Hematopoietic Stem Cell Transplant for Immune Deficiency and Immune Dysregulation Disorders

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KEYWORDS

• PIDD • HSCT • BMT • Conditioning • GVHD • GVT • Rejection

KEY POINTS

- Hematopoietic stem cell transplant (HSCT) is a curative therapy for many immunodeficiency/immune dysregulation disorders.
- Three major factors need to be addressed when considering HSCT: donor stem cell source, conditioning regimen, and graft-versus-host disease (GVHD) prophylaxis.
- In general, the risks of graft rejection and GVHD are proportional to the degree of HLA mismatch between the donor and the recipient.
- In general, the risk of toxicity and death from infection is proportional to the intensity of the pretransplant conditioning regimen.
- The appropriate HSCT regimen varies depending on the immunodeficiency being treated and must balance donor stem cell availability and intensity of the conditioning regimen with risks including death from infection or toxicity, possibility of graft rejection, and the chance of GVHD.

INTRODUCTION

Primary immunodeficiency disorders (PIDDs) are a group of heterogeneous diseases, many of which are caused by monogenic defects, resulting in susceptibility to life-threatening infections, uncontrolled inflammation, or autoimmunity. As most immune

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cells are derived from hematopoietic stem cells, HSCTs have long been considered a possible curative treatment of PIDDs.

In the late 1960s the fields of clinical immunology and bone marrow transplant became inseparably connected with the publication of the first successful bone marrow transplants for PIDD. Work had been underway for some time to develop a successful approach to perform HSCTs, but of the first 200 patients treated between 1957 and 1967, including 12 patients with immunodeficiency disorders, none survived the procedure.[1] The concept of HLA matching was in its infancy, so patients succumbed most commonly to graft rejection and GVHD. In 1968, 2 patients with PIDD underwent successful transplant: one for severe combined immunodeficiency (SCID)[2] and the other for Wiskott-Aldrich syndrome (WAS).[3] These cases represented the first successful HSCT procedures, changing forever how PIDD would be treated and ushering in the era of curative therapies for these disorders.

Over time, approaches to improve donor cell engraftment and decrease transplant-related mortality related to infections, organ dysfunction, and GVHD have led to progressively better HSCT outcomes; this has been driven by advances in 3 major technical aspects of HSCT, each of which are addressed in this article:

1. Selection of a suitable donor to provide stem cells capable of successfully engrafting, curing the underlying disease, and avoiding extensive reaction against the host (GVHD).
2. Selection of a conditioning regimen capable of opening sufficient space in the bone marrow to allow engraftment without creating severe life-threatening side effects.
3. Selection of a posttransplant immunosuppressive regimen capable of a preventing GVHD while allowing engraftment and expansion of donor cells.

Although there have been significant advances in the field, ongoing work continues to focus on improving and refining each of these 3 key aspects of the transplant approach.

IMPORTANT POINTS TO CONSIDER WHEN CONTEMPLATING HEMATOPOIETIC STEM CELL TRANSPLANT FOR PRIMARY IMMUNODEFICIENCY DISORDER

Unlike malignant diseases, in which transplant is a life-saving procedure applied primarily to allow the use of otherwise lethal doses of chemotherapy or radiation and to realize potential benefit from a graft-versus-tumor (GVT) effect, neither of these is important for patients with PIDD. Other key factors play a more significant role when considering HSCT for nonmalignant diseases such as PIDD.

In many patients with PIDD, an underlying molecular defect can be determined thus allowing a definitive diagnosis and providing some information regarding disease prognosis and potential utility of HSCT (**Table 1**). In these patients, it is relatively straightforward to proceed to transplant based on knowledge about the underlying disease. Problems arise, however, in patients who have a severe PIDD but lack a molecular diagnosis. Often in these cases, HSCT is delayed until the patient clearly demonstrates susceptibility to severe recurrent infections or autoimmunity, which can delay the decision to proceed to transplant for months to years. In these patients, the most important consideration before transplant is whether replacing the hematopoietic stem cells will be sufficient to cure or substantially improve the disorder. For example, in lymphocyte defects such as SCID, abnormalities are isolated almost exclusively to hematopoietic cells and HSCT can cure all aspects of the disease. There are, however, disorders that have a mixture of hematopoietic and nonhematopoietic defects such as autosomal dominant hyper-IgE syndrome (AD-HIES) caused by