following COVID-19 infection [3]. Immunocompromising conditions are defined as those that suppress humoral or cellular immunity as a result of health conditions or medications [4]. Based on data from Statistics Canada, about 14% of Canadians fit into this higher-risk immunocompromised category [5]. Examples of patients with immunocompromising conditions include [6]:

- Active treatment for solid tumor and hematologic malignancies;
- Receipt of a solid-organ transplant and taking immunosuppressive therapy;
- Chimeric antigen receptor (CAR) T-cell therapy or hematopoietic stem cell transplant (HSCT);
- Moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott–Aldrich syndrome);
- Advanced or untreated human immunodeficiency virus (HIV) infection.

In addition to having an increased risk of severe outcomes from COVID infection, studies have shown that people who are immunocompromised do not have the same level of protection from COVID-19 mRNA vaccines [7][8][9]. Real-world vaccine studies have shown high effectiveness in the general population, ranging from 65% to 90%

against infection or mild disease and 90% to 100% against severe infection after two doses of BNT162b2 (Pfizer), AZD1222 (AstraZeneca), or mRNA-1273 (Moderna) [10][11][12][13]. However, vaccine effectiveness rates in immunocompromised populations after two doses of an mRNA vaccine are lower, at around 60% against clinical disease [9] and 77% against hospitalization [4]. Vaccine effectiveness varies widely even within the immunocompromised population, ranging from 59% (e.g., solid organ transplant) to 81% (e.g., rheumatoid arthritis) against hospitalization [4]. Moreover, there is a lack of clinical access to effective antibody testing for vaccine response in Canada and these tests have not been adequately evaluated for their ability to determine immunity or protection from COVID-19 [14]. It is therefore difficult to predict how people will respond to vaccination and their level of protection from severe COVID-19 outcomes. In addition, with the advent of new variants of concern (VOCs), such as Omicron (subvariants BA.1, BA.1.1. and BA.2), vaccine effectiveness against hospitalization has been reduced, requiring three doses in order to achieve comparable protection to two doses with the Delta (B.1.617.2) variant [15]. As of 5 April 2022, the National Advisory Committee on Immunization has also recommended a fourth dose of a COVID-19 vaccine in Canada, prioritizing adults 80 years of age and over and residents of long-term care homes and congregate living centers [16]. A discretionary recommendation is also given for adults 70–79 years of age. It is expected that the introduction of a third and fourth dose of a COVID-19 vaccine will increase the response and provide additional protection in a proportion of patients [17][18].

2. Risk of COVID-19 in Patients with Hematologic Malignancies

Patients with hematological malignancies, such as leukemias, myelodysplastic syndromes, myeloproliferative neoplasms, lymphomas, and multiple myeloma, have an increased risk of infections as a result of disease-related immune dysregulation [19]. In addition, many commonly used treatments may have an immunosuppressive effect, adding to the risk of infection [19]. For example, treatment with B-cell-targeting therapies, resulting in B-cell depletion and/or disruption of the B-cell receptor signaling pathway, may adversely affect the production of antibodies in response to COVID-19 vaccination [20]. B-cell recovery may also be slow in these patients; for example, in lymphoma patients, recovery was shown to remain below normal controls one year after administration of rituximab [21]. In addition, patients undergoing HSCT are at particularly high risk of immunosuppression due to impairment in innate and adaptive immunity [22]. In the case of allogeneic HSCT, patients generally need ongoing immune suppressive therapy to treat and prevent graft-versus-host disease [22]. Although data are limited, preliminary studies suggest patients with hematological malignancies who are receiving CD19-directed CAR T-cell therapy also have a reduced response to COVID-19 vaccines [23].

Seroconversion rates following COVID-19 vaccination have shown to be reduced in patients with hematologic malignancies. An Israeli study in 427 people showed that a lower proportion of those with hematologic malignancies were seropositive after COVID-19 vaccination than in an immunocompetent comparator group (75% vs. 99%; $p < 0.001$) [24]. Moreover, patients treated for hematologic malignancies ($n = 164$) had significantly less seropositive responses (e.g., immunochemotherapy (29%); anti-CD20 antibodies (0%); or BCL2 (25%), BTK (40%), or JAK2 (42%) inhibitors; $p < 0.001$) [24]. In addition, the prospective CAPTURE (COVID-19 antiviral

response in a pan-tumor immune monitoring) study showed seroconversion rates following COVID-19 vaccination were lower in 21 patients with haematological malignancies (59%) than in those with solid tumours (85%) [25]. Overall, 81% had received chemotherapy, 48% had received targeted therapy, and 29% had received anti-CD20 therapies in the 12 weeks prior to vaccination. In addition, a study of 121 patients with non-Hodgkin's lymphoma, including chronic lymphocytic leukemia (CLL), showed an 85-fold reduction in mean anti-SARS-CoV-2 spike immunoglobulin G–binding titers in these patients compared with healthy controls, with seroconversion occurring in only 67% of patients [26]. Overall, 47% of patients had received anti-CD20-directed therapy within one year prior to COVID-19 vaccination. Finally, a systematic review of five studies examining the response to COVID-19 vaccination in a total of 70 patients receiving CAR T-cell therapy, showed a low cumulative humoral response rate of 31% [23].

A number of studies have shown patients with hematologic malignancies are at increased risk of severe outcomes following infection with COVID-19. A study by Mittelman et al. showed that among 32,516 vaccinated patients with hematologic malignancies, the relative risk for COVID-19 infection (1.60; 95% CI, 1.12–2.37) and hospitalization (3.13; 95% CI, 1.68–7.08) was significantly greater, compared with matched controls [27]. Overall, 5107 (15.9%) patients were receiving active treatment for a hematological malignancy. In addition, a study examined data from the VISION Network, which included 20,101 immunocompromised patients aged ≥ 18 years with COVID-19-like illness discharged from 187 hospitals across nine states in the United States [4]. Results showed that in patients with hematological malignancies, vaccine effectiveness against hospitalization was around 74% (95% CI: 62%, 83%), versus 90% (95% CI: 89%, 91%) in immunocompetent patients who had received two doses of an mRNA vaccine two weeks prior to hospitalization. In addition, a study in 2767 patients with non-Hodgkin lymphoma showed those receiving active treatment given within 30 days of COVID-19 diagnosis (n = 195) had more severe outcomes than those not receiving treatment (OR 1.4; 95% CI 1.0, 2.0) [28]. Two large multicenter retrospective studies have also reported high rates of severe COVID-19 disease and mortality in both untreated as well as treated patients with CLL [29][30]. In one of the studies [26], survival rates were not associated with active treatment, whereas in the second study [27], significantly more patients (91/151, 60.3%) in the severe COVID-19 group were off treatment within the last year or had never received treatment for CLL compared with less severe cases (15/39, 38.5%) ($p < 0.05$). Finally, The Center for International Blood and Marrow Transplant Research (CIBMTR) found that severe COVID-19 disease requiring mechanical ventilation occurred in 45/318 (14%) of HSCT recipients and thirty-day survival was around 67% [22]. Given the increased risk of severe COVID-19 outcomes in patients with hematologic malignancies, broader protection is needed beyond vaccination.

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