Current Issues in Vaccines for Adult Patients With Hematologic Malignancies

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Abstract

Vaccination is an important strategy for preventing infections in patients with hematologic malignancies. Hematopoietic cell transplant (HCT) recipients have diminished immunity against vaccine-preventable diseases after transplantation. Optimal timing for initiating immunization in the context of hematologic malignancies and after HCT, however, is not well defined, and data on the magnitude and duration of immune response to vaccines in this population are lacking. Factors such as degree of immunosuppression, administration of monoclonal antibodies, time after HCT, and presence or absence of chronic graft-versus-host disease may influence the immune response to vaccines and may pose safety concerns for certain vaccines, such as live-attenuated immunogens. Patients who received certain monoclonal antibodies (eg, rituximab, alemtuzumab) less than 6 months before vaccination have poorer immune responses to vaccines. New advancements in vaccine development are warranted to improve safety and immunogenicity of vaccination in immunocompromised patients. (*JNCCN* 2012;10:1447–1454)

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Discuss the appropriate immunization strategies for patients with hematologic malignancies, including HCT recipients.
- Describe some important considerations regarding timing of administration, safety, and efficacy of currently available vaccines.

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Vaccination, along with appropriate infection control measures and the use of antimicrobial prophylaxis, is a key aspect of preventing infections in patients with cancer. In autologous and allogeneic hematopoietic cell transplantation (HCT), declining immunity to vaccine-preventable diseases puts recipients at risk for severe infections, which may be mitigated partly by revaccination.[1–5] Patients with hematologic malignancies in general are at high risk for severe infections because of a combination of factors, including neutropenia, T-cell dysfunction, associated hypogammaglobulinemia, splenectomy, and receipt of biologic agents like rituximab or alemtuzumab. Inactivated vaccines are usually safe in patients with hematologic malignancies, but the ability to mount a protective immune response after vaccination varies depending on several factors, including the underlying disease, age, timing of administration after transplantation, presence or absence of graft-versus-host disease (GVHD), and whether biologic agents were used to treat the underlying disease or GVHD and the timing of administration of these agents.

In this article we review the immunization strategies for patients with hematologic malignancies, including HCT recipients, and highlight some important considerations regarding timing of administration, safety, and efficacy of currently available vaccines.

Vaccination Strategies After Allogeneic and Autologous HCT

Recipients of HCT should be considered immunologically naive after transplant and require an approach to immunization, similar to that in the pediatric population. Studies have suggested that the immune system recovers the ability to recognize and respond to new antigen stimulation 6 to 12 months after HCT through the immune reconstitution of B and T cells. Despite achieving normal counts by 3 months post-HCT, functionality of newly generated B cells is not complete and improves with more time after HCT, typically after 6 months.[6,7] Naïve T cells have limited ability to respond to new antigens for the first 6 months posttransplantation, and this may take even longer depending on the immunosuppression used.[6,7] Although data on clinical efficacy of vaccination after HCT are lacking, measurable antibody responses against antigens in inactivated vaccines have been demonstrated in HCT recipients without major side effects or safety concerns.[8] The response to different vaccines, however, varies depending on the timing after transplant, the type of vaccine administered (polysaccharide vs. conjugated), and whether the pathogen was previously encountered before HCT. For example, the immune response to vaccines for antigens previously encountered (diphtheria, tetanus, pertussis, *Pneumococcus*, *Haemophilus influenzae*) could be observed 6 to 12 months after HCT, whereas responses to pathogens that were not previously encountered (hepatitis A, hepatitis B) are usually observed 12 months or more after transplantation.[6]

The magnitude of the immunologic response and seroprotection provided also varies depending on the type of HCT, timing of vaccination after transplantation, age at time of transplantation, and whether chronic GVHD is present or absent.[7] GVHD and its treatment and the use of rituximab within 6 months of vaccination blunt the immune response to vaccines and are important to note because, even if vaccinated, patients may have an impaired immune response, and additional precautions are required to decrease the risk of acquiring infections.[9,10] Notably, limited data exist regarding vaccine response in umbilical cord blood or haploidentical stem cell transplant recipients.

The Advisory Committee on Immunization Practices (ACIP)[11] recently released updated guidelines for immunization, including for patients with hematologic malignancies and HCT recipients. Multiple societies, including the American Society of Blood and Marrow Transplant (ASBMT) and the European Blood and Marrow Transplantation (EBMT) group, have also published guidelines for vaccination after HCT.[6,12,13] Table 1 summarizes the current recommended vaccine schedule.

