Review

Vaccination in Multiple Myeloma: Review of Current Literature

Andinet Alemu,[1] John O. Richards,[1] Martin K. Oaks,[2] Michael A. Thompson[1]

Abstract

Multiple myeloma is a cancer of the immune system. Infection is a major cause of morbidity and mortality in patients with multiple myeloma. Some of these infections are preventable by vaccines available to the general population. However, little is known about the clinical effectiveness of these vaccines in patients with multiple myeloma, and the cellular and humoral immune response to vaccination has not been well characterized, especially in conjunction with modern myeloma therapies. The present report reviews the basics of multiple myeloma and the immune system, the available evidence on the immunologic response of patients with multiple myeloma after vaccination, and current practice recommendations regarding specific vaccines. Understanding the immune response to vaccines could help us understand how immuno-oncology–based therapies work in multiple myeloma and provide future directions for research.

Clinical Lymphoma, Myeloma & Leukemia, Vol. ■, No. ■, ■-■
Keywords: Immune system, Influenza, Multiple myeloma, Pneumonia, Supportive care

Introduction

Vaccines are the first line of prevention for common infectious diseases such as influenza and pneumonia. However, the optimal use of vaccines in the setting of cancers involving the immune system and in patients undergoing treatment for these cancers has not been defined. The purpose of the present review was to compile and clarify the existing data on the effect of vaccines on the immune system of patients diagnosed with multiple myeloma (MM) and the clinical recommendations for appropriate administration of vaccines.

Effect of Pneumonia and Influenza

Diseases that are preventable by vaccines still contribute to significant morbidity and mortality in the United States and globally. Among these, influenza and pneumonia account for the largest share of the problem. In 2005, influenza/pneumonia was listed as the eighth most frequent cause of death in the United States, accounting for 63,000 deaths.[1,2] The overall national economic burden of influenza-attributable illness for adults aged ≥ 18 years has been reported at $83.3 billion.[3] The direct medical costs for influenza in adults totaled $8.7 billion, including $4.5 billion for hospitalization resulting from influenza-attributable illness. Influenza is also responsible for substantial indirect costs ($6.2 billion annually), mainly from lost worker productivity.[3] Among adults aged 18 to 64 years, 17 million workdays are lost to influenza-related illness each year.

Thus, the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (ACIP) has recommended annual influenza vaccination for most age groups and pneumococcal vaccination in certain patient populations and the elderly.[4] Despite the theoretical benefit and hope of a preventive supportive care intervention, the effectiveness and utility of such vaccines have not been well characterized in patients with underlying immunosuppression such as MM.

MM and the Immune System

MM is a cancer of plasma cells. Plasma cells are terminally differentiated B lymphocytes responsible for the production of antibodies necessary to fight infection. Patients with MM have profound abnormalities in antibody production[5,6] and consequently have a significantly increased risk of bacterial infection.[2,7-12] MM is most commonly a disease of the elderly, and an age-related decline in both innate and adaptive immunity is common.[13] Thus, patients with MM have a compound immunologic deficit of declining overall immunity in the face of abnormal antibody production and

[1]Aurora Research Institute, Aurora Health Care, Milwaukee, WI
[2]Transplant Research Laboratory, Aurora St. Luke's Medical Center, Aurora Health Care, Milwaukee, WI

Submitted: Mar 24, 2016; Revised: May 13, 2016; Accepted: Jun 1, 2016

Address for correspondence: Michael A. Thompson, MD, PhD, Aurora Research Institute, Aurora Health Care, 960 North 12th Street, Suite 4111, Milwaukee, WI 53233
E-mail contact: Michael.A.Thompson@aurora.org

2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2016.06.006

function. However, the immune system in patients with extended survival has been found to be similar to that of age-matched controls, suggesting that with successful treatment, the immune status will return toward normal.[14]

Just as with normal plasma cells, myeloma cells are recruited to the bone marrow, where they engraft and grow.[15] The growth of myeloma cells has multiple effects on the bone marrow, which is instrumental in multiple immunologic functions, including hematopoiesis, B-cell development, antibody production, secondary lymphoid function, and a repository for memory T cells.[16,17] As such, alterations in the bone marrow architecture could affect immunologic outcomes at both a local and a systemic level.

Before myeloma engraftment, the bone marrow can be characterized as an immune suppressive or privileged site. Evidence for this has been shown by the isolation of antigen-specific T cells from the bone marrow that become responsive in vitro, which can prevent tumor engraftment when transferred to another host.[18] The immune suppressive environment is enhanced in the presence of MM. The interaction of myeloma cells with stromal cells leads to the release of multiple cytokines, such as transforming growth factor-β1 (TGF-β1), vascular endothelial growth factor (VEGF), interleukin (IL)-6, and hepatocyte growth factor (HGF), from the stromal cells or myeloma cells themselves.[19] Not only do these cytokines promote myeloma growth, they have been found to suppress immune responsiveness. For instance, HGF has been found to inhibit antigen-presenting cell function and, as a result, inhibits the activation of T cells.[20] This inhibition of antigen-presenting cells is associated with the production of indoleamine 2,3-dioxygenase 1, which catabolizes tryptophan into immunosuppressive metabolites.[21] Similar to HGF, VEGF inhibits antigen-presenting cell function by blocking dendritic cell maturation,[22] thereby blocking T- and B-cell function.

