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REVIEW

Vaccinations in patients with hematological malignancies

C. Tsigrelis [a,b], P. Ljungman [c,d,*]

[a] Division of Infectious Diseases, University Hospitals Case Medical Center, Cleveland, OH, USA
[b] Case Western Reserve University, Cleveland, OH, USA
[c] Depts. of Hematology and Allogeneic Stem Cell Transplantation, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden
[d] Div. of Hematology, Dept. of Medicine Huddinge, Karolinska Institutet, Stockholm, Sweden

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ABSTRACT

Patients with hematological malignancies are at risk for a number of infections that are potentially preventable by vaccinations such as pneumococcal infections and influenza. Treatment, especially with anti-B-cell antibodies and hematopoietic stem cell transplantation (HSCT), negatively impacts the response to vaccination for several months. It is therefore recommended that patients be vaccinated before initiating immunosuppressive therapy if possible. The risk of side-effects with inactivated vaccines is low, but care has to be taken with live vaccines, such as varicella-zoster virus vaccine, since severe and fatal complications have been reported. HSCT patients require repeated doses of most vaccines to achieve long-lasting immune responses. New therapeutic options for patients with hematological malignancies that are rapidly being introduced into clinical practice will require additional research regarding the efficacy of vaccinations. New vaccines are also in development that will require well-designed studies to ascertain efficacy and safety.

Contents

1. Introduction

Over the past several decades, the number of immunocompromised patients has rapidly increased. These patients are vulnerable to numerous infections against which vaccines exist. The 2009 H1N1 influenza A pandemic illustrated the importance of rapid design and implementation of

* Corresponding author at: Department of Hematology and Center for Allogeneic Stem Cell Transplantation, Karolinska University Hospital, 14186, Stockholm, Sweden. Tel.: +468 58582507.
E-mail address: per.ljungman@ki.se (P. Ljungman).

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vaccination strategies for patients with hematological malignancies including hematopoietic stem cell transplant (HSCT) recipients. Immunosuppressed patients were recognized early during the pandemic to be at increased risk for severe complications and vaccines were rapidly tested in these patient groups [1–6]. Safety of vaccines is also an important issue since severe and life-threatening complications can develop from live attenuated vaccines [7].

Vaccination in patients with hematological malignancies is complex as the background and characteristics of immunosuppressed states differ between different patient categories. Patients undergoing allogeneic HSCT are the most deeply immunocompromised and new transplant techniques are constantly developing that are challenging the knowledge regarding the immune responses to vaccination collected from earlier studies. Therapy for hematological malignancies has also changed substantially during the last decade with the introduction of drugs having different modes of action, including monoclonal antibodies, drugs with immunomodulatory effects such as lenalidomide, and targeted drugs such as thyrosine kinase inhibitors. Therefore prior vaccination studies might not accurately represent the current risks and benefits of vaccinations. In general, almost all vaccination studies have assessed surrogate endpoints, namely immune responses, since true efficacy studies are difficult to perform due to the number of patients required to assess prevention of infection or disease.

2. When is it meaningful to start vaccinations?

Since all types of immunosuppressive therapy, including transplantation, are likely to suppress the response to vaccination, it might be beneficial to administer vaccines before the start of therapy for hematological malignancies or before HSCT. Recovery of immune function after cessation of immunosuppressive therapy is an important factor that impacts the development of an adequate response to vaccination. Furthermore, vaccine safety has to be considered. The optimal time to administer vaccines after initiation of immunosuppressive therapy or after HSCT depends on a number of factors. Tables 1 and 2 outline indications for select vaccines before and after the initiation of immunosuppressive therapy. The recommendations are adapted by the authors from Rubin et al. [8] and Ljungman et al. [9].