Timing of Initiation of Immunization With Inactivated Vaccines

Both ACIP and ASBMT/EBMT guidelines recommend initiating vaccination with most inactivated vaccines as early as 6 months after HCT. The recommendations for initiating pneumococcal vaccination can be as early as 3 months after HCT. This recommendation was largely based on the results of a pneumococcal vaccine study in allogeneic stem cell transplant recipients that showed a protective antibody

Table 1 Vaccination Schedule for HCT Recipients

Inactivated Vaccine[a]	Timing After HCT	Number of Doses
DTaP (tetanus/dipthteria/acellular pertussis)	6–12 mo	3
Inactivated polio vaccine	6–12 mo	3
Haemophilus influenzae type b vaccine	6–12 mo	3
Pneumococcal conjugated 13-valent vaccine (PCV-13)	3–6 mo	3–4[b]
Hepatitis A vaccine	6–12 mo	2
Hepatitis B vaccine	6–12 mo	3
Meningococcal conjugate vaccine (MCV-4)	6–12 mo	1
Inactivated influenza vaccine	Annually, as available in the fall and as early as 4–6 months after HCT	1–2
	If given early (before 6 mo), a second dose must be given after 6 mo	
Live Vaccine		
Measles/mumps/rubella (MMR)[c]	At 24 mo (if no GVHD or ongoing immunosuppression)[d]	1
Varicella vaccine[c]	At 24 mo (if no GVHD or ongoing immunosuppression, or taking acyclovir)[d]	2

Abbreviations: GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation.
[a]Inactivated vaccines may be given together at the same time. Vaccination may be postponed for patients receiving >0.5 mg/kg of prednisone.
[b]After the initial 3 PCV-13 doses, a dose (4th) of pneumococcal polysaccharide vaccine (PPSV-23) to broaden the spectrum of pneumococcal serotypes might be given. For patients with chronic GVHD, a fourth dose of PCV-13 should be considered instead of PPSV-23.
[c]MMR and varicella vaccine should be given together at the same time or 4 weeks apart.
[d]Physicians should assess the immune status of each recipient on a case-by-case basis.

response as early as 3 months after HCT.[14] In this trial, a 23-valent pneumococcal polysaccharide vaccine (PPSV-23) after a 7-valent pneumococcal conjugate vaccine (PCV-7) generated similar antibody response at 3 months compared with 9 months after HCT.[14] Although in this study early vaccine administration likely afforded earlier protection against pneumococcal disease, it did not provide a boost to PPSV-23 as efficiently as late vaccination, and did not result in a longer-lasting antibody response than the latter.[14]

Influenza infection in HCT recipients carries a significant risk for life-threatening complications, with reported rates of pneumonia between 29% and 80% and case fatality rates of 10% to 25%[15–19](Figure 1). Influenza vaccination may help prevent severe complications from influenza infection and is recommended during the influenza season. The general recommendation for initiation of trivalent inactivated influenza vaccination is 4 to 6 months after HCT and annually thereafter. Live attenuated influenza vaccine should not be administered to HCT recipients or their household contacts. If influenza vaccine is administered before 6 months after HCT, then a second dose should be considered. Studies looking at the safety and immunogenicity of high-dose inactivated trivalent influenza vaccine compared with standard-dose influenza vaccine in patients with cancer and HCT recipients are currently underway (ClinicalTrials.gov identifiers: NCT01215734, NCT01205581).

Conjugated Vaccines are Preferred Over Polysaccharide Vaccines

In general, conjugated vaccines elicit improved immune responses in HCT recipients compared with pure polysaccharide vaccines, and are therefore preferred.[6,20–25]

Unlike polysaccharide vaccines, conjugated vaccines induce a robust T-cell–dependant immune response and generate long-term memory loss. A 13-valent pneumococcal conjugated vaccine (PCV-13) was recently approved by the FDA and replaced PCV-7. In addition to the 7 serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) contained in PCV-7, the vaccine contains 6 additional serotypes (1,

