Clinical Guidance on COVID-19 Vaccines for people with hematological malignancy at any stage of treatment and/or who have undergone hematopoietic stem cell transplant or CAR-T cell therapy in the past 6 months

This guidance is intended for healthcare providers and is based on known evidence as of April 26, 2021.

This document relates to people with hematological malignancies and those who have undergone hematopoietic stem cell transplant or CAR-T cell therapy. Please refer to other guidance document for people with solid cancers. For general information, please refer to BCCDC Guidance and information on COVID-19 vaccines for providers.

Background and Context

Hematologic malignancies (blood cancers such as leukemias, myelodysplastic syndromes, myeloproliferative neoplasms, lymphomas and multiple myeloma) can be treated with chemotherapy, hematopoietic stem cell transplant (HSCT) or chimeric antigen receptor T-cell (CAR-T) therapies with either a curative intent or to prolong survival. The hematologic malignancy itself or the anti-cancer therapies can result in long-lasting immunodeficiency, and COVID-19 infection in this population is associated with a significantly higher risk of hospitalization and death.1

This guidance is based on a review of the safety and efficacy data of three of the current Health Canada approved vaccines for the prevention of COVID-19 disease caused by the SARS-CoV-2 virus: Pfizer-BioNTech (BNT162b2)2 and Moderna (mRNA-1273)3, two mRNA vaccines, as well as AstraZeneca/COVISHIELD (ChADoX1-S)4,5 which is a replication-defective adenoviral vector vaccine.

Only the Pfizer-BioNTech mRNA vaccine is authorized for youth aged 16 and above.1 In some special circumstances in British Columbia, people with certain underlying health conditions or who take certain medications and treatments are eligible to receive the COVID-19 vaccine starting at age 16 (see www.gov.bc.ca/cevCOVID).

Future updates of this clinical guidance may include guidance specific to:

- Another replication-defective adenoviral vector vaccine, Janssen/Johnson & Johnson (Ad26.COV2.S)6, which has been authorized by Health Canada but not yet reviewed by the National Advisory Committee on Immunization (NACI).
- The emerging vaccine candidate by Novavax, a recombinant-subunit-adjuvanted protein vaccine, if approved by Health Canada.
COVID-19 Vaccines for People with a Hematologic Malignancies and HSCT and/or CAR-T recipients

Updated: April 26, 2021

Vaccine Induced Thrombotic Thrombocytopenia (VITT) has been reported as a rare complication of the AstraZeneca/COVISHIELD (ChAdOx1-S [recombinant]) vaccines. The literature related to this is evolving rapidly and current guidance from BCCDC and BC Public Health should be followed. At this time in British Columbia, AstraZeneca/COVISHIELD is currently being offered only to individuals aged 40 and above.

For two-dose vaccines, the current interval between doses observed in British Columbia is up to 120 days for all individuals, including for those with underlying conditions or who are immunocompromised due to disease or treatment.

Patients with cancer were generally excluded from the COVID-19 vaccine trials if they were immunosuppressed by disease or treatment. Therefore, there are uncertainties as to whether COVID-19 vaccines are efficacious and safe in patients with blood cancer or post-HSCT or CAR-T cell therapy, as well as to the optimal timing of vaccination in relation to their cancer treatments.

Is the COVID-19 vaccine recommended for people with hematologic malignancies and HSCT and/or CAR-T recipients?

The risk of mortality from COVID-19 disease is higher in patients with cancer, including patients with hematologic malignancies and HSCT recipients. One study found that more severe forms of COVID-19 disease, including those requiring ICU admission, were more frequent in patients with hematologic malignancies hospitalized with COVID-19, and led to mortality nearly four times higher than that of the general population with COVID-19 and 41 times higher than that of hematologic malignancy patients without COVID-19.

The Pfizer-BioNTech, Moderna, and AstraZeneca/COVISHIELD COVID-19 vaccines vaccines are not contraindicated and should be encouraged for people with hematologic malignancies and HSCT and/or CAR-T recipients and as per BC Public Health recommendation for age eligibility. This recommendation is based on the following:

- The National Advisory Committee on Immunization (NACI) recommends that immunosuppressed individuals be offered the vaccine if the benefits of vaccines outweigh the potential risks.
- Patients with blood cancer have an increased risk of death related to COVID-19 infection.
- The United Kingdom, the United States, France, and Australia have prioritized patients with cancer for COVID-19 vaccinations, highlighting the high COVID-19 risk faced by these patients.

Is the COVID-19 vaccine efficacious and safe in people with hematologic malignancy patients and HSCT and/or CAR-T recipients?

