The Current Role of Hematopoietic Stem Cell Transplant in Primary Immunodeficiency Diseases

By Michelle Greer, RN

The list of diseases for which hematopoietic stem cell transplant (HSCT) is a treatment option has been growing over the last several years, and it includes primary immunodeficiency diseases (PIs). With more than 100 types of PI, treatment options vary depending on the type and severity, as well as overall prognosis. HSCT (also known as bone marrow transplant [BMT]) is used to treat certain forms of PI, and it is becoming much more successful due to better tissue typing and matching of donors, less toxic chemotherapy, better virus detection and treatment, improved supportive care and graft-versus-host disease (GVHD) prophylaxis. However, HSCT does come with its share of risks, and it is a treatment option that should be carefully considered and discussed between patients and their physicians.

What Is HSCT?

A stem cell is the most basic cell in any organism that has the potential to become a specific type of cell. A hematopoietic stem cell is a stem cell in the blood. Immunoglobulins are made from B lymphocytes, also known as B cells, that mature in the bone marrow. They play a key role in the immune system, serving as protection against anything foreign entering the system. Immunoglobulins, which are also called antibodies, are produced in response to antigens (something foreign in the system). There are five types of immunoglobulins — IgG (the most prevalent), IgA, IgM, IgE and IgD — each of which serves a specific function in the immune system. When the body does not produce sufficient amounts of one or more immunoglobulins or other blood cells that play a role in immunity, the result is an immune deficiency. If the cause can be identified, treated and corrected, this is usually a secondary immune deficiency. If the cause is simply an inherent defect in the system’s ability to produce sufficient amounts, this is known as a primary immune deficiency.

HSCT may be warranted in PIs that are extremely rare such as severe combined immunodeficiency (SCID), chronic granulomatous disorder and Wiskott-Aldrich syndrome. Once the decision to undergo HSCT is made, the process is relatively simple, but it can involve side effects and complications that can impact the ultimate success of the transplant. Compliance with pre- and post-transplant protocols is also essential to the success and overall outcome. The goal of HSCT is to destroy the blood cells in the immune system that include the defect or disease and then to rebuild a normal and healthy immune system from stem cells from either bone marrow or peripheral blood cells.

Transplants can either be from one’s own tissue and cells, known as autologous, or from a matched donor, known as allogeneic. Typically for PI, a suitable donor is located. Finding a suitable donor is probably the No. 1 barrier to undergoing HSCT. Once a donor is located, the immune system is ablated with maximally tolerated chemotherapeutic agents chosen by the transplant physicians based on the underlying condition that is the reason for the transplant. For example, someone with a malignancy would receive a different chemotherapy regimen than someone with PI. Donor cells are then administered via a relatively short infusion.

After HSCT, complications, mainly involving potential for infections and GVHD, can arise while the immune system is rebuilding itself. To prevent infections, prophylactic medications, including antifungals, antibiotics, vaccinations and intravenous immune globulin (IVIG), are given. GVHD occurs in allogeneic transplants when the donor cells attack the patient’s body.
The attack most commonly occurs in the liver, skin and mucous membranes, including the eyes and gastrointestinal tract. GVHD can be acute (occurring in the first 100 days following a transplant) or chronic (occurring after 100 days following transplant).

A successful transplant can mean up to a 90 percent cure for SCID patients and a 70 percent to 80 percent cure for other PIs given a matched unrelated donor. This number can rise to a 95 percent cure rate for young patients with specific PIs such as Wiskott-Aldrich syndrome. 1

**HSCT for CVID**

While not routinely considered, there are some instances in which HSCT may be considered for patients with common variable immunodeficiency (CVID), the most common form of PI. Typically, CVID patients are treated with IG therapy for life because, in most cases, it is effective in maintaining sufficient antibody levels to protect from infection and any complications. However, those with CVID have a 20 percent to 30 percent chance of developing autoimmune diseases, and, in some cases, autoimmune diseases are diagnosed before CVID. CVID patients also have an increased incidence of lymphoma and, less common, stomach cancer. In these cases, HSCT may be warranted.

Only one study has been conducted on HSCT for CVID. 2 The multicenter retrospective study demonstrated that HSCT in patients with CVID was beneficial in most surviving patients; however, there was a high mortality associated with the procedure. Of 25 patients, aged 8 years to 50 years at the time of transplantation, there was an overall survival rate of 48 percent, and an 83 percent survival rate for patients undergoing transplantation for lymphoma. In 92 percent of surviving patients, the condition constituting the indication for HSCT resolved, and in 50 percent of surviving patients, IG therapy was stopped. The major causes of death were treatment-refractory GVHD accompanied by poor immune reconstitution and infectious complications. The study authors concluded that HSCT “should only be considered in carefully selected patients in whom there has been extensive characterization of the immunologic and/or genetic defect underlying the CVID diagnosis.”

According to Kathleen Sullivan, MD, PhD, chief of allergy and immunology at Children’s Hospital of Philadelphia and co-author of the retrospective study: “Although I would not recommend a BMT for my patients with CVID in general, I think it does represent a feasible therapy for some carefully selected patients. When I look back on the trajectory of BMT historically, it is clear that the success rates improve for all diseases over time. BMT is not a single procedure. There are components of a BMT conceptually that occur in all transplants, but the details vary according to the donor, recipient, disease and concurrent medical problems. Ongoing research on those details is what moves a disease from having a low success rate to a high success rate, and the good news is that there are now efforts to optimize those details for CVID transplants. Right now, the success for autoimmune complications. In the meantime, I think only CVID patients who have been found to have a genetic composition with an unfavorable prognosis or those for whom current treatments are simply failing should be considered as candidates. Research holds great promise for optimizing treatments for all CVID patients and ensuring good outcomes for everyone.”

**The Future of HSCT**

The list of diseases for which HSCT is a treatment option has been growing over the last several years, and there is a good deal of discussion about HSCT for PIs. While historically HSCT has been limited to PIs for which there are no effective treatments and for those with an increased risk of mortality, in the future, it could offer a cure for many other forms of PIs, including CVID.

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**References**
