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Haploidentical Peripheral Blood Stem Cell Transplantation Demonstrates Stable Engraftment in Adults with Sickle Cell Disease

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We report on the screening and development of haploidentical hematopoietic stem cell transplantation (HSCT) for adult patients with clinically aggressive sickle cell disease (SCD) at our institution. Of 50 adult SCD patients referred for HSCT between January 2014 and March 2017, 20% were denied by insurance. Of 41 patients initially screened, 10% lacked an available haploidentical donor, 29% had elevated donor-specific antibodies (DSAs), and 34% declined to proceed to HSCT. All 10 patients who were transplanted received peripheral blood stem cells. The initial 2 were conditioned with alemtuzumab/total body irradiation (TBI) 3 Gy followed by post-transplant cyclophosphamide and failed to engraft. The next 8 patients received the regimen developed at Johns Hopkins University with TBI 3 Gy. Granulocyte colony-stimulating factor was administered from day +12 in those with HbS < 30%. All 8 patients engrafted with a median time to neutrophil $>.5 \times 10^9/L$ of 22 days (range, 18 to 23). One patient subsequently lost the graft, and 7 (87.5%) maintained >95% donor cell chimerism at 1-year post-HSCT. Two patients developed acute graft-versus-host disease (GVHD) of at least grade II. One had chronic GVHD and died >1 year after HSCT of unknown causes. With a median follow-up of 16 months (range, 11 to 29), 7 patients (87.5%) are alive. Our findings suggest that limited insurance coverage, high rate of DSAs, and patient declining HSCT may limit the availability of haploidentical HSCT in adult SCD patients. The modified Hopkins regimen used here demonstrates high engraftment and low morbidity rates and should be tested in larger, multicenter, prospective clinical trials.

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INTRODUCTION

Allogeneic nonmyeloablative hematopoietic stem cell transplantation (HSCT) from HLA-matched related donors results in event-free survival rates of 87% to 92%, overall survival rates of 97% to 100%, and 0% acute or chronic graft-versus host disease (GVHD) in adults with sickle cell disease (SCD) [1,2]. There is an unmet need for alternative donors because only 18% of SCD patients have an HLA-matched sibling [3]. HSCT using HLA-matched unrelated donors is limited by the difficulty in finding HLA-compatible donors for this largely nonwhite patient population [4,5]. Additionally, a study reported high rates of chronic GVHD (62%) and transplant-related mortality (21%) in SCD patients receiving transplants from HLA-matched unrelated donors [6].

The discovery that post-transplant cyclophosphamide (PTCy) allows patients to engraft stem cells from haploidentical donors without an increased risk of GVHD has led to the rapid expansion of haploidentical HSCT in pa-

tients with hematologic malignancies [7]. This strategy was used in 14 SCD patients transplanted with bone marrow cells after conditioning with fludarabine, cyclophosphamide, 2 Gy total body irradiation (TBI), antithymocyte globulin, and GVHD prophylaxis with PTCy on days +3 and +4; mycophenolate mofetil for 30 days; and tacrolimus or sirolimus for at least 1 year (the Hopkins protocol) [8]. No severe transplant-related complications were reported, and 57% of patients achieved a stable donor cell engraftment. In a subsequent study the same regimen resulted in the engraftment of only 2 of 5 SCD patients [9]. Modifications to this regimen, including the addition of azathioprine and hydroxyurea for 3 months pre-HSCT, hypertransfusion, and thiotepa on day -7, improved engraftment to 91%, with 18% acute GVHD and 14% mortality in a pediatric series of SCD patients [9].

Our institution has the largest adult sickle cell program in the Chicago area. Because only 20% of our SCD patients eligible for HSCT had a matched related donor, we initiated a haploidentical HSCT program [1]. Here we report our center's real-life experience of screening and treating adult SCD patients with haploidentical HSCT.

