The Oncologist®

Commentary

Vaccination of Oncology Patients: An Effective Tool and an Opportunity Not to Be Missed

CAMILLE N. KOTTON,[a,b] MARK C. POZNANSKY[b,c]

[a]Infectious Diseases Division, Massachusetts General Hospital, Boston, Massachusetts, USA; [b]Harvard Medical School, Boston, Massachusetts, USA; [c]Vaccine and Immunotherapy Center, Infectious Diseases Division, Massachusetts General Hospital (East), Charlestown, Massachusetts, USA

Disclosures: Camille N. Kotton: None; **Mark C. Poznansky:** None.

Vaccinating immunocompromised patients for common infectious diseases, including influenza, is a commonly missed opportunity. Clinicians caring for immunocompromised individuals often focus on other more immediate health concerns, or may believe that vaccines do not provide worthwhile protection or could even be harmful. In a recent series of 112 oncology patients at a single center in France, only 34 (30%) had undergone vaccination against influenza in the past year [1]. Numerous studies have shown reasonable rates of seroprotection and seroconversion in a variety of immunocompromised hosts, including oncology patients, with very minimal downside. Therefore, seasonal flu vaccination is broadly recommended across immunocompromised patient populations [2–4]. Bogoch et al. [5] demonstrated that the recent H1N1 influenza pandemic caused severe illness in a cohort of immunocompromised solid organ and bone marrow transplant patients from our hospitals. The hospitalization rate in this transplant setting was 71%, which far exceeded the hospitalization rate among confirmed cases in the general population, generally <5%. Given the severity of the H1N1 pandemic, wide-scale vaccination was recommended for immunocompromised subjects, including oncology patients [6, 7].

Xu et al. [8] examined the immunogenicity of the 2009 H1N1 vaccine in a variety of cohorts, including patients with solid tumors on myelosuppressive chemotherapy, patients with solid tumors on nonmyelosuppressive treatment or no treatment, patients with hematologic malignancies, and healthy controls. The study was a single-center trial with a relatively small number of subjects ($n = 146$). Seroconversion, seroprotection, and increases in antibody titers were not statistically different in any of the cohorts, although there was a trend toward lesser immunologic responses in those on myelosuppressive chemotherapy. Immune responses were generally fairly robust, regardless of malignancy: seroconversion was noted in 80% of healthy controls and 72%–87% of oncology patients, whereas the seroprotection rate was 96% in healthy controls and 79%–91% in oncology patients. Myelosuppressive therapy was highly varied and included corticosteroids; biologics such as imatinib, sorafinib, sunitinib, and rituximab; and cytotoxic chemotherapy agents considered to have immunosuppressive potential, such as fludarabine, cyclophosphamide, 5-fluorouracil, 6-mercaptopurine, cytarabine, L-asparaginase, and vinca alkaloids. Because of the extremely varied nature of the therapy, no conclusions could be drawn about the impact of specific agents.

Immune responses in these patients were reasonably robust, especially when compared with other trials, and were comparable with those in healthy controls. In another recent oncology trial, for example, the seroprotection rates after influenza vaccination were 50% for those with solid tumors and 27% for those with hematological malignancies ($p = .11$), whereas the respective seroconversion rates were 45% and 19% ($p = .06$) [9]. In another trial of oncology patients published this year, protective antibody titers developed in 39% of patients with B-cell malignancies ($p < .001$), 46% of allogeneic stem cell transplant recipients ($p < .001$), and 85% of patients with chronic myeloid leukemia ($p = .086$), After a second dose, the seroprotection rates were 68% ($p = .008$), 73% ($p = .031$), and 95% ($p = .5$), respectively [10]. Responses in other trials have been similarly variable; nonetheless, most authors concluded that influenza vaccination is recommended [2].

Given the suboptimal immune responses to immunization of immunocompromised patients, various approaches have been developed to address this. The optimal timing,

Correspondence: Mark C. Poznansky, M.D., Ph.D., Harvard Medical School, Vaccine and Immunotherapy Center, Infectious Diseases Division, Massachusetts General Hospital (East), 13th Street, Charlestown, Massachusetts 02129, USA. Telephone: 617-724-6375; Fax: 617-726-5411; e-mail: mpoznansky@partners.org Received November 4, 2011; accepted for publication November 10, 2011; first published online in *The Oncologist Express* on January 12, 2012. 1083-7159/2012/$40.00/0 http://dx.doi.org/10.1634/theoncologist.2011-0383

dosing, use of adjuvants, and delivery method might maximize the immunologic benefit of vaccination in oncology patients. The most beneficial timing of vaccination in patients receiving chemotherapy has not been well studied. In the study by Xu et al. [8], it was strongly recommended, but not required, that the H1N1 vaccine be given between i.v. chemotherapy treatment cycles, and patients taking oral chemotherapy or biologic targeted therapy could continue therapy without interruption for the vaccination. In another trial, patients with solid tumors who were given vaccination midcycle developed the highest pH1N1 titers, although timing and blood count were not associated with seroconversion or seroprotection [9]. In general, deferring vaccination to a period of lower immunosuppression is recommended, with careful attention to the expected arrival of influenza in the community. For example, seasonal influenza usually arrives in the northern hemisphere in late December and lasts for several months; it would be prudent to vaccinate patients at least 2–4 weeks before this period starts. In addition, if a vaccine is given during a period of peak immunosuppression, clinicians may wish to repeat the vaccine at a later date to try to optimize the immunologic response. In the absence of strong evidence to drive the clinical decision, programs should develop local protocols.

