BC Cancer Influenza vaccine recommendations for adults with cancer

We recommend that providers should offer an age-appropriate **inactivated influenza vaccine** to all adult cancer patients without contraindications to the vaccine.[1-4] The *live* attenuated influenza vaccine is NOT recommended in cancer patients (i.e., intranasal FluMist®). Currently, there is not enough information to recommend the high-dose inactivated influenza vaccine over the standard-dose inactivated influenza vaccine in the general oncology population; the high-dose vaccine is Health Canada-approved for adults age 65 and older and is publicly funded in BC for adults age 65 and older who live in long-term care facilities or assisted living facilities.[5] Family, care providers and close contacts of patients with cancer should be encouraged to consider receiving either the inactivated or live attenuated influenza vaccine if not contraindicated.[2,6]

Influenza vaccine – Timing in adult cancer patients:

<table>
<tr><th>Patient population</th><th colspan="3">When should patients receive the influenza vaccine?</th></tr>
<tr><td>Before starting chemotherapy</td><td colspan="3">Ideal: 2 weeks or longer before starting first round of chemotherapy
Minimum: 2 days prior to starting first round of chemotherapy</td></tr>
<tr><td>On chemotherapy (may include treatment with rituximab)</td><td colspan="3">Within 2 to 3 days before the next chemotherapy cycle</td></tr>
<tr><td>On maintenance rituximab
(e.g., given every 3 months)</td><td colspan="3">At any time during maintenance therapy</td></tr>
<tr><td>On targeted therapy</td><td colspan="3">At any time during treatment</td></tr>
<tr><td>On radiation therapy</td><td colspan="3">At any time during treatment while blood counts are near normal range
(vaccine should be given on the opposite side if unilateral treatment is given)</td></tr>
<tr><td rowspan="4">On checkpoint inhibitor immunotherapy
Vaccine timing depends on the immunotherapy regimen</td><td>PD-1 inhibitor monotherapy</td><td>cemiplimab, nivolumab, pembrolizumab</td><td rowspan="2">At any time during therapy</td></tr>
<tr><td>PD-L1 inhibitor monotherapy</td><td>atezolizumab, durvalumab</td></tr>
<tr><td>CTLA-4 inhibitor monotherapy</td><td>ipilimumab, tremelimumab</td><td rowspan="2">Recommended to NOT receive any vaccine within 4 weeks of starting treatment or within 4 weeks of last dose</td></tr>
<tr><td>CTLA-4 inhibitor in combination</td><td>ipilimumab + nivolumab</td></tr>
<tr><td colspan="4">The recommendations in this table do not apply to Hematopoietic Stem Cell Transplant (HSCT) patients.
For more information, discuss with physician or see HSCT recommendations.</td></tr>
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Influenza vaccine – Additional timing considerations:

The influenza vaccine may administered at the same time as the COVID-19 vaccine, or at any time before or thereafter.[7]

Patients should ideally receive the influenza vaccine 2 weeks before starting chemotherapy to allow for adequate antibody production. Although some protection may be afforded if the influenza vaccine is received less than 2 weeks before starting chemotherapy, such timing may result in reduced efficacy.[3] It is still recommended and safe for patients to receive the influenza vaccine within 2 weeks, but no less than 2 days, before starting their first cycle of chemotherapy, rather than to not receive the vaccine at all.

If a patient has already started on chemotherapy, we recommend that patients receive the influenza vaccine within 2-3 days before their next chemotherapy cycle, when blood counts are most likely near the normal range. Although the optimal timing for efficacy when administering the influenza vaccine in patients on chemotherapy is not clear, this timing is recommended to avoid the confusion around the cause of mild flu-like symptoms, or infusion-related or other injection-related reactions, if the patient were to receive the vaccine on the day of or soon after receiving chemotherapy.[8-10] Such reactions may affect a patient's current or subsequent chemotherapy cycle if the reaction is thought to be infection- or chemotherapy-related.

Patients on maintenance rituximab therapy can receive the influenza vaccine anytime during maintenance therapy. While it is safe for these patients to receive the influenza vaccine, several small studies suggested that patients receiving rituximab have a reduced immune response to the influenza vaccine.[11-13] Patients should still be offered the influenza vaccine, however, even if it generates a reduced immune response.