METHODS

Patients

Transplant eligibility requirements were similar to those for match related donor transplants [1] and in accordance with the international expert panel for alternative donor transplantation in SCD [10], with the additional requirement that the recipient be negative for donor-specific HLA antibodies

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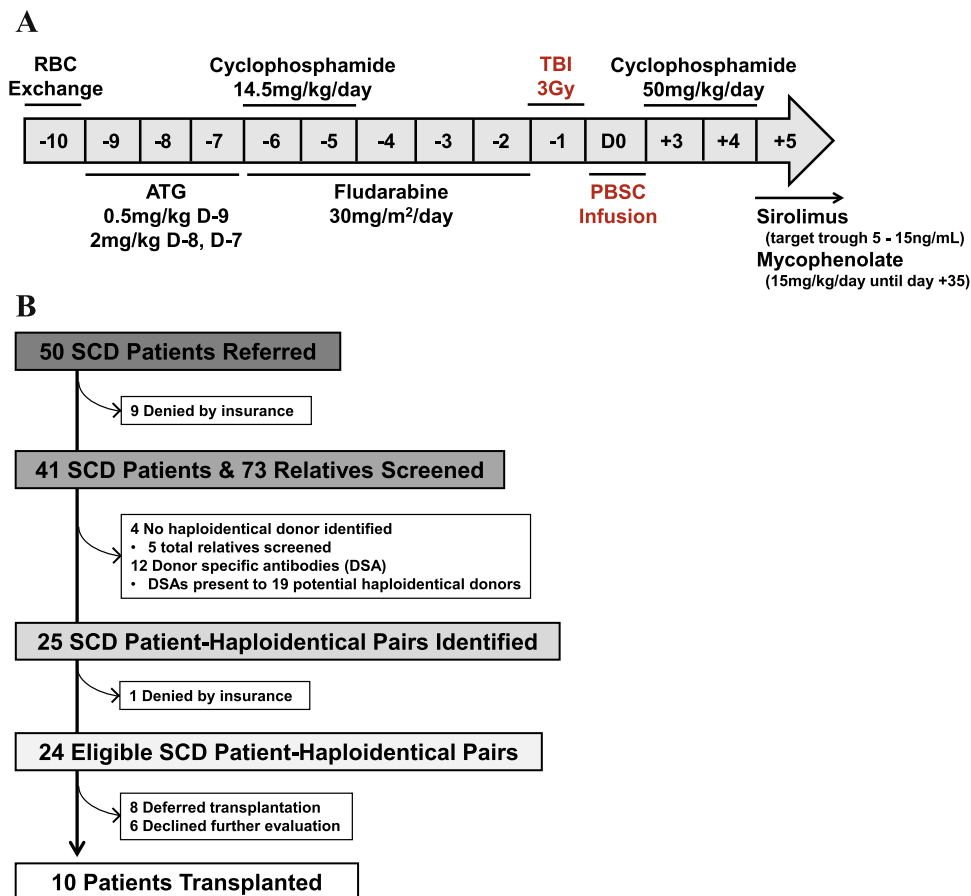


Figure 1. (A) Regimen for haploidentical transplantation in adult patients with SCD. (B) Screening process for haploidentical transplantation in adult patients with SCD. Of 50 patients referred to the SCD transplant clinic, 41 proceeded with HLA typing. Twenty-five (61%) had a suitable HLA-haploidentical donor with 4 (10%) lacking an available HLA-haploidentical relative and 12 (29%) having DSAs. In addition, 10 (20%) were denied by insurance and 14 (34%) declined or deferred transplantation. (C) Stable whole blood and CD3⁺ T cell engraftment after haploidentical transplantation in adult patients with SCD. (D) Improvements in hemoglobin concentration after haploidentical transplantation in adult patients with SCD.

(DSAs). Positivity for DSAs was considered moderate with a mean fluorescent intensity between 2000 to 5000 and high with a mean fluorescent intensity > 5000 [11]. Institutional Review Board approval was obtained before collecting and analyzing the clinical data.

Donors

Haploidentical donors were either HbAA or HbAS. The donors received granulocyte colony-stimulating factor (G-CSF) subcutaneously at a dose of 5 µg/kg/twice daily for 5 days followed by peripheral blood stem cell (PBSC) collection.