There are several additional ways in which responses to immunization can be augmented. Adjuvants are used to stimulate the immune system by attracting a greater number of antigen-presenting cells to the site of vaccination. This results in a more potent stimulation of both cellular and humoral responses to the vaccine. The vaccine used in the study by Xu et al. [8] did not contain any adjuvant. Some similar studies used adjuvanted vaccine. Whether or not it would be preferable to use adjuvanted vaccine, especially in immunocompromised hosts, remains to be determined. Intradermal injection (rather than intramuscular) is another technique that has been used with a variety of vaccines to augment immunity; thus far, it has not been well studied in oncology patients. Multiple doses of vaccine are another way to augment the immune response. One study in HIV^+ patients showed a significant augmentation of the immunologic response after repeat vaccination; the rate of seroconversion after the first dose of an adjuvanted H1N1 influenza A vaccine was 68%, which increased to 92% after a second dose [11], suggesting that repeat vaccination may be indicated as a means to augment immunity. Similarly, Rousseau et al. [12] demonstrated that, in oncology patients on cytotoxic chemotherapy and/or targeted therapy (the VACANCE study), after one and two doses of the H1N1 vaccine, the seroprotection rates were 48% and 73%, respectively, and seroconversion rates were 44% and 73%, respectively, suggesting that two doses may be beneficial.

Numerous studies have shown that, although vaccination in oncology patients may result in less robust immunologic responses, it is nonetheless worthwhile and recommended because many patients develop at least a moderate degree of immunologic response and protection against disease. The paper by Xu et al. [8] confirms this. Clinicians may wish to consider additional methods to enhance the immunologic response, such as using an adjuvanted vaccine or intradermal injection, especially in individual patients who might be less likely to respond to a single dose of vaccine. If vaccines are given during periods of potent immunosuppression, they may wish to repeat the vaccination once the immunosuppression has been diminished. In addition, if the influenza season lasts longer than usual, repeat vaccination may be helpful in providing additional protection. A growing dataset supports the view that vaccinating these vulnerable individuals is an opportunity that should not be missed.

Author Contributions

Conception/Design: Mark C. Poznansky, Camille N. Kotton
Collection and/or assembly of data: Mark C. Poznansky, Camille N. Kotton
Manuscript writing: Mark C. Poznansky, Camille N. Kotton
Final approval of manuscript: Mark C. Poznansky

References

1. Loulergue P, Mir O, Alexandre J et al. Low influenza vaccination rate among patients receiving chemotherapy for cancer. Ann Oncol 2008;19:1658.

2. Pollyea DA, Brown JM, Horning SJ. Utility of influenza vaccination for oncology patients. J Clin Oncol 2010;28:2481–2490.

3. Kumar D, Blumberg EA, Danziger-Isakov L et al. Influenza vaccination in the organ transplant recipient: Review and summary recommendations. Am J Transplant 2011;11:2020–2030.

4. Tomblyn M, Chiller T, Einsele H et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: A global perspective. Biol Blood Marrow Transplant 2009;15:1143–1238.

5. Bogoch II, Andrews JR, Hohmann EL et al. Pandemic H1N1 influenza infection in adult transplant recipients. Transplantation 2011;91:e80–e81.

6. Kumar D, Morris MI, Kotton CN et al. Guidance on novel influenza A/H1N1 in solid organ transplant recipients. Am J Transplant 2010;10:18–25.

7. Fiore AE, Shay DK, Broder K et al. Prevention and control of seasonal influenza with vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR Recomm Rep 2009;58:1–52.

8. Xu Y, Methuku N, Coimbatore P et al. Immunogenicity of an inactivated monovalent 2009 influenza A (H1N1) vaccine in patients who have cancer. ***The Oncologist*** 2012;17:125–134.

9. Mackay HJ, McGee J, Villa D et al. Evaluation of pandemic H1N1 (2009) influenza vaccine in adults with solid tumor and hematological malignancies on active systemic treatment. J Clin Virol 2011;50:212–216.

10. de Lavallade H, Garland P, Sekine T et al. Repeated vaccination is required to optimize seroprotection against H1N1 in the immunocompromised host. Haematologica 2011;96:307–314.

11. Bickel M, von Hentig N, Wieters I et al. Immune response after two doses of the novel split virion, adjuvanted pandemic H1N1 influenza A vaccine in HIV-1-infected patients. Clin Infect Dis 2011;52:122–127.

12. Rousseau B, Loulergue P, Mir O et al. Immunogenicity and safety of the influenza A H1N1v 2009 vaccine in cancer patients treated with cytotoxic chemotherapy and/or targeted therapy: The VACANCE study. Ann Oncol 2011 May 16 [Epub ahead of print].

See the accompanying article on pages 125–134 of this issue.