Although the optimal window to receive the influenza vaccine for patients on CTLA-4 inhibitor monotherapy or combination therapy is unknown, we recommend that these patients should not receive the influenza vaccine within 4 weeks of starting treatment or within 4 weeks of the last dose.[14] Anecdotal reports found cases of severe immune-related adverse events in patients on combination ipilimumab and nivolumab after receiving the influenza vaccine.[15] This adverse reaction was suspected to be related more to ipilimumab than to nivolumab.

The influenza vaccine appears to be safe for patients on other immune checkpoint inhibitors such as PD-1 and PD-L1 inhibitor monotherapy. While early studies suggested a risk of severe immune-related adverse events associated with the influenza vaccine in patients receiving immune checkpoint inhibitors, a recent large observational study suggested that there is no increase in the incidence or severity of new onset immune-related adverse events in patients on PD-1 inhibitor monotherapy who receive the influenza vaccine.[16]

References

1. BC Centre for Disease Control (BCCDC). Adults with Malignant Neoplasm (Including Leukemia and Lymphoma). Available from: http://www.bccdc.ca/health-professionals/clinical-resources/communicable-disease-control-manual/immunization/immunization-of-special-populations
2. Immunizations. Canadian Cancer Society 2019. Available from: https://www.cancer.ca/en/cancer-information/diagnosis-and-treatment/tests-and-procedures/immunizations/?region=on
3. National Advisory Committee on Immunization (NACI). Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2021-2022. Available from: https://www.canada.ca/en/public-health/services/publications/vaccines-immunization/canadian-immunization-guide-statement-seasonal-influenza-vaccine-2021-2022.html
4. Government of Canada. Immunization of immunocompromised persons: Canadian Immunization Guide. Available from: https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-3-vaccination-specific-populations/page-8-immunization-immunocompromised-persons.html
5. BC Centre for Disease Control (BCCDC). Fluzone® High-Dose Influenza Vaccine Question and Answer Document Updated – August 2021.
6. Zhao L, Young K, Gemmill I, on behalf of the National Committee on Immunization (NACI). Summary of the NACI seasonal influenza vaccine statement for 2019-2020. *Can Commun Dis Rep* 2019;45(6):149-155. https://doi.org/10.14745/ccdr.v45i06a01
7. National Advisory Committee on Immunization (NACI). Guidance on the use of influenza vaccine in the presence of COVID-19. Available from: https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/guidance-use-influenza-vaccine-covid-19.html
8. Taplitz RA, Kennedy EB, Bow EJ, et al. Antimicrobial prophylaxis for adult patients with cancer-related immunosuppression: ASCO and IDSA clinical practice guideline update. *J Clin Oncol* 2018;36(30):3043-3054. https://doi.org/10.1200/JCO.18.00374
9. Dulek DE, Halasa NB. Timing isn't everything: influenza vaccination in cancer patients. *Cancer* 2017;123(5):731-733. https://doi.org/10.1002/cncr.30467
10. Keam B, Kim M-K, Choi Y, et al. Optimal timing of influenza vaccination during 3-week cytotoxic chemotherapy cycles. *Cancer* 2017;123(5):841-848. https://doi.org/10.1002/cncr.30468
11. Yri OE, Torfoss D, Hungnes O, et al. Rituximab blocks protective serologic response to influenza A (H1N1) 2009 vaccination in lymphoma patients during or within 6 months after treatment. *Blood* 2011;118(26):6769-6771. https://doi.org/10.1182/blood-2011-08-372649
12. van der Kolk LE, Baars JW, Prins MH and van Oers MHJ. Rituximab treatment results in impaired secondary humoral immune responsiveness. *Blood* 2002;100(6):2257-2259. https://doi.org/10.1182/blood.V100.6.2257
13. Bedognetti D, Zoppoli G, Massucco C, et al. Impaired response to influenza vaccine associated with persistent memory B cell depletion in non-Hodgkin's lymphoma patients treated with rituximab-containing regimens. *J Immunol* 2011;186:6044-6055. https://doi.org/10.4049/jimmunol.1004095
14. Kerry Savage, personal communication. 23 October 2021.
15. Kerry Savage, personal communication. 03 November 2016.
16. Chong CR, Park VJ, Cohen B, et al. Safety of inactivated influenza vaccine in cancer patients receiving immune checkpoint inhibitors. *Clin Infect Dis* 2020;70(2):193-199. https://doi.org/10.1093/cid/ciz202