Conditioning Regimens

The conditioning protocol in the first 2 patients was as follows: alemtuzumab (.03 mg/kg on day -7, .1 mg/kg on day -6, .3 mg/kg on days -5 to -3), single-dose TBI 3 Gy on day -2, and cyclophosphamide (50 mg/kg on days +3 and +4). Because both patients failed to engraft donor cells, we adopted the Hopkins protocol [8] for the next 8 patients with 2 modifications aimed at improving engraftment: (1) increasing the dose of TBI from 2 Gy to 3 Gy and (2) infusing growth factor-mobilized PBSCs instead of bone marrow cells (Figure 1A). The conditioning was as follows: rabbit antithymocyte globulin (Sanofi Genzyme, Cambridge, MA) (.5 mg/kg on day -9, 2 mg/kg on days -8 and -7), cyclophosphamide (14.5 mg/kg on days -6 and -5), fludarabine (30 mg/m² on days -6 to -2), and single-dose TBI 3 Gy on day -1. GVHD prophylaxis consisted of cyclophosphamide (50 mg/kg i.v. on days +3 and +4), oral mycophenolate mofetil (15 mg/kg 3 times daily from days +5 to +35), and sirolimus from day +5 dosed for a target trough of 5 to 15 ng/mL. In patients with T cell chimerism > 50% at 1 year post-HSCT and without signs of GVHD, treatment with sirolimus was tapered off over 3 months.

Recipients underwent RBC exchange transfusion on day -10 (goal HbS < 30%), and hydroxyurea was permanently discontinued on day -9.

Platelet transfusions were administered to maintain platelet counts >50 × 10⁹ cells/L and penicillin V 250 mg p.o. was administered twice daily, in addition to standard antimicrobial prophylaxis. Donor cell engraftment was assessed by chimerism analysis on circulating mononuclear cells and CD3⁺ T cells on days +30, +60, +180, and +365.

Graft-versus-Host Disease

Patients were monitored in the University of Illinois at Chicago bone marrow transplant clinic at least weekly until day +60, monthly until day +180, and bimonthly until 1 year post-HSCT. Acute and chronic GVHD were graded according to standard consensus diagnostic criteria [12,13]

RESULTS

Between January 2014 and March 2017, 50 adult SCD patients meeting haploidentical HSCT eligibility requirements [10] were referred to our program (Figure 1B). Nine patients were initially denied by insurance, and therefore only 41 could be screened for donor availability. Of these, 4 (10%) lacked an available haploidentical donor and 12 (29%) had moderate (n = 7) or high (n = 5) levels of DSAs, a strong predictor of graft rejection in haploidentical HSCT [11]. Of the 25 patients (61%) with an identified haploidentical donor, 1 additional patient was denied by insurance before transplant and 14 (34%) ultimately declined or deferred HSCT, resulting in a total of 10 patients being transplanted. All recipients received PBSCs from their haploidentical donors. In 7 HbAS donors, mobilization with G-CSF did not lead to

