Curr Infect Dis Rep (2013) 15:486–490
DOI 10.1007/s11908-013-0368-7

Influenza Vaccination in Oncology Patients

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Published online: 22 November 2013

Abstract It is well established that the immunological response to the seasonal trivalent influenza vaccine is attenuated in cancer patients. Furthermore, rates of seroprotection and seroconversion vary by malignancy type and are higher in patients with solid tumors, as compared either with those with hematologic malignancies or with allogeneic hematopoietic stem cell recipients. In 2009, a novel influenza strain prompted development of new vaccines and evaluation of alternative dosing strategies in an attempt to increase the rates of seroconversion in immunocompromised patients, further complicating this issue. Recent literature has demonstrated that the use of myeloablative chemotherapy regimens and biologics is correlated with decreased immunogenicity and response to influenza vaccines. Much debate still exists as to the optimal timing of influenza vaccination. Delaying vaccination from 1 week following standard chemotherapy up to 6 months following rituximab is increasingly supported by studies in this heterogeneous population.

Keywords Influenza vaccination · Oncology · Hematology · Allogeneic hematopoietic stem cell transplantation

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Introduction

Influenza is an RNA virus from the *Orthomyxoviridae* family with two clinically relevant strains: influenza A and B. Influenza A is classified on the basis of its surface hemagglutinins (HA 1 to 16) and neuraminidases (NA 1 to 9) [1]. Influenza B is separated into two distinct genetic lineages of Yamagata and Victoria strains [2]. The annual seasonal influenza vaccine recommended by the World Health Organization (WHO) is either a trivalent inactivated vaccine (TIV) containing antigens against two circulating strains of influenza A and one strain of influenza B or a quadrivalent inactivated influenza vaccine (QIV) containing antigens against two strains of influenza A and two strains of influenza B. Small changes on a yearly basis, such as point mutations in HAs and NAs, lead to antigenic drift. The previous year's antibody response post-seasonal-vaccine is inadequate to neutralize the new circulating influenza virus, leading to increased susceptibility to infection. The subtly altered circulating strains of influenza virus are the driving force for the WHO's changing the antigens contained in the vaccine annually. When large changes occur in HAs and NAs, also known as antigenic shift, there is minimal recognition of the virus by the immune system, leading to a potential spread of influenza infection of endemic or pandemic proportions [3].

Influenza vaccines are either inactivated or live attenuated. Live attenuated vaccines are the preferred vaccine for pediatric patients or those receiving their first ever influenza vaccine. Live attenuated vaccine is not considered a safe option for the immunosuppressed or their family members. Inactivated intramuscular, intradermal, and adjuvanted vaccines (monovalent or trivalent) have been assessed to various degrees in immunosuppressed individuals, including oncology patients. Rates of seroprotection and seroconversion vary by malignancy type and are higher in patients with solid tumors, as compared either with those with hematologic malignancies or with allogeneic hematopoietic stem cell recipients (HSCT) [4•].

Annual outbreaks of influenza infection lead to a wide range of symptoms in healthy and immunosuppressed patients. Immunosuppressed individuals are at a higher risk of acquisition of infection and have significant infection-related morbidity and mortality [5, 6]. Secondary infections, such as sinusitis, bacterial pneumonia, and exacerbations of chronic illnesses like asthma and chronic obstructive lung disease (COPD), may occur after an influenza infection [7]. Cancer patients are at risk of progression of influenza from an upper respiratory infection (URI) to a lower respiratory tract infection (LRTI). Lymphopenia has been found to be a significant factor leading to progression of URI to pneumonia [8]. In allogeneic HSCT recipients, acquisition of influenza infection closer to the time of transplant is correlated with an increased rate of progression of infection from a UTI to a LRTI [9]. BOS leads to progressive circumferential fibrosis as seen in HSCT recipients, which leads to higher rate of mortality per Kaplan–Meier survival curves ($p = .002$), when compared with non-BOS cases [10].

A number of interventions that decrease the spread of influenza infection have been implemented in order to mitigate these issues, such as vaccinating the community (i.e., herd immunity) and at-risk individuals as defined by current guidelines [2, 11, 12]. Even with a TIV or QIV that is well-matched to the strains in circulation, it has been found that influenza B strains are less immunogenic in the vaccine, thus making it harder to meet the European Committee for Proprietary Medicinal Products' (CPMP) requirements in both immunocompetent and immunosuppressed populations [6, 13•]. The benchmarks dictated by CPMP in the 19- to 59-year-old group are the following: (1) There must be a mean geometric titer increase between pre- and postvaccination of >2.5; (2) more than 70 % of recipients must be seroprotected by 21 days postvaccination; and (3) more than 40 % of vaccine recipients must have seroconverted by 21 days postvaccination [14].