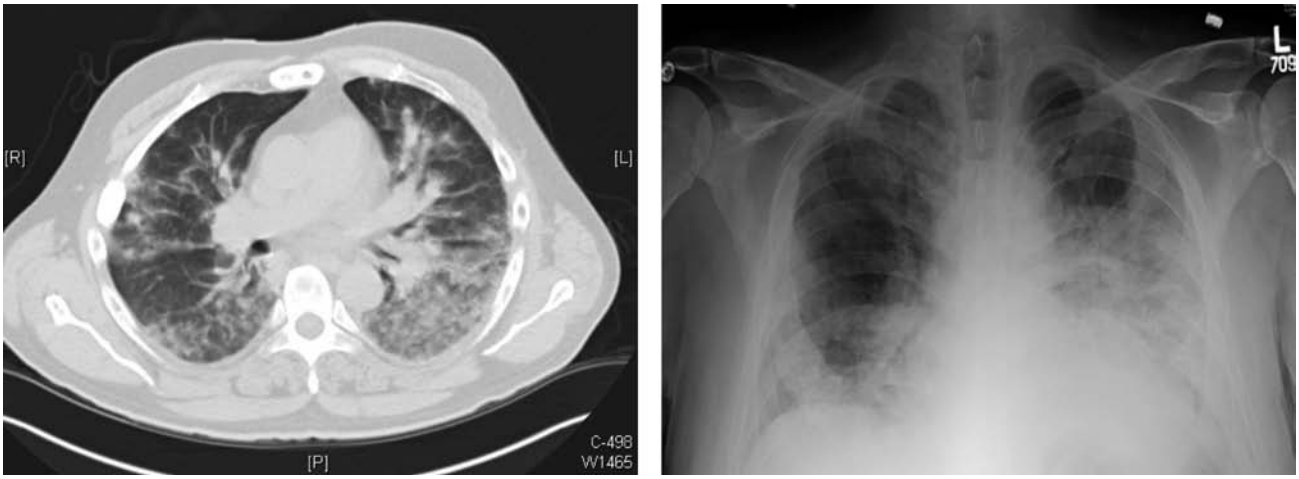

Figure 1 Severe pandemic H1N1 influenza pneumonia in a 47-year-old man with multiple myeloma 10 months after allogeneic hematopoietic cell transplantation who presented with fevers, cough, headaches, and myalgia. He had received the trivalent influenza vaccine 1 month before admission (pandemic 2009 H1N1 vaccine was not yet available). He subsequently died of hypoxemic respiratory failure caused by pandemic H1N1 infection despite receiving treatment with oseltamivir followed by peramivir.

3, 5, 6A, 7F, and 19A). PCV-13 protects particularly against serotype 19A, which has become the most common pneumococcal serotype since implementation of vaccination with PCV-7, and is often resistant to penicillins.[26] The ASBMT/EBMT guidelines recommend 3 sequential doses of PCV-13 starting 3 to 6 months after HCT. A fourth dose of PPSV-23 is recommended 8 weeks after the third dose of PCV-13 to broaden the immune response to include serotypes not included in PCV-13. However, for patients with active chronic GVHD who are likely to have a poor response to PPSV-23, a fourth dose of PCV-13 should be considered instead.[12] One-time revaccination with PPSV-23 at 5 years after the first dose is currently recommended for immunocompromised patients.[27]

Similarly, meningococcal conjugate vaccine (MCV-4) is preferred over meningococcal polysaccharide vaccine, although data on efficacy in HCT recipients are lacking. One dose is recommended 6 to 12 months after HCT.

Live-Attenuated Vaccines After HCT

Live-attenuated vaccines (eg, measles, mumps, and rubella [MMR]; varicella) are recommended 24 months after HCT in patients without GVHD and who are not on any immunosuppressive therapy for at least 3 months. Administration of MMR vaccines 24 months after HCT in patients free of GVHD and without immunosuppressive therapy was shown to be safe and immunogenic.[2,28]

HCT recipients are at high risk for herpes zoster reactivation because of diminished T-cell immunity against varicella-zoster virus (VZV). The risk is highest during the first year after HCT in the absence of prophylaxis.[29–31] Antiviral prophylaxis reduces the risk of herpes-virus associated diseases[31]; however, the duration of prophylaxis varies among transplant centers. Vaccination against VZV may help restore immunity against the virus and may reduce the risk of zoster reactivation in HCT recipients. However, no data are yet available on the safety and immunogenicity of the varicella vaccine after HCT. In 2 small studies, live-attenuated varicella vaccine was administered at least 12 months after HCT to children who were free of GVHD and off immunosuppression, and was shown to be both safe and immunogenic.[32,33] No data are available, however, on the safety and immunogenicity of varicella vaccine in adults.

Two main varicella vaccines are available: a vaccine for the prevention of chickenpox and a shingles vaccine for the prevention of zoster. The shingles vaccine has approximately 14-fold-higher plaque-forming units of attenuated virus compared with the varicella vaccine. In the absence of data, the EBMT group recommends against using the shingles vaccine after HCT because of the much higher viral titer contained in this vaccine.[6] The shingles vaccine, however, was found to be safe and immunogenic in adult patients with HIV who have CD4 counts of 200 cells/mm^3 or

greater and HIV RNA levels less than 75 copies/mL.[34] A phase II, randomized, observer-blind, placebo-controlled, multicenter clinical trial of an inactivated zoster vaccine in adult autologous HCT has been completed, and a phase III trial is currently underway. If successful, this might alleviate the existing concerns regarding the administration of live-attenuated varicella vaccine in HCT recipients.