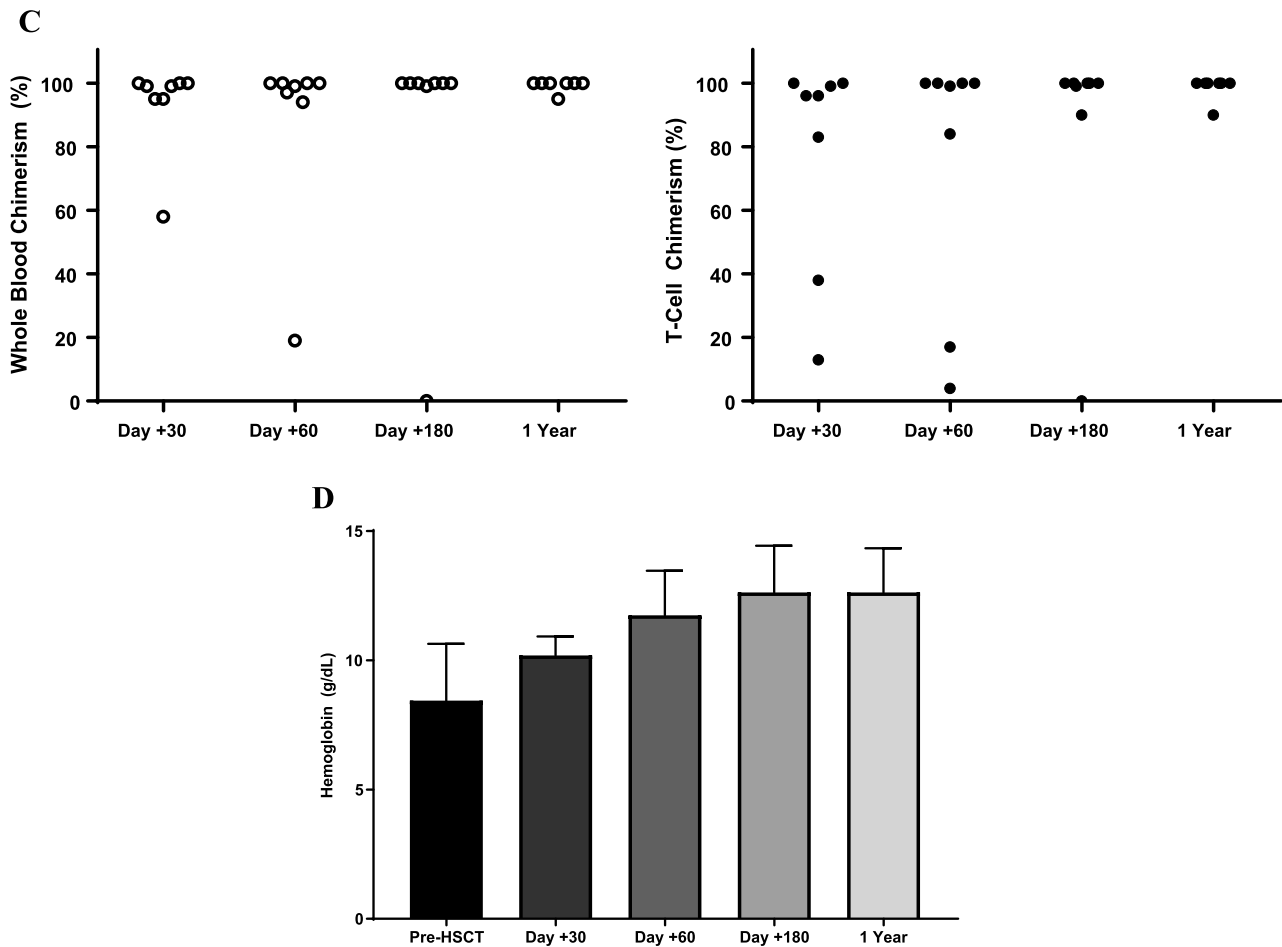


Figure 1. (continued)

increased side effects and produced similar stem cell collections as in HbAA donors.

The first 2 patients (Table 1, top) were conditioned with alemtuzumab/3 Gy TBI + PTCy but failed to engraft donor cells and recovered autologous neutrophils on day +39 and day +34, respectively. The following 8 patients (Table 1, bottom) were conditioned with the modified Hopkins regimen (TBI 3 Gy and PBSCs as the graft source) (Figure 1A). All 8 patients engrafted $> .5 \times 10^9$ neutrophils/L at a median of 22 days (range, 18 to 23). One patient had low donor T cell chimerism levels at days +30 and +60 that spontaneously improved by day +180 without any changes in immunosuppression. Another patient had a progressive decline of donor whole blood and T cell chimerisms and experienced secondary graft failure on day +90 with autologous hematopoietic recovery. At 1 year post-HSCT, 7 patients maintained an average donor mononuclear chimerism $> 95\%$ and T cell chimerism $\geq 90\%$ (Figure 1C).

Transplant-related toxicities included at least grade 2 mucositis in 3 patients and cytomegalovirus reactivation in 2 patients without occurrence of cytomegalovirus infection. Seven neutropenic patients with HbS $< 30\%$ received a median of 7 doses (range, 3 to 14) of G-CSF at 5 $\mu\text{g}/\text{kg}$ starting at day +12 post-HSCT. Only 1 patient experienced mild bone pain in the lower extremities. Small subarachnoid hemorrhages occurred in 2 patients. The first patient had a history

