Immunizing Cancer Patients: Which Patients? Which Vaccines? When to Give?

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ABSTRACT: Patients receiving treatment for cancer should be considered for age- and indication-appropriate vaccinations, and the responsibility for administration of these vaccines is shared between the oncologist and the primary care provider. Certain vaccine-preventable diseases have higher incidence rates among cancer patients and are associated with worse clinical outcomes. The Centers for Disease Control and Prevention and the Advisory Committee on Immunization Practices recommend certain vaccines for routine use in adults, including those with cancer. This article provides guidance to oncology clinicians on vaccine recommendations and safety of use in their patients.

Introduction
The number of cancer survivors in the United States is predicted to exceed 20 million by 2026, largely due to advances in treatment and early detection of cancer, along with the aging and overall growth of the population.[1] The Centers for Disease Control and Prevention (CDC), under guidance from the Advisory Committee on Immunization Practices (ACIP), recommends certain vaccines for routine use in all persons, stratified by age and clinical indication.[2] Patients receiving treatment for cancer should be considered for age- and indication-appropriate vaccinations, and the responsibility for administration of these vaccines is shared between the oncologist and the primary care provider. Although vaccine effectiveness may be lower in patients immunocompromised because of cancer or its therapy—in comparison with the effectiveness in immunocompetent persons—vaccination can still reduce morbidity and mortality.

Inactivated vaccines are prepared from fractional or whole components of bacteria or viruses, or their products, and are typically protein- or polysaccharide-based. Polysaccharide vaccines are typically less immunogenic and can be conjugated to proteins to enhance the immune response. Live-attenuated vaccines use a weakened form of the pathogen to induce an immune response. Recombinant vaccines consist of genetically engineered antigens and are typically inactivated, but can occasionally be live-attenuated. Both inactivated and recombinant vaccines can contain adjuvants to increase the immune response.[3,4]

This article will address several important vaccination considerations in adult patients with cancer. Stem cell transplantation recipients require primary re-immunization strategies that are addressed in other reviews.[5,6] In general, inactivated and recombinant (non-live) vaccines can be safely given to immunocompromised patients (see Table). Live-attenuated vaccines should not be administered to patients who are considered to be highly immunocompromised.

Immunocompromised Patients With Cancer
Highly immunocompromised cancer patients are those who have received chemotherapy and/or radiation therapy within the preceding 3 months, those who have generalized malignancy or hematologic malignancy, and those who have received the equivalent of ≥ 20 mg prednisone daily for ≥ 2 weeks, as well as stem cell transplant recipients within 2 years of transplant (or beyond 2 years if there is ongoing evidence of graft-vs-host disease).[7] Patients who receive regimens containing anti–B-cell antibodies are also highly immunosuppressed and unable to mount effective vaccine responses, and thus should have routine vaccinations delayed for at least 6 months. Other biologic agents, including both targeted agents and immune checkpoint blockade therapy (immunotherapy), have variable immunomodulatory and immunosuppressive effects. The degree and duration of immunosuppression are dependent on the individual drug, dose, and therapeutic context of administra-
Certain patients or survivors with cancer may have anatomical or functional asplenia and, if this is their sole immune deficit, they are not considered to be highly immunocompromised and may be able to receive live-attenuated vaccines.

### Timing of Vaccination

When feasible, vaccines should be administered prior to planned immunosuppressive chemotherapy. Inactivated vaccines should ideally be given at least 2 weeks prior to starting chemotherapy, or 3 months after completion. Live-attenuated vaccines should be administered ≥ 4 weeks prior to the onset of such therapy, or ≥ 3 months after immune restoration.[5] For patients undergoing elective splenectomy as part of their cancer therapy, indicated vaccines should be administered at least 2 weeks prior to the procedure.[8]