It is unknown if the currently available COVID-19 vaccines are efficacious in patients with blood cancer and/or have undergone HSCT or CAR-T cell therapy in the last six months. As with most vaccines, there is a potential for diminished immune response in individuals who are immunocompromised due to their disease or treatment. In addition, patients...
with active cancer or undergoing active cancer treatment seemed to be generally excluded from the COVID-19 vaccine trials. However, in the Pfizer-BioNTech vaccine trial, 3.9% of enrolled participants had a malignancy.\textsuperscript{14}

There are currently no known factors that would predispose these individuals to adverse events associated with the vaccines.\textsuperscript{2-5} At the time of authorization, there are no known serious warnings or precautions related to the vaccines in patients with cancer.\textsuperscript{2-5}

Theoretical concerns regarding use of mRNA/DNA-based and virus (usually adenovirus) vector-based vaccines in cancer patients include a hyper-inflammatory response observed in animal models; however, this response has not been demonstrated in humans.\textsuperscript{14} Inactivated vaccines post-HSCT have not caused or worsened graft-versus-host disease (GVHD).\textsuperscript{14} Observed short-term adverse effects with the mRNA-based COVID-19 vaccines have been similar to those seen with seasonal influenza vaccination. Still, they may be more pronounced after the second COVID-19 vaccine dose (e.g. injection site pain/erythema, fever, headache, fatigue, and myalgia/arthritis).\textsuperscript{14} Any long-term side effects of COVID-19 vaccines are not yet known, but Health Canada continues to monitor any adverse events following vaccination through their post-authorization surveillance process.

Immunocompromised patient populations are diverse and the relative degree of immunodeficiency will depend on the underlying condition, the progression of the disease, and the type and timing of treatment received. Therefore, the balance of potential benefit and risk associated with COVID-19 vaccination should be assessed on an individual basis (Table 1).

**Are there any specific contraindications or exceptions for those within the hematologic malignancy, HSCT and/or CAR-T recipient patient populations?**

**Blood counts**

Patients with blood cancer and HSCT or CAR-T recipients may experience low blood counts, either due to their disease or treatment, which could impact individual decision-making around receipt of COVID-19 vaccinations and timing of vaccinations relative to their treatments. COVID-19 vaccination should be deferred in patients unwell with neutropenia until well,\textsuperscript{2,3} but may be considered in well patients with disease-related chronic neutropenia where neutrophil recovery is not expected.\textsuperscript{15}

**Allergy**

The above noted COVID-19 vaccines are contraindicated in individuals with a history of severe allergic reaction to any component of the vaccines,\textsuperscript{2-5} including non-medicinal ingredients such as polyethylene glycol (PEG)\textsuperscript{2,3} or polysorbate-80,\textsuperscript{4,5} or a history of anaphylaxis after administration of a previous dose of COVID-19 vaccine using a similar platform (mRNA or viral vector).\textsuperscript{11} People with a history of anaphylaxis without known or obvious cause, and those with suspected hypersensitivity or non-anaphylactic allergy to COVID-19 vaccine components, are advised to consult with an allergist prior to immunization. Patients who have experienced a serious allergic reaction to another vaccine, medicine or food should be observed longer after vaccine administration to monitor for development of any allergic reaction.\textsuperscript{11}
COVID-19 Vaccines for People with a Hematologic Malignancies and HSCT and/or CAR-T recipients

Updated: April 26, 2021

For a list of components in the vaccine and packaging consult the respective COVID-19 vaccine product monographs found at:


Health Canada continues to monitor any adverse events following immunization through their post-authorization surveillance process.

Other vaccines
There is no data on co-administration of COVID-19 vaccines with other vaccines. Separation of other vaccines is recommended to avoid incorrectly attributing adverse effects or potentially attenuating response to either vaccine. Thus other vaccines ideally should not be administered for 14 days prior to COVID-19 vaccination and for 14 days after a COVID-19 vaccine dose.

Are there specific recommendations or considerations for safe and/or most effective administration?

1. Blood counts
Patients with blood cancer and HSCT or CAR-T recipients may have lowered blood counts related to the underlying disease or therapy. If blood counts (platelet count and neutrophil count) are low due to therapy and timing of recovery can be anticipated, e.g. 1 week prior to the next cyclical chemotherapy or maintenance cycle, the timing of vaccination should be scheduled accordingly (please see Table 1). However, where the timing of blood count recovery is unclear or not anticipated, e.g. marrow failure syndromes, then vaccination should not be delayed solely for this reason.

There is no consensus on an adequate platelet count for IM injections. Still, practical suggestions include using a platelet threshold of >20 x 10^9/L, administering the vaccine after platelet transfusion if receiving regular transfusions, and applying firm pressure at the injection site for at least 5 minutes.

