Hematopoietic Stem Cell Transplantation in Primary Immunodeficiencies Beyond Severe Combined Immunodeficiency

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Hematopoietic stem cell transplantation (HSCT) has been the standard of care for infants with severe combined immunodeficiency (SCID) for several decades due to the dismal prognosis early in life without immune reconstitution. In recent years, as HSCT conditioning regimens and supportive care have greatly improved, HSCT is gaining in acceptance for more non-SCID primary immunodeficiencies (PIDs) and outside the early childhood period. In addition, potential donor options for non-SCID PIDs are expanding with increasing success for haploidentical donor transplants. In this brief report of a presentation at the PIDS-St. Jude 2018 conference, PIDs for which transplants are increasingly performed outside of early childhood will be discussed.

Keywords. DOCK8, GATA2, hematopoietic stem cell transplantation, primary immunodeficiency.

DOCK8 DEFICIENCY

Homozygous or compound heterozygous mutations and/or deletions in DOCK8 deficiency were described in 2009 as causing a combined immunodeficiency in a group of patients previously described as having autosomal recessive hyper-immunoglobulin (Ig)E syndrome [1]. DOCK8 deficiency is a rare primary immunodeficiency characterized by eczema, recurrent sinopulmonary infections often leading to bronchiectasis, and cutaneous viral infections such as warts, molluscum, herpes simplex virus, and varicella-zoster virus (VZV) (Figure 1). Frequent immunologic findings include elevated serum IgE, low serum IgM, eosinophilia, T and natural killer (NK) cell lymphopenia, and poor specific antibody production. Poor control of human papillomavirus (HPV) leads often to widespread warts and squamous cell carcinomas, and NK dysfunction leads to Epstein-Barr virus (EBV) viremia and EBV-positive or -negative lymphomas. A vasculitis or vasculopathy, of unknown etiology or from VZV, and has led to significant cerebral artery stenosis and moyamoya, as well as aortic calcification and aneurysm, with complications such as renal artery stenosis (Figure 1) [2]. Chronic cryptosporidium infection, often recognized through polymerase chain reaction assays, has led to significant biliary disease, which can lead to cirrhosis [3].

Multicenter clinical studies of DOCK8 deficiency show an overall poor prognosis, with approximately half of patients dying before the age of 20 years and approximately 75% of patients having a life-threatening complication before the age of 20 years [4]. Therefore, hematopoietic stem cell transplantation (HSCT) is currently the treatment of choice for these patients. Because this is a disease that tends to worsen with age and has complications that can complicate HSCT, such as vasculopathy and liver dysfunction, HSCT discussion and evaluation should be performed promptly. These patients frequently present for transplant with a high burden of infection or possible sources of infection, and identifying and treating infections as much as possible can diminish the risk through HSCT. For instance, eczema with excoriations should be treated aggressively, frequently requiring antibiotics directed against *Staphylococcus aureus*, antiseptics (chlorhexidine or dilute bleach) to lower the microbial concentration, topical steroids, and at times wet wrap therapies. For patients with bronchiectasis, bacteria, molds, and nontuberculous mycobacteria (NTM) can cause chronic infection or colonize the airways, and identification of these colonizing microbes allows suppression or early treatment during the period of neutropenia. Screening for vascular abnormalities, such as cerebral artery stenosis, allows a plan to prevent strokes and bleeding. These patients are frequently EBV viremic and occasionally cytomegalovirus (CMV) viremic before transplant, and, if possible, the donor should be immune to these viruses, and the recipient should have CMV viremia suppressed before transplant. Biliary disease due to chronic Cryptosporidia will not resolve without immune reconstitution, and we treat with nitazoxanide in hopes of preventing worsened gut disease during the transplant period.

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Figure 1. (A) Abdominal magnetic resonance angiography showing bilateral renal artery stenosis in a 19-year-old with DOCK8 deficiency (arrows). The mid-aorta around the renal arteries had narrowing and calcification. (B) A 10-year-old with DOCK8 deficiency with bronchiectasis. (C) Warts in a 27-year-old with DOCK8 deficiency before transplant. (D) Significant skin excoriations in an 11-year-old with DOCK8 deficiency before transplant.