of multiple RBC antibodies, became refractory to platelet transfusions, and developed multifocal small subarachnoid hemorrhages in the left parietal lobe on day +10. Symptoms and brain imaging improved 4 days later after platelet counts were maintained at $>50 \times 10^9$ cells/L with cross-matched platelets. The second patient, who had a prior stroke history, developed a seizure when the platelet count was 68×10^9 cells/L. Magnetic resonance imaging of the brain demonstrated a right frontal subarachnoid hemorrhage on day +12. Symptoms and imaging results improved 2 days later, after initiating levetiracetam and maintaining platelets $>100 \times 10^9$ cells/L. Acute GVHD was observed in 2 patients and chronic GVHD in 1 patient. One patient developed acute on chronic GVHD involving the skin, liver, and eyes on day +83. Treatment with steroids and strict compliance with sirolimus improved eye symptoms and bilirubin levels, but the patient died unexpectedly at home on day +407. Another patient developed grade II acute gut GVHD that completely resolved after a short course of steroid therapy.

With a median follow-up of 17 months (range, 12 to 30), 7 patients are alive and 6 maintain $>95\%$ stable donor engraftment (Figure 1C) with improvements in their hemoglobin concentrations (Figure 1D). Three patients have stopped immunosuppression, and the other 3 are being tapered off immunosuppression.

Table 1
 Characteristics and Outcomes of 2 Patients with SCD Who Underwent HSCT from a Haploidentical, Related Donor Treated with Alemtuzumab, TBI, and PTCy (top) and of 8 Patients with SCD Who Underwent HSCT from a Haploidentical, Related Donor Treated with the Modified Hopkins Regimen(bottom)

No.	Transplantation Characteristics				Prior Therapy	Donor	CD34 ⁺ Dose ($\times 10^6$ /kg)	Transplantation Outcomes			Transplant-Related Toxicity				
	Age at HSCT (yr)	Sex	Hemoglobin Genotype	Indications*				Duration of Follow-up (mo)/Current Donor T Cell Chimerism	Living Status	Neutrophil Engraftment	Infectious Complications	CMV Reactivation	Acute GVHD	Chronic GVHD	
<i>Two patients treated with alemtuzumab, TBI, and PTCy</i>															
A	24	F	SS	20 VOC/year 3 ACS/lifetime	Hydroxyurea	Mother (Hb AS)	5.9	37	Alive	Autologous, day +39	None	None	None	None	
B	52	M	SC	10 VOC/year	Hydroxyurea	Sister (Hb AA)	5.4	36	Alive	Autologous, day +34	None	Day +11	None	None	
<i>Eight patients treated with modified Hopkins regimen</i>															
1	38	M	SS	8 VOC/year 3 ACS/lifetime	Hydroxyurea	Daughter (Hb AS)	14.2	30 / 100%	Alive	Day +23	<i>Escherichia coli</i> UTI	Day +19	None	None	
2	20	M	S β ⁺ -thal	10 VOC/year	Hydroxyurea	Sister (Hb AA)	6.0	23 / 90%	Alive	Day +20	None	None	None	None	
3	21	M	SS	10 VOC/year TRJV = 2.7	Hydroxyurea	Mother (Hb AS)	5.3	15	Deceased	Day +18	Oral HSV1 coronavirus influenza	Day +20	Grade II skin Grade IV liver	Moderate - eye - liver None	
4	27	M	SS	4 VOC/year 2 ACS/lifetime	Hydroxyurea	Father (Hb AS)	8.2	17 / 0%	Alive	Day +23	None	None	None	None	
5	31	M	SS	11 VOC/year 2 ACS/last 2 years	Hydroxyurea	Brother (Hb AA)	4.2	17 / 100%	Alive	Day +22	None	None	None	None	
6	27	F	SS	19 VOC/year 2 ACS/last 2 years	Hydroxyurea	Mother (Hb AS)	10.8	13 / 100%	Alive	Day +22	Enterococcus UTI	None	None	None	
7	37	M	SS	Stroke 3 VOC/year 2 ACS/last 2 years	Chronic transfusion	Mother (Hb AS)	12.2	13 / 100%	Alive	Day +19	None	None	None	None	
8	29	F	SS	7 VOC/year 2 ACS/lifetime	Hydroxyurea	Mother (Hb AS)	6.1	12 / 100%	Alive	Day +18	None	None	Grade II GI	None	

CMV indicates cytomegalovirus; VOC, vaso-occlusive crisis; ACS, acute chest syndrome; UTI, urinary tract infection; TRJV, tricuspid regurgitant jet velocity; GI, gastrointestinal.