Unfortunately, because of inherent immunological defects in oncology patients, due either to the primary malignancy or to the agents used for treatment, such as rituximab, they are at a higher risk of infection once exposed to the influenza virus. Subsequently, infections with influenza not only result in acute illness but also can lead to delays in vital treatments for the malignancy, such as successive dosing of chemotherapy or biologics. Vaccination continues to be the main way to boost immunity against seasonal influenza and, therefore, prevent infection. During the 2009 outbreak of the novel influenza H1N1 strain, the CDC broadened their recommendations for immunosuppressed patients, not only to receive the standard influenza vaccine, but also to receive a dose of the 2009 novel H1N1 vaccine despite a theoretical lower rate of response [15].

Current Recommendations and Updates in the Literature

Traditionally, patients who have received standard chemotherapy have a worse overall response to TIV if given within 7 days from their chemotherapy [16]. Within the hematology and oncology field, influenza vaccine is often delayed until the patient's immune system has a significantly higher chance of actually creating a sufficient response to meet the mark of seroconversion as dictated by CMPA. When novel H1N1 was initially circulating during the influenza season of 2009, an adjuvanted influenza vaccine was created using the same methodology as that for the seasonal vaccine and was aggressively given to immunosuppressed patients in Canada and Europe. At the time, adjuvanted influenza vaccination was unavailable in the U.S.

Hottinger and associates compared cancer patients given two doses of AS03-adjuvanted pandemic influenza vaccine with controls in a prospective manner during the 2009 influenza season in Geneva, Switzerland [4•]. The rates of seroprotection were similar between the two groups, but age and the use of recent chemotherapy, especially rituximab, continued to be independent determinants of poor vaccine response, by multivariate analysis [4•].

Xu and colleagues also utilized the opportunity of the novel H1N1 season to conduct a prospective trial assessing rates of seroprotection, geometric mean titers, and rates of seroconversion between a control group, patients with solid tumors on myelosuppressive chemotherapy, patients with solid tumors receiving nonmyelosuppressive therapies, and patients with hematologic malignancies [17]. Using a commercially available influenza A (H1N1) 2009 monovalent unadjuvanted vaccine, comparable rates of seroconversion were demonstrated between all four of the groups ($p = .512$). The authors theorized that their results contradicted those of other studies because they used an unadjuvanted vaccine and had overall higher levels of seroprotection at baseline than previously reported [17]. Despite the small sample size, it is significant that all of the patients within the hematologic malignancy arm who received rituximab had comparable rates of seroconversion, as compared with healthy controls.

Allogeneic HSCT recipients represent a unique and heterogeneous group of patients, due to the use of a number of different conditioning regimens and stem cell sources (i.e., reduced intensity vs. myeloablative, peripheral vs. cord blood). Studies assessing TIV responses in allogeneic HSCT recipients are further confounded by the relatively small numbers of patients included. Authors have repeatedly found that allogeneic HSCT recipients have decreased rates of seroconversion after TIV from the time of transplant up to 6–12 months posttransplant. There is a particular emphasis between the day of transplant to 6 months posttransplant, where there is still substantial suppression of both B- and T-cell populations, leading to decreased rates of seroconversion to

seasonal TIV. This phenomenon is also seen in other groups utilitizing immunosuppression with calcineurin inhibitors, mTOR inhibitors, and prednisone, such as solid organ transplant recipients, but to varying degrees [6, 18]. Two studies have demonstrated that the influenza vaccine is efficacious and does create a protective effect during this same relatively acute phase post-allogeneic-HSCT [19, 20]. Engelhard and colleagues performed a multivariate analysis and found age, a traditional issue with TIV response, and recent use of rituximab to be independent risks for poor vaccine response to the adjuvanted influenza A 2009 vaccine. Repeatedly reported risk factors contributing to decreased immunogenicity post-influenza-vaccination have been the receipt of rituximab or treatments for graft-versus-host disease—that is, an overall increased net state of immunosuppression [18, 21].

The number of influenza vaccine doses and type of administration strategy have been evaluated in attempts to increase the response rates to influenza vaccines in immunosuppressed patients. One randomized, prospective study of 65 allogeneic HSCT patients compared rates of seroconversion after one versus two influenza vaccine doses. In the arm receiving two doses of influenza vaccine, the doses were separated by 1 month. There was no difference in the primary endpoint as measured by seroconversion (≥4-fold increase) between the two groups. On the other hand, antibody responses to any one of the three vaccine strains was found to be dependent on whether the vaccine(s) were given less than or more than 1 year after transplant (RR 15.5, 95 % CI 3.2–76, $p < .01$) [22]. In parallel, peripheral blood mononuclear cells were also collected 8 weeks postvaccination in a total of 64 of the patients for measurement of IFN-γ by ELISpot testing. In a multivariate analysis of the T-cell responses, umbilical cord donors had significantly lower IFN-γ production, as compared with matched related or matched unrelated donors. Times from transplantation and steroid use were no longer significant variables in the T-cell response multivariate analysis [22].