Hematopoietic stem cell transplantations for DOCK8 deficiency have largely been with myeloablative or reduced intensity regimens. Our center uses a fludarabine- and busulfan-based regimen, with a preference for bone marrow over peripheral blood stem cells to hopefully reduce the graft-versus-host disease (GVHD) risk. For donors who do not have matched related or unrelated donors (MRD or MUDs), we prefer haploidentical donors using a T-cell replete donor marrow source with post-transplant cyclophosphamide for GVHD prophylaxis. Due to some significant GVHD seen with MUDs, we have amended our regimen to include posttransplant cyclophosphamide for the MUD and MRD transplants as well. Overall, for both the MRD/MUD and the haploidentical transplants, outcomes in this cohort with significant underlying disease have been promising with survival of approximately 85% [5, 6]. Some of the initial deaths were related to GVHD in the MUD cohort, and hopefully outcomes will improve with the additional posttransplant cyclophosphamide therapy. It is important to note that with the haploidentical transplant protocols, high fever is often seen between the day of transplant and the post-HSCT cyclophosphamide infusion. Viral infections posttransplant are a concern, but in our series they have been manageable with BK-related cystitis requiring symptomatic therapy in several patients and CMV reactivation needing courses of ganciclovir or foscarnet.

One patient with an underlying EBV-related lymphoma that was refractory to chemotherapy received EBV-directed cytotoxic T lymphocytes post-HSCT with good outcome. Before our current haploidentical HSCT protocol, one patient received a cord transplant and developed human herpesvirus 6 encephalitis with subsequent graft failure and eventual death.

GATA2 DEFICIENCY

GATA2 is a transcription factor involved in the development and proliferation of hematopoietic precursors. Loss of function mutations in GATA2 deficiency were described in 2011 as the cause of MonoMAC syndrome, which was an autosomal dominant syndrome characterized by monocytopenia and mycobacterial infection [7]. Around the same time, GATA2 deficiency was found to be the cause of familial leukemias and Emberger's syndrome, characterized by lymphedema and myelodysplasia. GATA2 deficiency tends to present in older children or young adults with opportunistic infections or bone marrow abnormalities including myelodysplasia or bone marrow failure. Infections include viral infections such as warts, disseminated mycobacteria, and, less frequently, fungal infections such as disseminated histoplasmosis. Although *Mycobacterium avium* complex infections have been most common in this disease

cohort (52% of the NTM infections), *Mycobacterium kansasii* is also fairly common (31% of the NTM infections), and the *M kansasii* frequently causes mediastinal infections [8] (Figure 2). Laboratories often show low monocytes, although as the disease progresses there may be increased monocytes with progression towards leukemia. Neutrophil count may be low. Lymphocyte phenotyping frequently shows low NK and T cell numbers. Despite frequently seeing very low or absent B cell numbers, Ig levels are usually normal—because the loss of B cells happens over time—and so plasma cells are present. Macrophages are likewise in the tissue, despite low circulating monocytes, but often have poor function leading to abnormalities such as pulmonary alveolar proteinosis (PAP) (Figure 2). Transmission is autosomal dominant, and there is a suggestion that there is worse disease with earlier presentation with subsequent generations.

Hematopoietic stem cell transplantation is the treatment choice for GATA2 deficiency, although the timing can be difficult because the disease worsens over time, and some adults have minimal signs or symptoms. Reasons for transplant include opportunistic infections such as disseminated NTM or progressive warts, progressive pulmonary disease with PAP, and marrow changes such with cytogenetic abnormalities and worsening signs of myelodysplasia. Once myelodysplasia is present, transition to leukemia may be rapid, making transplant outcomes worse. Therefore, close monitoring for signs of myelodysplasia and leukemia are essential.

At our center, a busulfan- and fludarabine-based myeloablative regimen is used for HSCT with an overall survival of 86% at 2 years [9]. A haploidentical protocol with posttransplant cyclophosphamide to diminish GVHD has had excellent outcomes thus far. A prior nonmyeloablative regimen had worse outcomes with a graft rejection and leukemia relapse, suggesting more ablation would improve the outcomes. Overall, the NTM infections have not been difficult to control through transplant, although immune reconstitution symptoms have occurred in a few patients. There has been resolution of precancerous HPV lesions, but some persistence of warts was seen with some later dysplastic lesions, so vigilance is required. Deaths with the

current HSCT protocol have included one each of refractory acute myelogenous leukemia, severe GVHD, and sepsis.

