Commentary (Forman/Zaia): Vaccinations Against Infectious Diseases in Hematopoietic Stem Cell Transplant Recipients

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With the increasing success of both autologous and allogeneic marrow transplantation in achieving cure of inherited and acquired disorders, the number of people who have become long-term survivors has steadily increased worldwide. Concomitant with this increase has been greater attention to the long-term health needs of these recipients. Many studies have outlined the problems experienced by long-term survivors and have better informed physicians about the medical problems that may require intervention and consultation.

Factors in Immune Recovery

Among the long-term issues in patients undergoing hematopoietic cell transplantation is the development of adequate humoral and cell-mediated immunity to protect against infectious complications. These problems are more prominent in allogeneic transplant recipients and are directly correlated with the presence or absence of chronic graft-vs-host disease, the ongoing need for immunosuppressive medication, and the type of graft received. Thus, the rate of immunologic recovery and of posttransplant infectious complications differs significantly, depending on whether the patient received an autologous graft, an allogeneic graft from either a sibling or an unrelated donor, a cord blood graft, or a haploidentical transplant.

In addition, there are substantial differences in the pace and adequacy of immune reconstitution, depending on the age of the patient—i.e., whether the patient is an infant or an older person. Transplants are being performed with increasing frequency in older patients to treat acute myelogenous leukemia, lymphoma, myeloma, and myelodysplasia. Based on these considerations, the US Centers for Disease Control and Prevention developed guidelines for the use of vaccinations against infectious disease following transplantation. Goldberg et al highlight those areas, with good data in support of a strategy of posttransplant immunization to reestablish pathogen-specific immunity. The review provides the basis for a pragmatic approach to the prevention of opportunistic disease in patients who are long-term survivors of transplantation and often return to the care of their primary oncologist or internist. In addition to giving these physicians useful advise, the article provides a rationale for further studies that would refine immunization strategies in transplant recipients.

'Herd' Immunity

Despite the gaps in our knowledge and in the immunologic repertoire of patients undergoing transplantation, most recipients do not develop infections related to the agents used in immunization of children and young adults. For many years, transplant recipients have benefited, in part, from the "herd" immunity in the general population, and infection with mumps, measles, rubella, and polio is limited because of lack of exposure. This does not apply to pathogens such as pneumococcus and Haemophilus influenzae, which are more common among allogeneic transplant patients, who often have defective immune responses. One important recommendation in the review concerns the need to immunize all allogeneic recipients against these bacterial pathogens even though some may not respond with a protective level of antibody. Another strategy used to determine the need for immunization in transplant recipients is to measure
the transfer of antigen-specific immune competence from donor to recipient at 9 months to 1 year posttransplant. Many patients will actually achieve adequate responses to a variety of viral pathogens based on the transfer of T-cell and B-cell immunity from donor to recipient. This process is most complete in patients who do not develop chronic graft-vs-host disease and in whom the combination of "herd" immunity and transfer of donor immunity is protective; boosters, such as that for tetanus, can be used as clinically appropriate.

Reimmunization

Questions have also been raised about the need for patients to undergo repeat immunization after autologous stem cell transplant. In this situation, it appears that the immunologic defects are, in part, related to the diagnosis and the amount and kind of prior therapy, but many of these patients will reconstitute a T-cell and B-cell repertoire containing adequate immunologic memory without reimmunization. Nevertheless, it is recommended that this group receive reimmunization, as noted by the authors. The authors also point out that the patients who most need effective immunization are least likely to respond. This is particularly true now that increasing numbers of patients undergo transplantation using cord blood, which is associated with prolonged reconstitution of T-cell immunity, or haploidentical transplant, which is associated with an even longer immune recovery process. Moreover, many of these patients are older recipients of allogeneic transplant from both related and unrelated donors. It is well known that thymic function diminishes with age and, thus, further studies are necessary to determine the efficacy of immunization and the adequacy of immune reconstitution in these recipients, particularly those who have had young donors.

Other Immunization Strategies

The transfer of immunity from donor to recipient has also highlighted pretransplant donor immunization as a potential approach that might benefit the recipient, particularly in the case of more life-threatening infections such as cytomegalovirus (CMV) or herpes zoster. Vaccines developed to protect against CMV and Varicella zoster virus infection could be used to immunize the bone marrow donor; then the degree of immunity transfer to the recipient could be determined, and booster injections could augment transplanted donor-derived memory cells.[7]

New Approach to Improve Immune Recovery

In addition, based on research in murine models, approaches to improving posthematopoietic immune function have been identified and some are currently undergoing testing in phase I studies. These include strategies that could either result in thymic protection, thymic replacement, lymphoid progenitor cell transfer, or adoptive therapy with antigen-specific cells. Keratinocyte growth factor can protect epithelial cells from the toxic effects of transplant chemoradiotherapy and, by protection of thymic epithelial cells, could improve immunologic function of both autologous and allogeneic hematopoietic stem cells.[8] The first successful attempt to improve posthematopoietic cell transplant immune function involved the administration of interleukin-7 (IL-7).[9,10] IL-7 is the central cytokine in early thymic differentiation, and has both proliferative and antiapoptotic effects on thymocytes. Recently, a common lymphocyte progenitor cell was identified in humans, and its differentiation is restricted to cells of lymphoid origin.[11] Preclinical studies in mice have shown that infusion of these cells into animals that received only purified stem cells improved posthematopoietic cell immunologic function when challenged against a common antigen, namely CMV. During the past decade, several investigators have shown that the infusion of antigenspecific CD4 and CD8 lymphocytes specific for viral pathogens like CMV and Epstein-Barr virus can produce both therapeutic and prophylactic benefits.[12,13]

Conclusions

Thus, this thorough and thoughtful analytic review should provide excellent guidance for physicians responsible for the long-term care of patients undergoing transplantation. With improvements in the transplant process, it is hoped that the adequacy of immune reconstitution will increase in all patient groups, reducing long-term complications among those who have been cured of their hematologic disorder.
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