* The VOC rate is an average of the rate over the 2 years preceding the date of consultation for transplantation.

Table 2
Current Published Experience for Haploidentical Transplantation in SCD

Study	No. of Patients	Age Range (yr)	Conditioning Regimen	Stem Cell Source	Acute GVHD	Chronic GVHD	Stable Engraftment	Overall Survival
Bolanos-Meade et al., 2012 [8]	14	15–42	Flu 30 mg/m ² /day, Cy 14.5 mg/kg/day, ATG, TBI 2 Gy, PTCy 50 mg/kg/day	Bone marrow	0	0	8	14
Dallas et al., 2013 [16]	8	4–17	1) Flu 150–200 mg/m ² , thiotepa 10 mg/kg, Bu (target 900 ng/mL), ATG (10 mg/kg), muromonab-CD3 (.1 mg/kg) 2) HU/azathioprine 3 months pretransplant; Bu (target 900 ng/mL), thiotepa, Cy (200 mg/kg), muomonab-CD3 (.1 mg/kg)	Bone marrow	4	3	5	6
Dhedin et al., 2016 [9]	5	12–50	1) Flu 30 mg/m ² /day, Cy 14.5 mg/kg/day, ATG, TBI 2 Gy, PTCy 50 mg/kg/day	Bone marrow	0	0	2	5
	8	7–26	2) Thiotepa 10 mg/kg/day, Flu 30 mg/m ² /day, Cy 14.5 mg/kg/day, ATG, TBI 2 Gy, PTCy 50 mg/kg/day		1	0	7	8
	23	3–18	3) Preconditioning for 3 months with azathioprine 3 mg/kg/day and HU 30 mg/kg/day; thiotepa 10 mg/kg/day, Flu 30 mg/m ² /day, Cy 14.5 mg/kg/day, ATG, TBI 2 Gy, PTCy 50 mg/kg/day		4	0	21	18
Fitzhugh et al., 2017 [14]	12	20–56	Alemtuzumab 1 mg/kg, TBI 4 Gy, PTCy 50 mg/kg/day	PBSCs	1	1	6	11
Pawlowska et al., 2018 [17]	4	13–23	Flu 40 mg/m ² /day, dexamethasone 25 mg/m ² /day × 2 cycles pre-HSCT Rabbit ATG 1.5 mg/kg/day, Flu 35 mg/m ² /day, Bu 130 mg/m ² /day, PTCy 50 mg/kg/day	3 Bone marrow, 1 PBSCs	1	3	4	4
Current Study	8	20–38	Flu 30 mg/m ² /day, Cy 14.5 mg/kg/day, ATG, TBI 3 Gy, PTCy 50 mg/kg/day	PBSCs	2	1	7	7
Summary	82	3–51	—	—	13 (16%)	8 (10%)	60 (73%)	73 (89%)

Flu indicates fludarabine, ATG, antithymocyte globulin; Bu, busulfan; HU, hydroxyurea.

DISCUSSION

In this single-center experience of a haploidentical HSCT program for adults with SCD, we demonstrated several real-life barriers for access to haploidentical transplantation, the safety of G-CSF post-HSCT, and a high rate of long-term engraftment using PBSCs with a modified Hopkins regimen. After our positive results in match related donor HSCT [1], we initially attempted to apply the same alemtuzumab-based regimen with the addition of PTCy in 2 patients undergoing haploidentical HSCT. Both experienced graft failure, consistent with the experience reported using the same approach at the National Institutes of Health [14].

Because the risk of transplant-related mortality is higher in adults with SCD using standard myeloablative regimens [15], we transplanted the next 8 patients with a nonmyeloablative regimen developed at Johns Hopkins University [8]. To decrease the high rate of rejection reported in the original study (43%), we modified the Hopkins protocol by increasing the dose of TBI from 2 Gy to 3 Gy and using PBSCs instead of marrow cells. This led to improvements in stable donor cell engraftment from 40% to 57% previously reported [8,9] to 87.5%, while maintaining manageable toxicities. The findings we report here should be considered in the context of the few small series of haploidentical HSCT in SCD patients that have been published to date (Table 2).

