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Haploidentical related donor hematopoietic stem cell transplantation with post-transplantation cyclophosphamide for DOCK8 deficiency

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TO THE EDITOR

Dedicator of cytokinesis 8 (DOCK8) gene mutations are responsible for a combined immunodeficiency characterized by atopy, sinopulmonary infections, and DNA viral infections including varicella zoster, herpes simplex 1 and 2 (HSV 1 and 2), human

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papilloma virus and molluscum contagiosum, and Epstein-Barr virus (EBV)-driven lymphomas (reviewed in Aydin et al¹). In that study of 136 patients with DOCK8 deficiency, the median survival at 20 years was 47%, and the event-free survival at 20 years was 18%.¹

Allogeneic hematopoietic stem cell transplantation (HSCT) using 10/10 HLA-matched related and unrelated donors represents an effective therapy for DOCK8 deficiency.²⁻⁴ In the absence of a 10/10 matched related or unrelated donor, alternative donor options consist of umbilical cord blood, a 9/10 HLA-matched related or unrelated donor, or a haploidentical related donor. Although the short search time and high likelihood of finding compatible units are an advantage with using umbilical cord blood, the frequent discrepancy between recipient body weight and the number of HSC in a standard cord blood unit frequently leads to delays in hematologic and immune reconstitution; the latter is particularly problematic in patients with diseases such as DOCK8 deficiency with active infections before HSCT. The high rate of graft-versus-host disease (GVHD) that accompanies the use of 9/10 matched donors limits their use in DOCK8 deficiency where there is no advantage of alloreactivity. HSCT from HLA haploidentical related donors has the advantage in that almost every patient has a donor, and there is no delay in obtaining the graft. To overcome the GVHD associated with haploidentical transplantation, post-transplant, high-dose cyclophosphamide (PT/CY) has been used to ablate alloreactive donor T cells.⁵ This platform enables haploidentical HSCT to be carried out without the expense or expertise required for *in vitro* T-cell depletion.

Here, we report successful haploidentical related donor HSCT in a young woman with DOCK8 deficiency using PT/CY for post-transplant GVHD prophylaxis.

CASE DESCRIPTION

A 20-year-old woman (patient 5-2 in the initial report of DOCK8 deficiency)⁶ who presented during childhood with eczema, food allergies, asthma, sinopulmonary infections with bronchiectasis, warts, and molluscum contagiosum (Figure 1, A), was found to have deleterious, compound heterozygous mutations in the *DOCK8* gene (158 kilobase pair deletion of at least exons 1-13 on one allele and R249X stop codon on the second allele). At age 15, she was diagnosed with stage IV EBV-negative Burkitt's lymphoma with kidney and meningeal involvement; this was successfully treated with EPOCH-R chemotherapy along with intrathecal methotrexate. She subsequently developed severe eosinophilic esophagitis and gastritis (Figure 1, C), renal insufficiency, and congestive heart failure, the latter 2 secondary to renal artery stenosis-induced hypertension due to DOCK8-related vasculopathy (Figure 1, E). Renal artery angioplasty before transplant improved her hypertension, renal insufficiency, and heart failure, but her ejection fraction remained severely reduced at 30% to 35%.

The patient, as well as her older sister, who also had DOCK8 deficiency, had no 10/10 matched related or unrelated donors. Because her sister had died from graft failure and human herpesvirus 6 (HHV6) encephalitis after a double cord blood transplant several years earlier, the current patient received a haploidentical related donor HSCT from her 21-year-old brother. The donor was ABO blood type-matched, cytomegalovirus (CMV)-negative,