2. Anti-coagulant therapy
As per Thrombosis Canada recommendations, anti-coagulation should not be a barrier for administering COVID-19 vaccination to patients on warfarin (INR monitoring not required prior to vaccination), novel oral anticoagulants (apixaban, dabigatran, edoxaban, rivaroxaban) or antiplatelet agents (aspirin, clopidogrel, ticagrelor). Patients on therapeutic dose low-molecular weight heparin (dalteparin, tinzaparin, enoxaparin, nadroparin) or fondaparinux may consider delaying their anti-coagulant dose on the day of vaccination until after the IM injection. For patients on any of the above, applying pressure to the injection site for 3 to 5 minutes post vaccination is recommended to reduce bruising.
3. Special considerations for immunotherapy

a. Therapies targeting B-cells including anti-CD20, CD19, CD22 targeting antibodies, BiTEs or CAR-T cell therapy:
   Patients receiving these agents may have a reduced immune response to vaccines in general that can extend to up to 6 months following treatment completion.

b. Checkpoint inhibitors:
   Previous studies have not signalled an increased risk of complications of COVID-19 for patients on checkpoint inhibitors such as CTLA-4 inhibitors (e.g., ipilimumab), PD-1 inhibitors (e.g., nivolumab, pembrolizumab) and PD-L1 inhibitors (e.g., atezolizumab, durvalumab). There have been theoretical concerns of an enhanced immune reaction, particularly with CTLA-4 inhibitors. However, given the seriousness of COVID-19 infection, vaccination is still recommended in this group even if a four-week window cannot be confirmed.

4. Timing of COVID-19 vaccines in relation to therapy

There are no known studies regarding the timing of COVID-19 vaccination in relation to therapy for blood cancer. The Pfizer-BioNTech, Moderna and AstraZeneca/COVISHIELD vaccines are given as two injections with optimal protection assumed after the second dose for the general population.\textsuperscript{2,5} The efficacy and duration of immunity after one dose are continuously being evaluated and recommendations are evolving rapidly. Therefore, patients should follow current BCCDC guidance for the recommended number of and interval between COVID-19 vaccine doses.

In general, it is preferred that patients complete their two dose COVID-19 vaccination series ideally 14 days prior to starting immunosuppressive therapy.\textsuperscript{15}

*However, life-saving or prolonging therapy should not be delayed solely to complete vaccination.

Recommendations for timing of COVID-19 vaccination for patients with hematologic malignancies (either completed, starting or already receiving treatment) and patients who have undergone HSCT or CAR-T cell therapy in the past 6 months are described in Table 1 below.

Any other timing should involve a case-by-case assessment based on:
   a. Risk of morbidity related to COVID-19 infection (including local incidence of the pandemic, cancer type, comorbidities that confer higher risk categories in general population, etc.),
   b. Cancer-related morbidity due to delay of active treatment, and
   c. Suboptimal immunity due to insufficient time window between vaccination and immunosuppressive therapy.

\textbf{Table 1. Suggested timing of COVID-19 vaccination in patients with hematologic malignancies\textsuperscript{12,15,16,21-24}}

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Suggested timing of COVID-19 vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclical chemotherapy – prior to starting</td>
<td>1) Ideally complete vaccination at least 2 weeks prior to starting*</td>
</tr>
<tr>
<td>(including hypomethylating agents)</td>
<td>2) Alternatively, complete vaccination between cycles of therapy if clinically not appropriate to wait to complete vaccination</td>
</tr>
</tbody>
</table>