OTHER NONSEVERE COMBINED IMMUNODEFICIENCY PRIMARY IMMUNODEFICIENCIES

With improved outcomes for HSCT protocols including with the use of MUDs and haploidentical donors, HSCT is being considered and performed more frequently for primary immunodeficiencies (PIDs). Outside of HSCT for severe combined immunodeficiency, which is typically performed in infancy, HSCT is performed most frequently for chronic granulomatous disease (CGD). Chronic granulomatous disease predisposes individuals to predominantly catalase positive organisms through a disrupted neutrophil oxidative burst. Patients are prone to infections with predominantly *S aureus*, *Burkholderia cepacia*, *Serratia marcescens*, *Nocardia* species, and *Aspergillus* species. In addition, inflammatory complications are frequent causing significant colitis and bladder complications. Hematopoietic stem cell transplantation is performed both for the infectious and for the inflammatory complications. Long-term studies in CGD have shown that there is a better long-term survival with improved quality of life in CGD with HSCT [10]. Outside the United States, HSCT has been performed more routinely for CGD, and outcomes have been excellent in Europe, with transplants being performed at a younger age with less disease burden that has been typical at our center.

Overall survival in a recent publication of the National Institutes of Health experience for patients with CGD treated with a reduced intensity transplant with busulfan, alemtuzumab, and low-dose total body irradiation was 82.5% [11]. Graft failure has been more common in CGD than in some other PIDs, and many poor outcomes have been associated with graft failure, leading to donor lymphocyte infusions to improve graft function but causing severe GVHD. Some patients have undergone transplant with significant infectious burden that was failing medical therapies, such as *Aspergillus nidulans* pneumonia with osteomyelitis, *Scedosporium* pneumonia with osteomyelitis, and *Phellinus* pneumonias. For these patients, granulocyte transfusions are typically used during neutropenia.

Figure 2. (A) A 33-year-old with GATA2 deficiency with pulmonary alveolar proteinosis with pulmonary hypertension. (B) A 19-year-old with GATA2 deficiency with *Mycobacterium szulgai* thoracic lymphadenitis (arrow).

Trials are ongoing for gene therapy for CGD and currently enrolling patients with resistant infections who do not have a good HSCT option. Over time, as gene therapy regimens are optimized, it will be interesting to see how patients are selected for HSCT or gene therapy.

There is less HSCT experience for other PIDs such as STAT3-deficient hyper IgE (Job's) syndrome. Job's syndrome presents early in life with eczema, recurrent skin and lung infections, as well as with connective tissue, skeletal, and vascular abnormalities. Early experience with HSCT was not encouraging, with initial reports including a transplant reported as a failure and a fatality [12]. However, in recent years, the role of HSCT is being reconsidered with reported successes, with suggestion of improved infection susceptibility as the immune deficits are corrected and potentially some improvement in somatic complaints such as bone density [13]. However, it remains unclear whether other aspects of this disease, such as scoliosis and vascular abnormalities, will be improved with HSCT. In addition, with earlier recognition and improved therapies, individuals with Job's syndrome are living longer, frequently into the fifth and sixth decades, making the risks or benefits decision around HSCT difficult.

Increasing diagnosis of other PIDs and transplant experience will allow development of fine-tuned HSCT protocols. For instance, gain of function STAT1 is a more recently recognized immune dysregulation disorder that has a phenotype of both a broad spectrum of infections as well as autoimmunity. Initial transplant outcomes were poor, with primary and secondary graft failures and overall survival of approximately 40% [14]. However, more specific therapy with Janus kinase inhibitors may ameliorate some of the immune dysfunction from increased STAT activity and lead to better overall outcomes, although further experience is necessary. Interferon- γ (IFN γ) receptor defects, associated with disseminated NTM, have also been associated with difficult engraftments. However, improved outcomes have been seen more recently with better control of the NTM infections pre-transplant associated with lower IFN γ serum levels [15].

CONCLUSIONS

Primary immunodeficiencies comprise a heterogeneous group of disorder, with different spectrums of infection and inflammatory complications. Each PID has unique considerations around HSCT that affect the approaches to minimizing infection pretransplant, the conditioning regimens to optimize engraftment, and the donor choice. Recent years have brought not

only greater delineation of these PIDs but also safer approaches to transplant, with great advances in haploidentical donors greatly extending the number of individuals who can be considered for HSCT. Future directions will also include the use of specific immune modulators instead of or in addition to HSCT, as well as determining the role of gene therapy or gene editing.

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