Other live-attenuated vaccines that are generally contraindicated 24 months or less after HCT include intranasal influenza, bacille Calmette-Guérin, oral poliomyelitis vaccine, rotavirus vaccine, oral typhoid vaccine, and yellow fever vaccine. In certain circumstances live-attenuated vaccines may be considered, such as for patients living in or traveling to endemic areas where inactivated alternative vaccines are unavailable (eg, yellow fever). Household contacts of HCT recipients should not receive the oral poliomyelitis vaccine because of the risk of person-to-person transmission. When available, the inactivated types of vaccines, such as for influenza, poliomyelitis, and typhoid fever, should be given to HCT recipients and their household contacts.

Should Patients With Active Chronic GVHD be Vaccinated?

Patients with chronic GVHD are at increased risk for severe infections because of the associated prolonged immunodeficiency and functional asplenia.[35–37] Patients with chronic GVHD respond poorly to polysaccharide vaccines[20,21]; therefore, conjugated vaccines (Hib, PCV-13, MCV-4) are preferred where available. Administration of inactivated vaccines, especially against *Streptococcus pneumoniae*, *H influenzae* type b, and influenza, is recommended in patients with chronic GVHD regardless of the intensity of immunosuppressive therapy. The vaccination response is generally poor, however, for patients on substantial immunosuppression, such as those receiving greater than 0.5 mg/kg of prednisone or on combination immunosuppressive treatment. Vaccination for other than *S pneumoniae*, *H influenzae* type b, and influenza in this setting could be postponed but not for more than 3 months.[13]

Live attenuated vaccines are generally contraindicated in patients with active chronic GVHD.

Checking Titers After Vaccination

Immunologic response to vaccines administered after HCT varies significantly among recipients. Several factors, including underlying disease, age, conditioning regimens (antithymocyte globulin), type of transplant (autologous, allogeneic, haploidentical, cord blood), and whether GVHD is present, can influence immune response to vaccination.[13]

Assessing baseline antibody titers before a vaccination series and after (1 month after last dose) would be ideal to determine the level of seroprotection afforded by particular vaccines. This is particularly important in patients with active chronic GVHD. It would also allow knowledge to be gained about a particular vaccine immune response and how to modify the current vaccine strategies to improve immunogenicity, because data on immune responses against specific vaccines after HCT are largely lacking. Testing at 1 year and 2 years postvaccination would help assess long-term immunity and whether a vaccination booster is warranted. However the cost-effectiveness of serotesting in this context has not been studied.

Notably, quantitative correlates of protection after vaccination have been suggested for many vaccines in the general population but not in HCT recipients.[13,38] Potential pitfalls in assessing antibody response after vaccination in HCT recipients include passively transferred antibodies via immunoglobulin administration, and recipient-derived antibodies that may linger during the first few months after transplantation.[39]

Antibody Response to Vaccines in Patients Who Received Rituximab or Alemtuzumab

Rituximab

Rituximab is a monoclonal antibody against CD20 that results in a rapid and prolonged depletion of B cells.[40] Patients with lymphoma and chronic lymphocytic leukemia (CLL) and recipients of allogeneic HCT who receive rituximab as part of combination chemotherapy for the treatment of lymphoma or CLL or as treatment of active chronic GVHD (allogeneic HCT), may have an impaired ability to mount humoral response to vaccination during or within 6 months after treatment.[41–43]

In a recent study involving patients with lymphoma (n=67), none who received rituximab within 6 months

before vaccination were able to mount seroprotective titers against a monovalent adjuvanted H1N1 influenza A vaccine when compared with healthy volunteers (0% vs. 82%, respectively).[44] In another smaller study of patients with lymphoma, none who were treated with rituximab and received 1 or 2 doses of influenza vaccine achieved seroprotective titers.[45] Separating the effect of treatment from that of the underlying disease is difficult. Patients in this group require special consideration and additional preventative measures.

Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody against CD52 that causes a rapid and profound lymphopenia mainly affecting CD4+ T cells.[46] Although B-cell numbers recover to baseline levels within 3 months after alemtuzumab, the B-cell pool is dominated by immature B cells that are unable to mount an antibody response to vaccination.[47] No published data are available on vaccine responses after alemtuzumab in patients with hematologic malignancies. The manufacturer does not provide clear guidance on when a live vaccine can be administered safely post alemtuzumab, other than to say that no live vaccines should be given to patients who "recently" received alemtuzumab. Guidelines for immunizations issued by the United Kingdom Department of Health give some guidance on the timing of live vaccines administration in patients who received biologic agents.[48] The suggested timeline is as follows: at least 4 weeks before first administration of any biologic agent or 12 months after rituximab, 6 months after infliximab, 3 months after adalimumab, or 4 weeks after etanercept. No timeline for administration was given for patients who received alemtuzumab.