EBV-negative, and heterozygous for the *DOCK8* mutation. The patient's EBV and CMV status was unknown due to long-term immune globulin replacement therapy; however, she was persistently CMV and EBV blood PCR negative. Conditioning consisted of fludarabine, low-dose cyclophosphamide, busulfan, and 200 cGy total body irradiation (see the Methods section in this article's Online Repository at www.jaci-inpractice.org). On day 0, she received a fresh infusion from her brother after a marrow harvest; the cell product contained 5.4×10^8 total nucleated cells/kg and 6.7×10^6 CD34+ cells/kg of recipient body weight. Post-transplant immunosuppression consisted of cyclophosphamide 50 mg/kg recipient body weight on day +3, followed by tacrolimus starting at day +4 until day +180, and mycophenolate mofetil on day +4 until day +35. She also received daily granulocyte-colony stimulating factor starting on day +4 until neutrophil engraftment. A single day of post-transplant cyclophosphamide compared with the more standard 2 days (days +3 and +4) was chosen due to concern for underlying heart failure.

Her post-transplant course was characterized by rapid donor engraftment, neutropenic fevers, viral reactivation, and grade 2 skin GVHD. Fever occurred on day +3, as described with T-cell replete haploidentical donor HSCT, and resolved with PT/CY.⁷ Neutrophil engraftment occurred on day +13, and platelet engraftment occurred on day +24. Day +30 chimerisms were 99% donor for whole blood, CD3+, and myeloid components (Table I). Limited skin GVHD, grade 1, developed at 2 weeks after transplant and responded to topical steroids. The patient received HSV prophylaxis with acyclovir, and CMV, EBV, HHV6, adenovirus, and *Toxoplasma* screening were performed weekly. Both BK virus and HHV-6 reactivated transiently, but without clinical consequence. Molluscum-related skin disease and warts improved significantly by 3 months after transplant with almost complete resolution by 1-year after HSCT (Figure 1, *A* and *B*). All immunosuppression was stopped at 6 months after transplant, and she remains with 100% donor chimerism.

Her clinical manifestations of *DOCK8* deficiency all stabilized, improved, or resolved within 2 months of transplant. Despite mild bronchiectasis before transplant, pulmonary function tests and imaging were stable at 1 year after transplant. Dysphagia resolved and repeat endoscopy 6 months after transplant demonstrated marked improvement of her eosinophilic disease (Figure 1, *C* and *D*). Food allergies were persistent 1 year after transplant. Left ventricular ejection fraction improved from 30% before transplant to 45% at 18 months after transplant. Worsening renal function and hypertension responded to repeat renal artery dilation 15 months after transplant.

HSCT is increasingly utilized for treatment of *DOCK8* deficiency because of its high morbidity and mortality arising from infections and virus-driven malignancies.¹ However, many affected individuals will not have 10/10 HLA-matched related or unrelated donors, necessitating the use of alternative donors. The delayed immune reconstitution and increased viral reactivation seen with umbilical cord blood, and the increased incidence of GVHD observed with 7/8 donors, support the use of haploidentical related donors in these situations.

In haploidentical related donor HSCT, depletion of donor T cells in the graft product—either by CD34+ selection or by selective T-cell depletion—is required to avoid lethal GVHD.

Recently, *in vitro* depletion of T-cell receptor (TCR $\alpha\beta$) and CD19+ donor cells has been shown to be a promising approach in haploidentical HSCT.^{8,9} TCR $\gamma\delta$ T cells are not major histocompatibility complex restricted and have a low likelihood of causing GVHD. Depletion of CD19+ donor cells is designed to prevent post-transplant lymphoproliferative disease.

In DOCK8 deficiency, Ghosh et al² reported a successful haploidentical related donor HSCT using TCR $\alpha\beta$ /CD19 depleted peripheral blood cells. The 13-year-old female patient underwent a parental haploidentical HSCT with 13.8×10^6 CD34+ cells/kg recipient body weight. Conditioning consisted of Fresenius-anti-thymocyte globulin, fludarabine, thiotepea, and melphalan. The patient engrafted on day +8 and was discharged on day +37 with 100% donor chimerism, 22 CD3+/CD4+ T cells/ μ L, and 605 CD3+/CD8+ T cells/ μ L. Although JC virus, BK virus, and CMV reactivated after transplant, there was no evidence of clinical disease. Her molluscum and warts resolved in a similar time course to DOCK8-deficient recipients of HLA-matched products.³ The main complication in her case consisted of lower gastrointestinal GVHD on day +160 that responded to corticosteroids.

