Influenza Vaccination in Patients With Cancer: an Overview

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Influenza infection is a potential cause of additional morbidity and mortality in patients who are immunocompromised because of cancer or its treatment. Of particular note, influenza infection may delay or interrupt chemotherapy and necessitate hospitalization. Successful immunization depends on an intact immune system that can produce antibodies in response to antigen exposure. Patients with cancer often have a suppressed immune system, resulting from their disease and/or immunosuppressive therapies, and as a consequence they may have a suboptimal serologic response to influenza vaccination. Since vaccination is the only proven method for preventing influenza infection, the Advisory Committee on Immunization Practices recommends seasonal influenza vaccination for adults without contraindications who have disease- or medication-related immunosuppression. Patients with cancer should be given the trivalent inactivated vaccine. Preliminary data suggest that administering the vaccine between cycles of chemotherapy may yield the best results.

Yearly influenza vaccination is the most effective way to prevent influenza infection and its complications.[1] The efficacy of influenza vaccination in patients with cancer has not been well studied in general, and in patients with solid tumor malignancies in particular. The optimal timing for administration of the influenza vaccine in patients with cancer who are receiving chemotherapy is not clear. This review highlights the burden of influenza in patients with cancer, the response to influenza immunization in this patient population, and vaccination recommendations.

Influenza Viruses

Influenza A viruses are negatively-stranded RNA viruses with eight segmented RNA components in the genome. Two of the proteins coded by the genome are glycosylated proteins on the cell surface—hemagglutinin (H) and neuraminidase (N)—that facilitate viral attachment and release from the cells of the host, as well as determining how the virus strains are named (eg, H1N1, H3N2: the numbers refer to the subtypes of the H and N antigens).[2] The virus is capable of genetic variability as a result of two features. First, its segmented genome allows reassortment of genetic material, which explains why the H1N1 virus contains genetic material from pigs, humans, and birds. Second, inefficient proofreading during viral RNA replication causes transcription errors and amino acid substitutions in H and N; this results in new variants that can evade pre-existing immunity and thus cause epidemics.[2]

Influenza Vaccination

Circulating human influenza viruses are subject to antigenic shifts that require annual adaptation of the vaccine formulation. The vaccine is adapted to help ensure the closest match between circulating strains and those found in the vaccine.[3] In the past, there have been monovalent and bivalent vaccines. Since 1977, however, trivalent vaccines, which contain influenza A virus subtypes H1N1 and H3N2 and influenza B viruses, have been used.[4] The rapid global spread of a novel influenza A virus of swine origin (H1N1) prompted the World Health Organization (WHO) to declare a pandemic on June 11, 2009.[5,6] According to data from the Centers for Disease Control and Prevention (CDC), the virus had infected at least 1 million individuals as of August 2009.[6,7] As of October 3, 2009, 99% of circulating influenza viruses in the United States were 2009 H1N1 influenza virus.[8] The trivalent seasonal influenza vaccines in use at the time did not provide protective immunity against the H1N1 virus.[6] Thus, a new vaccine against the H1N1 influenza virus was developed, and this product was approved by the FDA in September 2009.
Influenza Vaccines Recommended by the Advisory Committee on Immunization Practices (ACIP) for the 2010–2011 Influenza Season

Vaccines for the 2010-2011 northern hemisphere influenza season contain the following: A/California/7/2009 (H1N1-like virus); A/Perth/16/2009 (H3N2-like virus); and B/Brisbane/60-2008-like antigens.[9] The Table lists the influenza vaccines recommended by the Advisory Committee on Immunization Practices (ACIP) for the 2010-2011 influenza season.[9]

**The Burden of Influenza in Cancer Patients**

Influenza infection is a potential cause of additional morbidity and mortality in patients who are immunocompromised because of cancer or its treatment.[10] During the Asian influenza epidemics of 1957 to 1966, increased mortality was noted in cancer patients.[11] Of particular note, influenza infection may delay or interrupt chemotherapy and necessitate hospitalization.[10,11]

