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Haploidentical Related Donor Hematopoietic Stem Cell Transplantation for Dedicator-of-Cytokinesis 8 Deficiency Using Post-Transplantation Cyclophosphamide

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A B S T R A C T

Dedicator-of-cytokinesis 8 (DOCK8) deficiency, a primary immunodeficiency disease, can be reversed by allogeneic hematopoietic stem cell transplantation (HSCT); however, there are few reports describing the use of alternative donor sources for HSCT in DOCK8 deficiency. We describe HSCT for patients with DOCK8 deficiency who lack a matched related or unrelated donor using bone marrow from haploidentical related donors and post-transplantation cyclophosphamide (PT/Cy) for graft-versus-host disease (GVHD) prophylaxis. Seven patients with DOCK8 deficiency (median age, 20 years; range, 7 to 25 years) received a haploidentical related donor HSCT. The conditioning regimen included 2 days of low-dose cyclophosphamide, 5 days of fludarabine, 3 days of busulfan, and 200 cGy total body irradiation. GVHD prophylaxis consisted of PT/Cy 50 mg/kg/day on days +3 and +4 and tacrolimus and mycophenolate mofetil starting at day +5. The median times to neutrophil and platelet engraftment were 15 and 19 days, respectively. All patients attained >90% donor engraftment by day +30. Four subjects developed acute GVHD (1 with maximum grade 3). No patient developed chronic GVHD. With a median follow-up time of 20.6 months (range, 9.5 to 31.7 months), 6 of 7 patients are alive and disease free. Haploidentical related donor HSCT with PT/Cy represents an effective therapeutic approach for patients with DOCK8 deficiency who lack a matched related or unrelated donor.

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INTRODUCTION

Dedicator-of-cytokinesis 8 (DOCK8) deficiency is a combined primary immunodeficiency disease initially described as autosomal recessive hyper-IgE syndrome [1,2] and characterized by allergic/atopic manifestations, DNA viral infections, central nervous system (CNS) events, autoimmunity, vasculopathy, and malignancy [3-5]. DOCK8 deficiency is associated with a high degree of morbidity and mortality—including life-threatening infections and virus-driven malignancies—with an estimated overall survival of 50% at 20 years [3]. Allogeneic hematopoietic stem cell transplantation (HSCT) represents a curative therapy for DOCK8 deficiency [6-14].

We previously reported our experience with allogeneic HSCT in patients with DOCK8 deficiency using matched related or unrelated donors and a high-dose fludarabine/busulfan-based conditioning regimen [13]. All 6 patients had prompt engraftment with reconstitution of the deficient lymphocyte compartments and reversal of the clinical phenotype with minimal regimen-related toxicity.

For patients with DOCK8 deficiency who lack an HLA-matched sibling donor, and for whom a full phenotypic

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HLA-matched unrelated donor is unavailable, haploidentical related donor transplantation represents a potential option. However, there are only a few reports of transplantations using haploidentical related donors in DOCK8 deficiency [9,14,15]. The success of haploidentical transplantation in other primary immunodeficiency syndromes suggested the feasibility of this approach in patients with DOCK8 deficiency [16-19]. Paramount to the success of haploidentical HSCT is the ability to prevent graft-versus-host disease (GVHD). This can be addressed using in vitro techniques with T cell depletion by $CD34^+$ selection or selective T cell depletion (eg, depletion of T cell receptor, depletion of $TCRab^+$ (T cell receptor alpha beta) T cells, associated with depletion of $CD19^+$ B lymphocytes) [19,20]. Alternately, in vivo depletion of T cells can be accomplished by pretransplantation serotherapy [21,22] or by using post-transplantation cyclophosphamide (PT/Cy) [16,23].

We describe the results for 7 patients with DOCK8 deficiency who received a busulfan/fludarabine-based haploidentical related donor HSCT utilizing T cell–replete bone marrow harvest grafts with PT/Cy for GVHD prophylaxis. Our results indicate that haploidentical HSCT represents an effective therapeutic approach for patients with DOCK8 deficiency who lack a matched related or unrelated donor.

METHODS

Patients

All patients were prospectively enrolled on a clinical trial specifically designed for transplantation of adults and children with DOCK8 deficiency. Recipients were enrolled to 1 of 2 arms depending on donor source: (1) matched related or unrelated donor or (2) haploidentical related donor (ClinicalTrials.gov NCT01176006). This report focuses on the outcomes of patients who underwent haploidentical related donor transplantation. The primary objective of the study was to determine whether allogeneic HSCT reconstitutes T lymphocyte and B lymphocyte cells and myeloid cells with normal donor cells at 1 year after transplantation and reverses the clinical phenotype of severe recurrent infections. The secondary objective of the study was to evaluate the safety of this regimen including, transplantation-related toxicity, the incidence of acute and chronic GVHD, immune reconstitution, overall survival, and disease-free survival. The study was approved by the institutional review board of the National Cancer Institute and was independently monitored for safety and data accuracy. Written informed consent and assent were obtained for all patients and donors, with parental permission obtained for minors.