Our engraftment results are comparable with those obtained in a pediatric series where azathioprine, hydroxyurea, and thiotepa were added to the preparative regimen [8]. Use of PBSCs has been associated with a greater risk for acute and

chronic GVHD compared with unstimulated bone marrow in patients with hematologic malignancies undergoing a T cell-replete haploidentical HSCT [18]. Although we observed chronic GVHD in only 1 of 8 patients, this risk should be carefully considered in future studies testing the benefits of PBSCs for reducing rejection in patients with nonmalignant diseases conditioned with low intensity regimens.

In our experience of 50 adult SCD patients referred for HSCT, only 20% ended up receiving a haploidentical HSCT. Medical insurance denial accounted for 20% of the lack of access for HSCT. Other factors, such as high rates of DSAs in frequently transfused SCD patients and personal decisions to decline HSCT, also played significant roles. Our rate of available haploidentical donors is lower than was previously observed at Johns Hopkins University, where 90% of SCD patients referred had haploidentical donors [8]. This difference may be because many of the SCD patients reported on here were already being followed in our clinics and had not been prescreened or selected by referring physicians. The presence of DSAs is a major barrier to haploidentical HSCT in SCD that should be addressed when discussing treatment options with patients. A possible strategy to increase the donor pool could be to select patients with low DSA titers and a negative cross-match result. Desensitization protocols used in hematologic malignancies [11] should also be tested in clinical trials for SCD patients with clinically aggressive disease. Our findings are consistent with a previous report showing that a substantial proportion of eligible SCD patients do not proceed to HSCT because of fear of toxicity and satisfaction with the current quality of life [19]. The 2 main reasons that

patients reported for declining HSCT were the risk of GVHD in an HLA-mismatched HSCT and the toxicity associated with chemotherapy in the conditioning regimen. Interestingly, in previous studies the severity of SCD was not associated with the degree of risk that a parent or a patient is willing to accept for cure [20–23]. Only 35% of adolescents and 46% of parents would accept HSCT if recommended by their hematologist [24]. Thirty-two percent of adolescents believe that SCD will shorten their life span, and only 26% believe that SCD will prevent the achievement of life goals, which is in contrast to 86% of adults who perceived that employment opportunities are affected by SCD [21,24]. There is a need for better education of patients about the course of SCD and for large, prospective haploidentical HSCT studies to guide the decisions of patients and their families for the risk-to-benefit assessment of HSCT. The risks of curative treatment with alternative donors will need to be carefully considered as new therapies, such as gene therapy [25] and nontransplant therapies [26], are being developed for SCD.

We also observed that G-CSF could be safely administered to SCD adults to shorten the duration of post-HSCT neutropenia. Concern for the safety of G-CSF was highlighted in a previous case series of 11 SCD patients receiving G-CSF to reduce the duration of neutropenia after chemotherapy or to mobilize autologous stem cells [27]. In that case series 7 of 11 patients had serious adverse events with G-CSF use, and a lower HbS level did not reduce the rate of adverse events. In contrast, in a pediatric cohort of children with SCD undergoing matched related donor HSCT, G-CSF 5 µg/kg/day was safely given starting on day +7 until full neutrophil recovery [28]. Only 1 patient in our study had mild lower extremity pain while receiving G-CSF consistent with tolerability of G-CSF post-HSCT in SCD. Although sickle cell trait donors did not experience any severe side effects with G-CSF mobilization, an alternative strategy to mobilize stem cells in sickle cell trait donors and to mobilize autologous stem cells from SCD patients may be the use of plerixafor, as safely demonstrated in gene therapy studies [29].

In conclusion, our findings suggest that a nonmyeloablative haploidentical PBSC transplant using TBI 3 Gy and PTCy could cure many adult patients with advanced SCD, and larger clinical studies are warranted. Based on our findings, barriers limiting the access to haploidentical HSCT for SCD patients should also be addressed by the transplant community with multilevel interventions.