\textit{Clinical Guidance on COVID-19 Vaccines for People with hematological malignancies and those who have undergone hematopoietic stem cell transplant or CAR-T}
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Suggested timing of COVID-19 vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclical chemotherapy – between cycles (including hypomethylating agents)</td>
<td>Give vaccine dose(s) between cycles:</td>
</tr>
<tr>
<td></td>
<td>- Upon count recovery <em>(if anticipated to recover)</em>* about 1 week prior to starting subsequent cycle</td>
</tr>
<tr>
<td></td>
<td><em>Note: Avoid on same day as treatment</em></td>
</tr>
<tr>
<td>Single agent small molecule inhibitors (e.g. kinase inhibitors or continuous oral chemotherapy, BTK inhibitors)</td>
<td>No specific timing</td>
</tr>
<tr>
<td>Immunomodulatory agents</td>
<td>Avoid on same day as treatment</td>
</tr>
<tr>
<td>Proteasome inhibitors (e.g. bortezomib)</td>
<td>Avoid on same day as treatment</td>
</tr>
<tr>
<td>Check point inhibitors</td>
<td>Avoid on same day as treatment</td>
</tr>
<tr>
<td>CD19, CD20, CD22 targeted therapy (e.g. monoclonal antibodies, CAR-T cell therapy)</td>
<td>No specific timing †</td>
</tr>
<tr>
<td>Other monoclonal antibodies</td>
<td>No specific timing</td>
</tr>
<tr>
<td>Systemic Corticosteroids</td>
<td>Cyclical corticosteroids as part of chemotherapy regimens – ideally vaccinate on days when not receiving corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Continuous corticosteroids – no specific timing ***</td>
</tr>
<tr>
<td>Autologous HSCT § ¥</td>
<td>Pre-HSCT: ≥ 2 weeks prior to starting conditioning chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Post-HSCT: &gt; 3 months post-HSCT</td>
</tr>
<tr>
<td>Allogeneic HSCT § ¥</td>
<td>Pre-HSCT: ≥ 2 weeks prior to starting conditioning chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Post-HSCT: &gt; 3 months post-HSCT †</td>
</tr>
<tr>
<td>Aplastic Anemia</td>
<td>Not on therapy or completed therapy with counts in acceptable range: No specific timing required</td>
</tr>
<tr>
<td></td>
<td>Post-therapy: &gt; 3 months post-initiation of cyclosporine/ATG †</td>
</tr>
<tr>
<td>Intravenous immunoglobulin (IVIG) - Not COVID-19 specific</td>
<td>No specific timing</td>
</tr>
<tr>
<td>Under Observation - Not scheduled for therapy OR completed planned therapy</td>
<td>No specific timing</td>
</tr>
</tbody>
</table>
COVID-19 Vaccines for People with a Hematologic Malignancies and HSCT and/or CAR-T recipients

Updated: April 26, 2021

* In general, it is preferable to complete vaccination before starting immunosuppressive therapy if possible (based on timing of therapy and vaccine availability). However, life-saving or prolonging therapy should not be delayed solely to complete vaccination. Some immunity may be achieved following the first dose of the vaccine.

** Some patients may not have adequate counts either prior to or between cycles of therapy. The benefit likely outweighs the risk, and these patients should proceed to vaccination regardless of neutrophil count and with platelet transfusion support if required.

*** Ideally high dose systemic corticosteroids (> 0.5 mg/kg/day prednisone or equivalent) should be avoided or completed 28 days prior to vaccination; if this is not possible, proceed with vaccination.

† Due to likelihood of impaired immune response to vaccination within 3 months of receiving B-cell directed monoclonal antibodies, CAR-T cell therapy and ATG, consider delaying to 3 months post-therapy.

§ Rationale for consideration of delaying COVID-19 vaccination in HSCT recipients includes:
- Vaccine response is expected to be sub-optimal
- Antibody testing cannot be evaluated as standard of practice;
- Currently, revaccination after therapy completion is not recommended or expected (unlike annual influenza vaccinations) and therefore optimized timing should be considered.

¶ If local COVID-19 transmission rates are high, consider prioritization of COVID-19 vaccination and defer initiation of routine post-HSCT vaccinations until at least 14 days after completion of a COVID-19 vaccine dose.²⁴

References


Clinical Guidance on COVID-19 Vaccines for People with hematological malignancies and those who have undergone hematopoietic stem cell transplant or CAR-T


COVID-19 Vaccines for People with a Hematologic Malignancies and HSCT and/or CAR-T recipients

*Updated: April 26, 2021*

### Authors

Dr Sujaatha Narayanan, MBBS, MRCP, FRCPath; Medical Director, Leukemia/Bone Marrow Transplant Program of British Columbia, Vancouver General Hospital

Carmen Mountford, BSc, BScPharm, ACPR; Clinical Pharmacist, Leukemia/Bone Marrow Transplant Program of British Columbia, Vancouver General Hospital, Lower Mainland Pharmacy Services

### Reviewers

Dr Alissa Wright, BSc, MD, FRCPC, MSc; Head, Division of Infectious Diseases, Vancouver General Hospital

Dr Helen Anderson, Program Medical Director, Systemic Therapy, BC Cancer

Dr Stephen Nantel, Head, Division of Hematology, Leukemia/Bone Marrow Transplant Program of British Columbia, Vancouver General Hospital

Dr Paul Yenson, Medical Lead, General Hematology, Vancouver General Hospital

Dr Maryse Power, Associate Medical Director, Leukemia/Bone Marrow Transplant Program of British Columbia, Vancouver General Hospital

Dr Kerry Savage, Medical Oncologist, BC Cancer

Dr Laurie Sehn, Lymphoma Tumor Group Chair, BC Cancer

Nursing leadership, Leukemia/BMT Program of BC, Vancouver General Hospital

---

Clinical Guidance on COVID-19 Vaccines for People with hematological malignancies and those who have undergone hematopoietic stem cell transplant or CAR-T