Active immunization by way of influenza vaccination relies on an intact immune system that can produce antibodies in response to antigen exposure. Persons with cancer, however, often have immune deficiencies as a result of their disease and/or immunosuppressive therapies. Thus, a suboptimal serologic response to influenza vaccination may be seen in this population.[10] However, these high-risk patients are at risk for complications from influenza infection and need to be protected with immunization. Misconceptions among both patients and physicians about the benefits of the vaccine in these patients, including concerns about safety and side-effect profiles, may hinder timely administration of the vaccine.[10]

**CDC Recommendations for Influenza Vaccination**

The ACIP provides annual recommendations for use of the influenza vaccine. This year, the ACIP recommends seasonal influenza vaccination for adults without contraindications who have disease- or medication-related immunosuppression.[9] Patients with hematologic and solid malignancies are considered to be functionally immunosuppressed secondary to their disease and/or treatment and should be given the trivalent inactivated vaccine.

**Assessing Response to Influenza Vaccination**

In the FDA’s “Guidance for Industry” document regarding inactivated influenza vaccines, results of hemagglutination (HI) assays are considered appropriate for assessing immunogenicity.[4] HI assays provide a standardized method for comparing serologic responses to various vaccines.[12] The basis of the HI assay is that antibodies to influenza virus prevent virus attachment to red blood cells. Hemagglutination is therefore inhibited when antibodies are present.[13] Post-vaccination HI antibody titers of 1:40 or greater, or a four-fold rise in titers from those measured before vaccination, is indicative of protective immunity. Studies have also shown that these same HI titers correspond with a 50% decreased risk of active influenza infection in patients.[14]

Prospective studies in healthy persons demonstrate the inactivated influenza vaccine to have an efficacy of 70% to 90% for the prevention of influenza.[15] A question frequently asked by patients receiving chemotherapy is whether they will benefit from vaccination against influenza.[16]

**Influenza Vaccination in Patients With Hematologic Malignancies**

Lymphoreticular malignancies, in particular, are inherently immunosuppressive. Active chemotherapy administration further increases the insult to patients’ immune systems. Studies have consistently shown the rate of response to influenza vaccination in patients with hematologic malignancies to be poor.[17]

Mazza and colleagues administered the trivalent, inactivated influenza vaccine to 29 adult patients with a diagnosis of lymphoma (Hodgkin disease or non-Hodgkin lymphoma). All patients were either actively receiving chemotherapy or had completed chemotherapy within the prior 3 months. Ten percent of patients with lymphoma and 45% of controls mounted a four-fold rise in HI titers to any influenza A antigen. A serologic response to the influenza B antigen was seen in 31% of patients with lymphoma, compared with 48% of controls. None of the patients with lymphoma developed protective immunity to both influenza A and B antigens.[17]

In an attempt to increase the serologic response to influenza vaccination in patients with lymphoma, Lo and colleagues studied a two-dose influenza vaccine regimen. Forty-one adult patients with lymphoma who were receiving chemotherapy were immunized with trivalent, inactivated influenza vaccine. The vaccine was administered on day 1 of two consecutive cycles of chemotherapy that were given 4 weeks apart. Seroconversion to the H1N1, H3N2, and B virus occurred in 32%, 24%, and 20% of patients, respectively, following one dose; and in 49%, 41%, and 46% of patients, respectively, following the second dose. A four-fold rise in HI titers was considered consistent with protective immunity. There were no statistically significant differences between responders and non-responders when stratified by age, gender, history of prior influenza vaccination, type of
lymphoma, or stage of disease.[18]

Another study, by Robertson and colleagues, used a single dose of trivalent, inactivated influenza vaccine to assess response to vaccination in 52 patients with multiple myeloma. Sixteen patients had received chemotherapy within the prior week, and seven patients had received an autologous stem cell transplant within the previous 6 months. Twenty-one patients were receiving interferon-α therapy during the study. An HI titer of 1:40 or greater was considered protective. Only 19% of patients developed protective titers against all three influenza virus strains. Poor response to vaccination was seen in patients who had had a stem cell transplant within the previous 6 months and in patients who had received chemotherapy during the 7 days prior to vaccination.[19]