Vaccination for Patients With Multiple Myeloma

No large studies have been performed regarding vaccine response in patients with multiple myeloma. Wide ranges of responses have been reported, depending on intensity of chemotherapy and whether purine analogues or monoclonal antibodies were used. Immune response to influenza vaccination, for example, has been historically very poor, with significant differences in responses to various components of the trivalent influenza vaccine. Robertson et al[49] reported a response rate of 19% (protective antibody titer of ≥ 40 for each vaccine antigen) in patients with multiple myeloma. Ljungman et al[45] showed that giving 2 doses of the influenza vaccine in patients with hematologic malignancies did not improve the antibody response. In this small study, patients with multiple myeloma responded poorly to influenza vaccine compared with those with myeloproliferative disorders, with 0 of 16 patients with multiple myeloma having seroprotective titers against H1N1, 4 of 16 (25%) with titers against H3N2, and 1 of 16 (6%) with titers against influenza B.

Patients with multiple myeloma have an impaired ability to mount a humoral response to specific vaccine antigens, and for the most part have poor response to vaccination. Therefore, additional preventative strategies also should be considered in this population.

Vaccination for Adults With Other Hematologic Malignancies

In general, all inactivated vaccines, if indicated, should be administered more than 10 days before initiation of chemotherapy or 3 months after completion of chemotherapy in adults with other hematologic malignancies, including acute leukemia and myeloproliferative diseases. Patients do not need to be revaccinated after chemotherapy as long as they received their scheduled vaccines before initiation of chemotherapy.

In general, live-attenuated vaccines should not be administered until 3 months after completion of the last chemotherapy cycle.[11]

Vaccination of Family Members

Most patients with hematologic malignancies may not achieve seroprotection after vaccination and remain at risk for life-threatening infections because of vaccine-preventable illnesses. Therefore, vaccination of family members, household contacts, and health care workers of patients with hematologic malignancies and HCT recipients is highly recommended to minimize potential exposures.[6] Inactivated influenza vaccine, inactivated poliomyelitis vaccine, DTaP (dipthteria/tetanus/acellular pertussis) for children younger than 7 years, and Tdap (tetanus/dipthteria/pertussis) for adolescent and adults family members are recommended. Household contact and family members may also receive live-attenuated vaccines, such as MMR and varicella vaccines. The risk of person-to-person transmission is rare. However, if a postvaccination rash develops after vari-

cella vaccination in a household member, then direct contact with the immunocompromised patient should be avoided until all skin lesions are crusted or the rash has resolved. Acyclovir prophylaxis might be indicated in this case.

Conclusions

Vaccination is an important strategy for preventing infections in patients with hematologic malignancies. Revaccination after HCT is recommended for preventing life-threatening infections in this high-risk population and should be initiated between 6 and 12 months after HCT for inactivated vaccines and after 24 months for live-attenuated vaccines, provided patients are free of GVHD and are off immunosuppression. Patients who received monoclonal antibodies (rituximab, alemtuzumab) less than 6 months before vaccination have poor antibody response to vaccines. New advancements in vaccine development, such as the development of subunit vaccines to replace live-attenuated vaccines, are promising and may lead to more immunogenic and safer vaccines.

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Instructions for Completion

To participate in this journal CE activity: 1) review the learning objectives and author disclosures; 2) study the education content; 3) take the post-test with a 70% minimum passing score and complete the evaluation at **http://education.nccn.org/node/4516;** 4) view/print certificate. After reading the article, you should be able to answer the following multiple-choice questions. Credit cannot be obtained for tests completed on paper. You must be a registered user on NCCN.org. If you are not registered on NCCN.org, click on "New Member? Sign up here" link on the left hand side of the Web site to register. Only one answer is correct for each question. Once you successfully answer all post-test questions you will be able to view and/or print your certificate. Software requirements: Internet

Post-Test Questions

1. True or False: In general, conjugated vaccines elicit earlier and stronger immune responses in HCT recipients compared with pure polysaccharide vaccines, and are therefore preferred in this patient population.
2. Which of the factors listed below does NOT influence immune response to vaccination administered after HCT?
   a. Underlying disease
   b. Age
   c. Ethnicity
   d. Type of transplant
3. True or False: Live attenuated vaccines are generally contraindicated in patients with active chronic GVHD.