Patients with multiple myeloma are severely immune-compromised and fail to make antibody responses to common vaccines. The immune deficiency is only made worse by ASCT, and posttransplantation infection is a major cause of treatment failure. In this issue of Blood, Stadtmauer and colleagues succeed in restoring immunity to influenza in myeloma ASCT recipients by adoptive transfer of T cells previously stimulated by multivalent flu vaccine on day 2 posttransplantation, followed by a vaccine boost 2 weeks later. These findings underline the potential of combining in vivo priming with vaccine before T-cell transfer followed by posttransplantation vaccine boost to induce not only specific immunity against common pathogens but also tumor-specific immunity.

Patients with multiple myeloma (MM) are at high risk from bacterial and viral infections. They tolerate influenza virus infections badly, being at especial risk from complicating pneumococcal pneumonias because of poor antibody production. Autologous stem cell transplantation (ASCT), regularly used in consolidation treatment for MM, further deepens the immune deficiency, creating prolonged T-cell and B-cell immune defects and predisposing MM patient to serious and life-threatening infections. The defective antibody response of MM, even in patients who have not received transplants, renders flu vaccine ineffective and leaves MM patients essentially unprotected from influenza after ASCT, significantly contributing to the morbidity and mortality of ASCT in this disease. To develop a better vaccine strategy, Stadtmauer and colleagues used a multistage approach to generating B-cell and T-cell immunity to flu by exploiting the unique immune perturbations around the time of the transplantation. In a randomized study, 11 patients received flu vaccine 14 days before an apheresis to collect lymphocytes while 10 patients had apheresis without prior vaccination. Both groups then underwent stem cell mobilization after cyclophosphamide and granulocyte-colony-stimulating factor, followed by high-dose melphalan, reinfusion of stem cells, and reinfusion of the apheresis collection on day +2 posttransplantation. On day 14 posttransplantation, both groups received the flu vaccine. Patients were followed up for 6 months and monitored for B-cell and T-cell immunity to flu (see figure). Global T-cell and B-cell recovery was comparable between the 2 groups. However, only patients who had received the pretransplantation vaccine and had virus-specific T cells transferred on day 2 were able to generate protective immunity to flu as measured by influenza HAG titers, B-cell ELISPOT for Ig production, and T-cell responses to flu antigen.

How was immunity restored in this challenging scenario? The transfer of vaccine-primed lymphocytes into the posttransplantation milieu could not alone be sufficient to restore immunity because MM patients have suboptimal vaccine responses. Similarly, the 10 patients who only received unprimed lymphocytes and vaccine posttransplantation were incapable of generating influenza immunity. Rather, the combination of infusing already primed T cells into a posttransplantation lymphopenic host, allowing for IL-15- and IL-6-driven homeostatic expansion, respectively, of the T-cell and B-cell flu response appears to have been the critical factor in resurrecting immunity.

Adoptive transfer of influenza immunity before stem cell transplantation for multiple myeloma.
immunity to flu virus posttransplantation. This study is further evidence of the unique opportunity provided by pretransplantation immunoblastation to expand antigen-specific lymphocytes. 1 It is possible that primed T cells have the advantage over unprimed cells in the posttransplantation immune milieu. The current study suggests that the effect may also extend to B-cell function promoted by a robust recovery of influenza specific CD4+ T cells providing help for already primed B cells.

Did the vaccination protect against the flu after transplantation? Unfortunately, we cannot tell from this study because fortunately no patient developed influenza, and the 6-month survival was comparable between the 2 groups. That aside, the implications of this study go beyond improving infectious immunity for MM patients, because this primed T-cell transfer/vaccine boost strategy could equally be used in both autologous and allogeneic transplantations to promote immune responses to many other infectious agents or solid tumors after transplantation. After allogeneic transplantation, the opportunity to adoptively transfer lymphocytes from a healthy donor, rather than from patients tolerant to their own tumor antigens with reduced immunity from prior chemotherapy, promises to provide tumor-specific primed T-cell populations ready for further expansion after vaccination. Even in the face of immunosuppression to prevent graft-versus-host disease, the opportunity to vaccinate the donor may still result in improved tumor-specific T-cell responses. However, while vaccination using viral antigens to common DNA viruses such as cytomegalovirus and adenovirus seems readily applicable, giving tumor antigen vaccines to healthy donors other than myeloma idiootypes may be viewed with caution because of potential (but so far only theoretical) risks from autoimmunity.10 The second important message from this study is that to be effective it is not necessary to delay vaccination until full recovery of lymphocyte counts. Although vaccination skewed the T-cell populations to effector and effector memory (especially the CD4+) cells with an accompanying increase in activated B cells, the immune response to flu was achieved without global changes in T-cell or B-cell absolute numbers.

In conclusion, the association of vaccinating the patient so as to collect and deliver antigen-primed lymphocytes early posttransplantation with revaccination early posttransplantation defines an exciting new strategy for boosting important virus-specific and tumor-specific immune responses. It deserves further exploration in the context of autologous stem cell transplantation for other malignant diseases, and the lessons learned from this approach could be applied to boosting the graft-versus-leukemia effect after allogeneic stem cell transplantation.

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Fighting the flu in multiple myeloma

A. J. John Barrett