### Influenza Vaccines

Adult patients undergoing treatment for cancer are at a higher risk for developing serious complications from influenza, with 3 to 4 times higher odds of hospitalization compared with age-matched controls. [9] Despite their limited effectiveness in preventing influenza, existing studies suggest that inactivated influenza vaccines are safe, and offer protection to cancer patients by reducing influenza-related hospitalizations, interruption of chemotherapy cycles, and risk of death.[10-13] Antibody responses to vaccines are generally lower in patients receiving chemothera-

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**Table. Recommendations for Routine Vaccinations in Adults With Underlying Cancer**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Safety</th>
<th>Schedule</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Influenza</strong></td>
<td></td>
<td>One dose annually</td>
<td>High dose recommended for age 65 yr and above</td>
</tr>
<tr>
<td>Trivalent inactivated</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quadrivalent inactivated</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-dose inactivated</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live-attenuated (FluMist)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell culture–based (Flucelvax Quadrivalent)</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recombinant (Flublok Tri- and Quadrivalent)</td>
<td>✓</td>
<td>Use for severe egg allergy; age indication: ≥ 18 yr</td>
<td></td>
</tr>
<tr>
<td><strong>Pneumococcal</strong></td>
<td></td>
<td>One dose of PCV-13 followed by one dose of PPSV-23 at least 8 weeks after PCV-13</td>
<td></td>
</tr>
<tr>
<td>13-valent pneumococcal conjugate (PCV-13; Prevnar-13)</td>
<td>✓</td>
<td>One dose of PCV-13 followed by one dose of PPSV-23 at least 8 weeks after PCV-13</td>
<td></td>
</tr>
<tr>
<td>23-valent pneumococcal polysaccharide (PPSV-23; Pneumovax)</td>
<td>✓</td>
<td>(additional booster for Pneumovax may be recommended)*</td>
<td></td>
</tr>
<tr>
<td><strong>Zoster</strong></td>
<td></td>
<td>Two doses 2–6 mo apart</td>
<td>Age indication: ≥ 50 yr; if previously vaccinated with ZVL, wait 2 mo</td>
</tr>
<tr>
<td>Recombinant zoster vaccine (RZV; Shingrix)</td>
<td>✓</td>
<td>Two doses 2–6 mo apart</td>
<td>Age indication: ≥ 50 yr; if previously vaccinated with ZVL, wait 2 mo</td>
</tr>
<tr>
<td>Live zoster vaccine (ZVL; Zostavax)</td>
<td>X</td>
<td>Two doses 2–6 mo apart</td>
<td></td>
</tr>
<tr>
<td><strong>Tetanus, diphtheria, and pertussis</strong></td>
<td></td>
<td>Once in adulthood, if not previously vaccinated</td>
<td>Td booster every 10 yr (following Tdap)</td>
</tr>
<tr>
<td>Tdap</td>
<td>✓</td>
<td>Once in adulthood, if not previously vaccinated</td>
<td>Td booster every 10 yr (following Tdap)</td>
</tr>
<tr>
<td>Td</td>
<td>✓</td>
<td>Td booster every 10 yr (following Tdap)</td>
<td>Td booster every 10 yr (following Tdap)</td>
</tr>
</tbody>
</table>

✓ = safe.
X = contraindicated.
py compared with healthy individuals or cancer patients who are not actively receiving treatment. For those with solid tumors, immunogenicity of the standard-dose trivalent inactivated influenza vaccine has ranged from 21% to 89% across heterogeneous groups of patients undergoing treatment with different cytotoxic chemotherapies.[14] 

Newer influenza vaccines and recent developments
Trivalent inactivated influenza vaccines, which include two type A strains and one type B strain, have been the most widely used prevention strategies among patients with cancer. Several notable developments in this area are:

- Quadrivalent inactivated vaccines include an additional B antigen that provides expanded coverage of strains from both influenza B genetic lineages that are expected to co-circulate within the same season. These vaccines are the current standard of care for influenza prevention at Memorial Sloan Kettering Cancer Center (MSKCC), with the exception of adults ≥ 65 years of age who are eligible for the high-dose vaccine.
- The live-attenuated influenza vaccine (LAIV) is administered as a nasal mist; the vaccine strain virus replicates in the upper airway to mimic natural infection and induce mucosal immunity. LAIVs are not considered safe for patients undergoing cancer treatment. However, while the LAIV is not offered to healthcare workers at MSKCC, use among household contacts of solid tumor patients is not discouraged. Secondary transmission of vaccine strain virus to susceptible high-risk contacts is a recognized risk, but severe disease due to vaccine strain has rarely been reported.[15] In recent seasons, the CDC issued interim recommendations against the use of LAIVs due to efficacy concerns; the vaccine is now reapproved for the upcoming 2018–2019 season.
- The high-dose influenza vaccine (https://www.cdc.gov/flu/protect/vaccine/qa_fluzone.htm) contains four times the amount of antigen as the standard dose, eliciting higher antibody responses and yielding clinically superior efficacy for the prevention of influenza and related respiratory illnesses among older adults.[16-18] The high-dose vaccine also induces higher seroprotection rates in non-elderly cancer patients,[19,20] and has the potential to incrementally enhance the clinical effectiveness of inactivated vaccines. Due to a lack of data on clinical efficacy, routine use of the high-dose vaccine among cancer patients < 65 years old is not currently recommended by the ACIP.[21] At MSKCC, the high-dose influenza vaccine is routinely used only for patients ≥ 65 years. The benefit of second doses of standard or high-dose vaccine to achieve superior immune and clinical responses remains unproven, and second doses are not currently given at our institution.
- Recombinant and cell culture–based vaccines utilize shorter and more rapidly scalable manufacturing processes, compared with other influenza vaccine formulations that utilize traditional egg-based manufacturing methods; the former thereby preserve genetic and antigenic similarity to circulating viruses. It is conceivable that retention of genetic identity between vaccine and circulating strains translates into a higher level of protection, and this has been substantiated by a single study in adults > 50 years, which demonstrated superior efficacy of quadrivalent recombinant vaccines compared with standard-dose egg-based vaccines during a single influenza season.[22] Until further data are available on the relative efficacy of recombinant vaccines compared with other high-dose formulations, and their benefits are confirmed to extend across different strains and seasons, their use at MSKCC remains solely for patients with a history of severe egg allergy.
- Adjuvanted influenza vaccines are another promising frontier in vaccine development that may enhance the immunogenicity in immunocompromised patients.[23] None of the existing randomized controlled trials of newer vaccine formulations have specifically assessed their performance in oncology populations.

Safety, contraindications, and timing of influenza vaccine in relation to chemotherapy
There is no specific concern regarding the safety of the inactivated influenza vaccine among cancer patients undergoing chemotherapy. Most reported adverse effects are mild and local. High-dose vaccines may be more reactogenic at the site of administration, but the general safety profile and incidence of Guillain-Barré syndrome matches what is seen with standard-dose vaccines. Immunization between September and December, or later, is likely to be beneficial in most influenza seasons. Based on limited evidence, the preferred timing for the influenza vaccine during treatment with chemotherapy is either more than 2 weeks before receiving chemotherapy or between chemotherapy cycles. Due to the unpredictable nature of the influenza season and unexpected delays in vaccine production, such precision in tim-
Influenza vaccine for patients receiving immunotherapy

Recent reports have questioned the safety of the influenza vaccine in patients receiving immunotherapy, postulating that it acts as an unrecognized antigenic trigger that amplifies immune-related adverse events (irAEs).[24,25] In our experience, the incidence of irAEs in vaccine recipients receiving anti–programmed death 1 (PD-1) therapy, or combination therapy with ipilimumab and an anti–PD-1, is no different from the irAE rates reported in clinical trials of immune checkpoint inhibitors. Based on these data and the robust T-cell and humoral response to influenza vaccine in patients treated with checkpoint blockade,[26] we believe that co-administration of influenza vaccine with US Food and Drug Administration–approved immune checkpoint blockade therapy is safe and effective.