For patients with hematological malignancies, cancer chemotherapy can result in severe impairment of immune function, and the timing of recovery of immune function is variable depending on the duration and type of chemotherapy. In one study of children with ALL, the number of blood B-lymphocytes increased to normal levels one month after stopping chemotherapy, although it took 6 months for serum IgG to recover in most patients suggesting defective B-lymphocyte function [10]. In another study of children with ALL and Hodgkin lymphoma, although improvement occurred during the 1st year after cessation of chemotherapy, 81% of patients continued to show one or more immune abnormalities after 9–12 months [11]. Severe impairment of immune function similarly occurs following HSCT, including a loss of pre-transplant immunity to a number of vaccine-preventable conditions including measles, mumps, and rubella [12], poliovirus [13], and tetanus [14], which underscores the importance of vaccination after HSCT. However, pre-exiting recipient immunity can frequently be retained for several months after HSCT; therefore if indicated and if patients are not already immunosuppressed, vaccination prior to HSCT may provide transient protection until vaccination can be performed later on in the patient's course [8,15].

Inactivated vaccines are safe to administer in immunocompromised patients but the strength of the elicited immune responses can vary depending on the timing of vaccine administration with respect to the given immunosuppressive therapy. For patients with hematological malignancies, good responses can be obtained with inactivated vaccines if there is sufficient time prior to initiation of chemotherapy (e.g. >=2 weeks) [16,17]. However, patients receiving intensive chemotherapy, such as induction or consolidation chemotherapy for leukemia, have poor immune response to vaccination [18]. Patients with hematological malignancies are likely to respond favorably to vaccination after chemotherapy has been completed, while there has been a more variable response to vaccination during maintenance chemotherapy [19–22]. Existing guidelines suggest administering inactivated vaccines at least two weeks prior to chemotherapy or during maintenance chemotherapy, or 3 months after cancer chemotherapy is completed, with the exception of those receiving anti-B-cell antibodies, where administration should be delayed for at least 6 months [8,15,23].

Similarly, for HSCT patients, who are not already immunosuppressed, vaccination prior to transplant may improve immunity [24], and guidelines suggest administering inactivated vaccines prior to HSCT if there is an interval of ≥2 weeks before initiation of immunosuppressive therapy [8,15]. Following HSCT, patients may develop an adequate immune response to vaccination as early as 3–6 months after allogeneic HSCT. This was shown in a randomized study with 7-valent pneumococcal conjugate vaccine (PCV7) in which the immune response at 3 months was similar to the response at 9 months after HSCT [25]. Following HSCT, guidelines recommend administering inactivated vaccines starting as early as three months with PCV13,

Table 1
Vaccinations in patients with hematological malignancies.

Vaccine	When[a]	Recommendations
PCV13 followed by PPSV23	Before therapy	Indicated in lymphoma, myeloma, and CLL patients if possible
	After therapy	Response to vaccination is poor for at least 6–12 months after treatment with anti-B cell antibodies. Unclear if repeated doses of PCV13 are beneficial.
Inactivated influenza vaccine	Before therapy	Likely to be beneficial although studies are lacking
	After therapy	Administer annually to all patients Intensive immunosuppressive therapy will decrease response to vaccination Anti-B-cell antibody therapy suppresses response to vaccination for 6–12 months
Varicella vaccine	Before therapy	Negative risk – benefit ratio in patients with active disease[b]
	After therapy	For patients in remission, administer no earlier than 3 months after completion of chemotherapy and at least 12 months after anti-B-cell antibody therapy
Zoster vaccine	Before therapy	Negative risk – benefit ratio in patients with active disease[b]
	After therapy	For patients in remission, administer no earlier than 3 months after completion of chemotherapy and at least 12 months after anti-B-cell antibody therapy
MMR	Before therapy	Negative risk – benefit ratio in patients with active disease[b]
	After therapy	Seronegative adults depending on the local epidemiological situation. For patients in remission, administer no earlier than 3 months after completion of chemotherapy and at least 12 months after anti-B-cell antibody therapy
Travel vaccines	After therapy	Efficacy of inactivated vaccines (e.g. hepatitis, poliovirus, diphtheria) are unclear, although they lack risks Live vaccines (e.g. yellow fever) have unclear efficacy and safety

PCV13: 13-valent pneumococcal conjugate vaccine; PPSV23: 23-valent pneumococcal polysaccharide vaccine; MMR: measles, mumps, rubella vaccine.
[a] Timing of vaccine administration with respect to initiation of immunosuppressive therapy.
[b] Do not administer live vaccines unless indicated, patient is not immunosuppressed, and there is ≥4 weeks before start of immunosuppressive therapy.