Reference

Therapeutic Agents

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<tbody>
<tr>
<td>Live attenuated influenza vaccine</td>
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<td>Oseltamivir (Tamiflu)</td>
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<td>Trivalent inactivated influenza vaccine</td>
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Influenza vaccine serologic response was studied in 48 patients who received bone marrow transplants (13 autologous and 35 allogeneic). Fifteen patients had primary nonmalignant diseases; the diseases in the remaining 33 patients included acute and chronic leukemias, lymphomas (Hodgkin and non-Hodgkin), neuroblastoma, and myelodysplastic syndrome. Two doses of trivalent, inactivated influenza vaccine were administered 1 month apart, 2 to 82 months post-transplant. An HI titer of 1:40 or greater was considered protective. Only 25% of patients developed protective immunity against the H1N1 and B virus strains at 4 weeks, and 27% of patients had a serologic response to H3N2. There was a statistically significant association between development of protective immunity and longer time between transplant and immunization.[3]

These studies confirm the poor rates of response to influenza vaccination seen in patients with hematologic malignancies.[17]

Influenza Vaccination in Patients With Epithelial Malignancies

Knowledge of serologic response to seasonal influenza vaccine remains scanty in patients with cancer and is particularly sparse in those with solid tumors.[1,4]

A study conducted by Ganz and colleagues investigated the serologic response to bivalent inactivated influenza vaccination in 17 patients with either a solid tumor (lung, head and neck, breast, or melanoma) or a hematologic malignancy (lymphoma or Sezary syndrome). A four-fold rise in HI titers was considered consistent with protective immunity. Protective immunity against each of the two influenza A strains in the vaccine was achieved by 41% and 47% of patients, respectively.[8]

A study of 41 patients with lung cancer (small-cell and non–small-cell) conducted by Anderson and colleagues showed a rate of response to the inactivated trivalent seasonal influenza vaccination of...
78%. [4] An HI titer of 1:40 or greater was considered protective. This response is similar to that seen in historical controls: typically, more than 80% of healthy adult volunteers develop protective immunity against influenza following vaccination. [10] Lung cancer histology, chemotherapy within the previous 4 weeks, or systemic corticosteroid medication had no significant effect on protective HI response. This was a small study, however, and no large trials exist to replicate this information.

Timing of Influenza Vaccination With Regard to Chemotherapy

It has been suggested that antibody response is weaker in patients receiving chemotherapy. [20] A small number of studies, with heterogeneous patient populations, have documented rates of seroconversion following vaccination in patients with malignant disease who were receiving chemotherapy. The majority of these studies have been conducted in patients with hematologic malignancies and are not stratified for tumor type or stage, chemotherapy administration schedule, or vaccine type. [10,11]

The timing of influenza vaccination with regard to chemotherapy administration schedule was addressed in a 1977 study by Ortbals and colleagues. This study looked at 42 patients and included those with both hematologic and solid malignancies. Patients were randomly assigned to receive a bivalent inactivated influenza vaccine either on day 1 of chemotherapy or at the time of count nadir between cycles. A four-fold rise in HI titers was considered protective. Fifty percent of patients vaccinated at the time of chemotherapy administration showed seroconversion, compared with 95% of patients who were vaccinated between chemotherapy cycles when their counts were at nadir. [11]

Antivirals

Antiviral treatment within 48 hours of onset of symptoms may make influenza infection milder, shorten the duration of illness, and decrease complications. Oseltamivir (Tamiflu) and zanamivir (Relenza) target the neuraminidase enzyme and are effective treatments for influenza infection. The standard dosage for oseltamivir is 75 mg by mouth twice a day, and that for zanamivir is 10 mg (as two 5-mg inhalations) twice daily. Both drugs are typically given for 5 days, although therapy duration may be extended if clinically indicated. [2,21] Oseltamivir or zanamivir administration should be considered for all patients with disease- or medication-related immunosuppression who have suspected or confirmed influenza infection.

Conclusions

The available literature shows that patients with cancer do mount an immune response to influenza immunization. It is unclear, however, whether this response is as robust as that seen in otherwise healthy persons. The CDC recommends annual influenza vaccination for this patient population. Preliminary data suggest that influenza vaccination between cycles of chemotherapy may be more effective than vaccination on day 1 of chemotherapy. Larger, well-designed prospective studies are needed to assess the efficacy of the influenza vaccination in patients with cancer, and the optimal timing of vaccination relative to chemotherapy administration.

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