Pneumococcal Vaccines

Patients undergoing chemotherapy for solid tumors are at a 40- to 50-fold higher risk for the development of invasive pneumococcal disease (IPD) compared with healthy adults,[27] with case fatality rates approaching 35%. Polysaccharide-based vaccines (Pneumovax) are poorly immunogenic in cancer patients despite the broad coverage against 23 capsular serotypes.[28] The highly immunogenic conjugate vaccines were first licensed in the United States in 2000 (Prevnar-7); capsular serotype coverage was expanded with approval of Prevnar-13 for adults in 2011. Among older adults, Prevnar-13 demonstrated a vaccine efficacy rate of 45% in reducing pneumonia, and a rate of 75% in reducing IPD.[29] With the advent of conjugate vaccines, a marked reduction in IPD rates has been observed among cancer patients—widely believed to be a consequence of the universal vaccination of children.[30] The ACIP recommends that both pneumococcal vaccines be administered to adults with generalized malignancy, regardless of age.[31]

Co-administration of the pneumococcal vaccine and the influenza vaccine is safe and effective. Unfamiliarity with the frequently changing administration schedules for the two pneumococcal vaccines, and lack of access to vaccination records, have been major barriers to improving vaccination rates among patients in the oncology setting. To facilitate influenza and pneumococcal vaccine uptake among patients at MSKCC, a nurse-initiated protocol was developed and implemented in 2017. Patients are assessed for eligibility for influenza vaccines and pneumococcal vaccines at each ambulatory visit as a mandatory component of the nursing care assessment. Both vaccines may be administered by nurses, as guided by a logic tool built into the electronic medical record (EMR), and without a specific physician order. The logic tool screens for past vaccination history, eligibility for each type of vaccine, and potential contraindications.[32] This program has led to a substantial increase in vaccine coverage.

Zoster Vaccines

Following primary infection, varicella zoster virus persists in latent form in sensory ganglia. Reactivation of virus can occur in those with impaired cell-mediated immunity and can cause herpes zoster infection (“shingles”), postherpetic neuralgia, and other serious complications associated with varicella reactivation. Cancer patients have a higher overall incidence of zoster, compared with age-matched controls, particularly those with hematologic malignancies.[33] Two zoster vaccines are now licensed for use in the United States. The older vaccine, Zostavax (ZVL), is live-attenuated and therefore has had limited use in the oncology setting. The new recombinant subunit vaccine, Shingrix (RZV), is superior to ZVL and is available for adults ≥ 50 years of age, including those with a previous episode of zoster or those who have previously received ZVL, and is considered to be the preferred zoster vaccine by the ACIP.

Studies have demonstrated that RZV is highly effective at preventing herpes zoster infection and postherpetic neuralgia in all age groups, including the elderly (91% in adults ≥ 70 years old, 97% in adults 50–69 years old).[34-36] The ACIP has made no specific recommendations for RZV use in immunocompromised cancer patients, citing lack of efficacy data. However, a recent study found significant efficacy among autologous stem cell transplant recipients who received the vaccine 50 to 70 days post-transplant. The vaccine was about 68% effective at preventing herpes zoster reactivation and 89% effective at preventing postherpetic neuralgia; it reduced overall complications by nearly 78%.[37] Further studies to evaluate the efficacy of this vaccine in patients who have solid or hematologic malignancies are underway, as are studies assessing immune responses in patients who have previously received ZVL. At MSKCC, we offer RZV to patients we deem eligible, based on currently published data and ACIP recommendations; these are primarily adult patients ≥ 50 years who are not considered highly immunocompromised. We suggest administering the first dose of the vaccine prior to the first administration of the irAE trigger before the irAE rates are reported in clinical trials of immune checkpoint inhibitors.