The Use of Biologics

The increased use of biologics such as rituximab (monoclonal antibody against CD 20) and alemtuzumab (monoclonal antibody against CD 52) poses a growing issue within the cancer population from an infectious diseases perspective and in regard to appropriate timing of influenza vaccination [23]. Rituximab use results in the rapid loss of B-cells for a minimum of 6 months, and the patients traditionally do not reach pretreatment levels for up to 1 year [24]. Examples of regimens with rituximab include but are not limited to the treatment of lymphoma and EBV-related infections in recipients of allogeneic HSCT. The use of rituximab leads to significant defects in humoral immunity, ultimately resulting in a profoundly decreased vaccination response for 6–12 months post-last-rituximab-dose [23]. Yri and associates described rates of seroprotection in 67 lymphoma patients who received rituximab within 6 months of influenza vaccination. As compared with an 82 % seroprotection of healthy volunteers, the patients had a 0 % rate of seroprotection [25]. The potential bias in the study involves the innate issues of the particular disease state versus the effect of rituximab, but the bottom line is that the lack of seroprotection is significant.

Another study of 31 non-Hodgkin's lymphoma (NHL) patients during the 2008–2009 influenza season compared their rates of seasonal TIV vaccine response with those of healthy controls. The rates of seroconversion were statistically lower in the NHL patients, despite being disease free, as compared with the healthy controls in each of the three strains tested. Notably, 50 % of the NHL patients had their last dose of chemotherapy more than 29 months prior to the TIV [7]. Multivariate analysis also found that low serum IgA or IgM, the use of multiple chemotherapeutic agents in the past, and the use of fludarabine in the patient population had an association with poor serological response after standard influenza vaccination [7].

Alemtuzumab, another biologic with increasing use in the oncology setting, rapidly depletes lymphocytes, particularly CD4+ T-cells [26]. Due to the complex interplay of the human immune system, B-cells start to repopulate approximately 3 months after the last dose of alemtuzumab, but the majority of B-cells are still immature and unable to create a suitable response to vaccination [27]. At this time, scant information about measurable influenza vaccination responses following alemtuzumab in oncology patients is available in the literature.

The Future of Influenza Vaccination

When the WHO issues its recommendation for strains to include in influenza vaccines in the upcoming year, it attempts to pick which strains of influenza A and influenza B will be in general circulation in the following season. In the past 6 of 11 years, the influenza B strain that was ultimately in circulation was not the one included in the TIV vaccine [28, 29]. Novel QIVs include two strains of influenza A and two strains of influenza B have been developed to address this problem. The first of many studies comparing the QIV with the TIV in immunocompetent adults suggests that QIV could potentially improve the breadth of protection in immunosuppressed populations [30]. Importantly, the addition of a second influenza B strain to the vaccine did not decrease the rates of seroconversion to the other antigens in the vaccine, leading to an overall broader range of antibody production for both influenza A and B. Both the QIV and the low-dose QIV with adjuvant created a noninferior immunological response, as compared with the TIV and low-dose TIV with adjuvant [30]. Adverse events were comparable in all four arms.

Conclusion

An increasing volume of data suggests that patients will not create a sufficient seroconversion response to influenza vaccination soon after chemotherapy or 6 months after HSCT. Although this is what the available literature notes, we are still a proponent of giving inactivated influenza vaccination to all of our oncology patients, for a variety of reasons. Influenza vaccination is less costly than the treatment of a single infection in a standard patient and, therefore, also most likely cost effective in the immunosuppressed population [31]. The vaccine is relatively well tolerated by all, including those who receive intradermal, TIV, or adjuvanted influenza vaccine. A recent meta-analysis found that after influenza vaccination, patients with cancer and posttransplant (solid organ and HSCT) patients had significantly lower odds of developing an influenza-like illness, as compared with patients who received placebo. They also noted that the vaccine was well tolerated and had minimal side effects [32]. The data discussing poor influenza vaccination response rates in cancer patients include a very heterogeneous population, making it difficult to extrapolate trends to an individual group of cancer patients. Not to be overlooked are the issues with numerous influenza trials done during years where the match was not ideal between the seasonal TIV and the circulating strains of influenza.

In conclusion, influenza vaccination should still be attempted in all cancer patients but should be deferred as late as possible after the last chemotherapy regimen or biologic intervention. In the midst of an influenza epidemic, consideration should be given on a case-by-case basis for accelerating the timing of the influenza vaccine administration, depending on the individual's level of risk for increased morbidity and mortality from influenza infection. Due to the evolution of the influenza vaccine including adjuvants, or combination vaccines such as the QIV, these new interventions should soon be available for cancer patients in an attempt to reach a higher level of seroconversion. The improved seroconversion and hopefully cell mediated response will lead to fewer episodes of influenza infection.

Compliance with Ethics Guidelines

Conflict of Interest Aliyah Baluch declares that she has no conflict of interest.

Yanina Pasikhova declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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