The inclusion criteria for recipients enrolled on the haploidentical arm included the following: (1) age of 6 to 40 years with confirmed homozygous or compound heterozygous mutations in the *DOCK8* gene performed by a Clinical Laboratory Improvements Amendments–certified laboratory, (2) 1 or more life-threatening infections, a viral-driven lymphoma, or squamous cell carcinoma, and (3) adequate organ function. Recipients who received a haploidentical donor source included only those patients for whom a 10/10-matched related or unrelated donor could not be identified. Exclusion criteria consisted of active CNS involvement by malignancy, chronic active hepatitis B, human immunodeficiency virus, or those who were pregnant or lactating. Donor selection was based on prioritizing identification of the best available adult donor over a minor-aged donor, and other selection criteria based on cytomegalovirus (CMV)/Epstein-Barr virus exposure and ABO blood type. Mutation on 1 allele of *DOCK8* did not represent a donor exclusion criterion. Additionally, all recipients were screened for the presence of donor-specific anti-HLA antibodies against potential donors and were excluded if positive, given the concern for primary graft failure [24].

Transplantation Conditioning Regimen

The pretransplantation conditioning regimen consisted of cyclophosphamide 14.5 mg/kg/day on days -6 and -5, fludarabine 30 mg/m^2/day on days -6 to -2, busulfan 3.2 mg/kg/day on days -4, -3, and -2 (pharmacokinetically targeted based on a test dose of .8 mg/kg of busulfan given approximately 1 week before the start of conditioning), and 200 cGy total body irradiation (TBI) on day -1 (Figure 1). The dose of fludarabine was based on actual body weight and adjusted for renal dysfunction. Busulfan was dose adjusted, based upon a test dose of .8 mg/kg of busulfan—according to the lower of the actual or the ideal body weight—given before the start of the preparative regimen [25-27] to determine the conditioning dose needed to target an area under the curve (AUC) of 3600 to 4800 μmol/minute. Busulfan was given as an i.v. infusion over 3 hours once daily for 3 days.

Stem Cell Collection

All donors underwent bone marrow harvest with a planned fresh infusion on day 0. The target minimum dose was 2×10^8 total nucleated cells per kilogram recipient body weight.

Post-Transplantation GVHD Prophylaxis

GVHD prophylaxis consisted of PT/Cy 50 mg/kg/day i.v. once daily × 2 doses on days +3 and +4 (based on the lesser of the actual or ideal body weight in obese patients), tacrolimus i.v./per oral from day +5 to day +180 (goal levels, 5 to 10 ng/mL), and mycophenolate mofetil 15 mg/kg i.v./per oral every 12 hours from day +5 to day +35. Immunosuppression was tapered or stopped at 6 months after transplantation if there was no evidence of GVHD.

Lymphoid and Myeloid Engraftment

$CD4^+$ and $CD8^+$ T lymphocytes, B cells, and natural killer cells were quantified by flow cytometry before transplantation and at designated intervals after transplantation, including at days +30, +60, and +100 and at 6, 12, 18, and 24 months after transplantation. *Neutrophil engraftment* was defined as a neutrophil count of $> .5 \times 10^9$ cells/L for 3 consecutive days. *Platelet engraftment* was defined as a nontransfused platelet count of $>20 \times 10^9$ cells/L for 7 consecutive days.

Analysis of Chimerism

Engraftment of donor cells was assessed using polymorphisms in regions known to contain short tandem repeats. Peripheral blood $CD4^+$ and $CD8^+$ T lymphocytes, and $CD19^+$ and $CD3^-/CD56^+$ lymphocytes were selected by cell sorting using flow cytometry at the designated time points, and chimerism was assessed on these subpopulations. In addition, $CD14^+/CD15^+$ myeloid cells and $CD3^+$ T lymphocytes were selected using immunobeads, and chimerism was assessed on the selected cells. The lower limit of sensitivity for this method is 1% to 3% of donor-type polymorphic markers in the mixture; these sensitivities are determined by studies using mixtures of known proportions of allogeneic DNA samples.

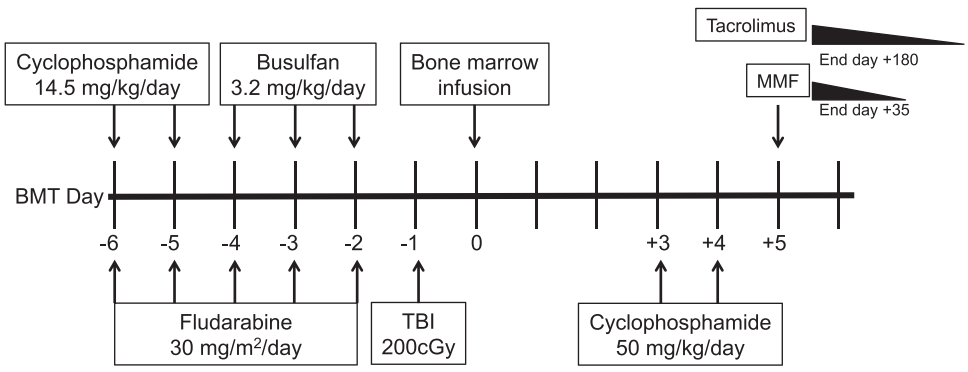

Figure 1. Schema of conditioning regimen for haploidentical related donor recipients.

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