KEY POINTS

- Indicated vaccines are ideally administered before cancer treatment is initiated.
- Live vaccines are contraindicated due to risk of severe vaccine-induced infection.
- Injectable influenza vaccine is given annually, and both pneumococcal vaccines should be administered according to the recommended schedule from the Centers for Disease Control and Prevention.
- The newer recombinant zoster vaccine (RZV) is the safer and preferred vaccine.
- Family members and close contacts of cancer patients can be safely immunized with most, but not all, live vaccines.
onset of cancer-directed therapy or ≥ 3 months after chemotherapy. We vaccinate with RZV even patients who have previously received ZVL; the ACIP recommends waiting at least 2 months between the vaccines.

Other Routine Vaccines
All patients should be up to date on tetanus and diphtheria toxoid (Td) immunization. Adults who have never received the tetanus-diphtheria-pertussis (Tdap) vaccine should receive this as soon as possible; that dose can replace one of the Td booster doses. Human papillomavirus (HPV) vaccine should be offered to all immunocompromised young adults with cancer (through 26 years of age) if they have not previously received the series. Meningococcal, pneumococcal, and Haemophilus influenzae type b (Hib) vaccines should be given to cancer patients with anatomical or functional asplenia, to reduce the risk of sepsis caused by these organisms. Two different types of vaccines (against serogroups A, C, W, and Y and serogroup B) are available to target different serogroups of Neisseria meningitidis. Hepatitis A and B vaccines can be considered in cancer patients if another indication for vaccination is present. Live-attenuated vaccines—such as measles, mumps, and rubella (MMR) and varicella—are contraindicated in highly immunocompromised cancer patients.

Travel Vaccines
Recent studies have highlighted the fact that international travel is common among patients living with cancer, even highly immunocompromised patients. [38,39] Some vaccines that are considered prior to travel are based on specific epidemiologic risks that may be encountered at the travel destination(s). Country-specific vaccine recommendations are available from the CDC.[40] Live-attenuated yellow fever vaccine, oral typhoid vaccine, and oral cholera vaccine cannot be given to highly immunocompromised patients. Certain countries require proof of receipt of yellow fever vaccination upon disembarkation, based on the individual traveler’s prior travel history, irrespective of actual risk at the destination. For patients who cannot safely receive yellow fever vaccine but who will be visiting a location where there is little epidemiologic risk of yellow fever, a waiver letter can be written by a certified provider of yellow fever vaccine. For patients who are planning a trip that may result in natural exposure to disease, attendant risks of travel should be carefully discussed; this can be done in conjunction with a travel medicine provider.[41]

Household Contacts, Including Children
All immunocompetent household members of highly immunocompromised cancer patients should receive age-appropriate vaccinations as recommended by the ACIP, including all inactivated vaccines, as well as most live-attenuated vaccines, to protect the health of the immunocompromised household member. Live-attenuated vaccines such as MMR and varicella can be given, but immunocompromised patients should avoid contact with persons who develop skin lesions after receipt of the varicella vaccine until the lesions clear. Rotavirus vaccine can also be safely given, but immunocompromised patients should avoid handling diapers of infants who have been vaccinated for 4 weeks after vaccination. LAIVs should not be given to household contacts of patients who have received stem cell transplantation. Live-attenuated oral polio vaccine, which is not available in the United States, cannot be safely given to household contacts; the inactivated polio vaccine should be used.[5] Most travel vaccines can also be given to household contacts as indicated. Live-attenuated travel vaccines, such as yellow fever and oral typhoid vaccinations, can be given. There are limited data on the use of oral cholera vaccine among household contacts.

Conclusion
Routine vaccination in cancer patients and their household contacts is an important strategy for reducing morbidity and mortality in this vulnerable population. Vaccine type and categorization of the underlying degree of immunocompromise are essential considerations in the timing and feasibility of administration of each recommended vaccine. Complications from influenza and pneumococcal disease are significantly higher in patients with cancer compared with the general adult population, and we have found improved vaccine uptake with integrated EMR logic tools in our oncology patient population. The new recombinant zoster vaccine is highly promising, and forthcoming efficacy data in immunosuppressed patients will help guide possible expanded use.

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