We used PT/CY to reduce the risk of significant viral reactivation observed with serotherapy.⁵ We modified the previously described nonmyeloablative haploidentical related donor regimen with PT/CY to include 3 days of busulfan for additional myelosuppression because of evidence that DOCK8-expressing cells have a competitive advantage over DOCK8-deficient cells in the T-cell lineage, but not in the myeloid and B-cell lineage.⁴ We also reduced PT/CY to 1 day due to the patient's heart failure. Despite significant pretransplant comorbidities with renal insufficiency, cardiomyopathy, bronchiectasis, and toxicity from prior lymphoma chemotherapy, there was no worsening of renal or cardiac function, nor pulmonary complications. Thus, haploidentical HSCT with PT/CY represents an effective therapy for DOCK8 deficiency, even in the setting of impaired organ function.

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Clinical Implications

- Haploidentical hematopoietic stem cell transplantation with post-transplant cyclophosphamide was found to be safe and effective in reversing the phenotype of dedicator of cytokinesis 8 deficiency. Utilizing this approach to transplant will greatly increase the number of patients with appropriate bone marrow donors.

FIGURE 1.

A, Molluscum contagiosum lesions on face before haploidentical related donor transplant, with **B**, clearance 12 months after transplant. Biopsy of the midesophagus **C**, before transplant showing eosinophilic esophagitis ($\times 400$ magnification), and **D**, 6 months after transplant showing complete resolution of eosinophilic inflammation in a proximal esophageal biopsy ($\times 400$ magnification). **E**, Abdominal magnetic resonance angiography revealing narrowed distal aortic section with bilateral renal artery stenosis (arrows).

TABLE I

Immune reconstitution after haploidentical related donor transplant

	Pre	Day 14	Day 30	Day 100	1 y	1.5 y	Reference range
% Donor chimerism							
CD3		93	99	100	100		
Myeloid		99	99	98	100		
CD4		ND	99	100	100		
CD8		ND	ND	99	100		
NK		ND	98	99	100		
CD19		ND	ND	99	100		
Cell totals							
CD3	188	ND	179	377	517	978	615–2348/ μ L
CD4	159	ND	140	315	377	684	334–1556/ μ L
CD8	34	ND	42	61	122	257	149–787/ μ L
NK	48	ND	68	55	45	170	109–607/ μ L
CD19	102	ND	1	37	86	166	81–493/ μ L
Other							
IgG	1003 [*]	694 [*]	535 [*]	689 [*]	487 [†]	637 [†]	700–1600 mg/dL
IgA	120	42	20	21	20	26	70–400 mg/dL
IgM	92	36	18	126	39	56	40–230 mg/dL
IgE	5970	ND	143	121	67.8	69.9	0–90 IU/mL
Anti-tetanus IgG					0.23 [‡]	0.18 [‡]	
Anti-diphtheria ab					0.03 [‡]		
Anti-pneumococcal ab (serotypes > 1.2 mc/mL)					12/13 [§]	12/13 [§]	
Abs Eos	2.27	ND	0.50	0.12	0.06		0.04–0.36 K/ μ L

ab, Antibodies; Abs Eos, absolute eosinophils; ND, not determined; NK, natural killer.

^{*} Intravenous immunoglobulin was being given at approximately 4-wk intervals.[†] Off immune globulin for 3–4 mo.

*Vaccine response after 2 doses of diphtheria/tetanus/acellular pertussis vaccine.
§Vaccine response after 3 doses of the pneumococcal 13-valent protein conjugate vaccine.

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