Inflammation is one of the hallmarks of cancer. Inflammatory cytokines such as IL-6 and VEGF have also been found to influence the development of myeloid cells and have been implicated in the development of immature myeloid cells (also called myeloid suppressor cells [MDSCs]).[23] MDSCs are a heterogeneous population of cells with 2 major subgroups of monocyte and granulocyte lineage. Both types of suppressor cells can be found in the bone marrow or circulation and are very effective at inhibiting lymphocyte activation. Not only can they suppress antigen-specific lymphocytes, they are known to induce regulatory T cells, further enhancing an environment of immune suppression. In a study by Broder et al,[5] the removal of phagocytes from culture, obtained from a patient with MM, was able to restore the impaired ability to produce polyclonal antibodies. The ability to obtain MDSCs in the blood and eliminate them to restore lymphocyte function implies that these cells can suppress both local and systemic immune responses.

The development of MDSCs in the bone marrow is an indication that hematopoiesis is changed in myeloma, although probably not very noticeably. However, the clinical symptom of normochromic-normocytic anemia has been shown to occur in 75% of MM-diagnosed patients. In a much smaller group of individuals, leukopenia has been observed, showing defects in hematopoiesis and cell number.[24] The alteration of hematopoiesis might partially be due to myeloma altering the niche for normal progenitor cells.[25] Bruns et al[26] showed that TGF-β1 inhibits hematopoietic stem and progenitor cell renewal. Thus, a small infiltrate of tumor might have much greater effect on hematopoiesis. Immunomodulatory drugs (IMiDs), such as thalidomide, which blocks TGF-β1 signaling, can restore normal hematopoiesis.

The engraftment of myeloma in the bone marrow can have far-reaching effects, because it modifies hematopoiesis and produces an immunosuppressive environment locally and systemically. Systemic immune deficiencies are associated with the development of suppressor cells and reduced numbers of generated cells in the local environment of the bone marrow. Patients with long-term survival of MM were found to have unique immunologic profiles associated with reduced immunosuppression.[27]

How Do Vaccines Work?

Immunity produced in response to vaccines is largely antibody driven.[12] T cells play a significant role in sustaining and maintaining the immune response after vaccination. CD8 T cells (cytotoxic T lymphocytes) are crucial in containing the spread of infection and in recognizing and killing infected cells. Generating and maintaining both B and CD8 T cells requires a signal from CD4 T-helper cells (Th1 and Th2 subtypes). Various vaccine groups induce the immune response through different mechanisms. For example, capsular polysaccharides elicit a B-cell response in a T-cell–independent manner. In contrast, other vaccines, including toxoids, proteins, and live attenuated vaccines, induce the antibody response and immune memory in a T-cell–dependent fashion. Immunity generated by a T-cell–dependent mechanism is highly specific and long-lasting.[11,12,28,29] Adaptive immunity can be passive and short term, such as in maternal IgG transported across the placenta or infusion of intravenous immunoglobulin in MM patients. Active immunity/memory is (usually) long term and can be acquired by infection-induced B- and T-cell response or vaccines.[11]

Immune suppression can result from MM itself or be secondary to MM therapy. Various biologic factors are accountable for innate immune dysfunction in patients with MM. These include a decrease in uninvolved (nonclonal) antibody production from B cells.[5,6] The resulting hypogammaglobulinemia or immunoparesis is a poor prognostic feature of MM.[30] A functional defect is also present in upregulation of costimulatory molecules (CD80) on dendritic cells, with an inverse CD4/CD8 population ratio and defective natural killer cells.[31]

Bacterial infections, in particular, those caused by *Streptococcus pneumoniae*, *Escherichia coli*, *Staphylococcus aureus*, and *Haemophilus influenzae*, are very common. Specifically, the often present underlying polyclonal hypogammaglobulinemia in MM increases the risk of infection from encapsulated pathogens such as *S. pneumoniae* and *H. influenzae*.[31] A recent population-based study by Blimark et al[8] indicated that MM patients have a 7-fold and 10-fold increased risk of bacterial and viral infections, respectively, compared with non-MM patients. Their reported hazard ratios for the risk of infection in MM patients versus matched controls are listed in Table 1. A total of 51 meningitis cases were noted in 9253 MM patients compared with 28 cases in 34,253 controls, for a hazard ratio of 16.6. However, no clinical practice recommendations have been published to provide meningitis vaccinations to patients with MM.