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REFERENCES

- Saraf SL, Oh AL, Patel PR, et al. Nonmyeloablative stem cell transplantation with alemtuzumab/low-dose irradiation to cure and improve the quality of life of adults with sickle cell disease. *Biol Blood Marrow Transplant.* 2016;22:441–448.
- Hsieh MM, Fitzhugh CD, Weitzel RP, et al. Nonmyeloablative HLA-matched sibling allogeneic hematopoietic stem cell transplantation for severe sickle cell phenotype. *JAMA.* 2014;312:48–56.
- Mentzer WC, Heller S, Pearle PR, Hackney E, Vichinsky E. Availability of related donors for bone marrow transplantation in sickle cell anemia. *Am J Pediatr Hematol Oncol.* 1994;16:27–29.
- Eapen M, Horowitz MM. Alternative donor transplantation for aplastic anemia. *Hematol Am Soc Hematol Educ Progr.* 2010;30:43–46.
- Gragert L, Eapen M, Williams E, et al. HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry. *N Engl J Med.* 2014;371:339–348.
- Shenoy S, Eapen M, Panepinto JA, et al. A trial of unrelated donor marrow transplantation for children with severe sickle cell disease. *Blood.* 2016;128:2561–2567.
- Luznik L, O'Donnell PV, Symons HJ, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. *Biol Blood Marrow Transplant.* 2008;14:641–650.
- Bolanos-Meade J, Fuchs EJ, Luznik L, et al. HLA-haploidentical bone marrow transplantation with posttransplant cyclophosphamide expands the donor pool for patients with sickle cell disease. *Blood.* 2012;120:4285–4291.
- Dhedin N, Fuente J, Bernaudin F, et al. Haploidentical bone marrow transplant with post-transplant cytoan plus thiotepa improves donor engraftment in patients with sickle cell anemia: results of an international multicenter learning collaborative. *Blood.* 2016;128:1233.
- Angelucci E, Matthes-Martin S, Baronciani D, et al. Hematopoietic stem cell transplantation in thalassemia major and sickle cell disease: indications and management recommendations from an international expert panel. *Haematologica.* 2014;99:811–820.
- Ciurea SO, de Lima M, Cano P, et al. High risk of graft failure in patients with anti-HLA antibodies undergoing haploidentical stem-cell transplantation. *Transplantation.* 2009;88:1019–1024.
- Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease. I. Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant.* 2005;11:945–956.
- Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus conference on acute GVHD grading. *Bone Marrow Transplant.* 1995;15:825–828.
- Fitzhugh CD, Hsieh M, Taylor T, et al. Cyclophosphamide improves engraftment in patients with SCD and severe organ damage who undergo haploidentical PBSC. *Blood Adv.* 2017;1:652–661.
- Gluckman E, Cappelli B, Bernaudin F, et al. Sickle cell disease: an international survey of results of HLA-identical sibling hematopoietic stem cell transplantation. *Blood.* 2016;29:1548–1556.
- Dallas MH, Triplett B, Shook DR, et al. Long-term outcome and evaluation of organ function in pediatric patients undergoing haploidentical and matched related hematopoietic cell transplantation for sickle cell disease. *Biol Blood Marrow Transplant.* 2013;19:820–830.
- Pawlowska AB, Cheng JC, Karras NA, et al. HLA haploidentical stem cell transplant with pretransplant immunosuppression for patients with sickle cell disease. *Biol Blood Marrow Transplant.* 2018;24:185–189.
- Bashey A, Zhang MJ, McCurdy SR, et al. Mobilized peripheral blood stem cells versus unstimulated bone marrow as a graft source for T-cell-replete haploidentical donor transplantation using post-transplant cyclophosphamide. *J Clin Oncol.* 2017;35:3002–3009.
- Hansbury EN, Schultz WH, Ware RE, Aygun B. Bone marrow transplant options and preferences in a sickle cell anemia cohort on chronic transfusions. *Pediatr Blood Cancer.* 2012;58:611–615.
- Meier ER, Dioguardi JV, Kamani N. Current attitudes of parents and patients toward hematopoietic stem cell transplantation for sickle cell anemia. *Pediatr Blood Cancer.* 2015;62:1277–1284.
- Chakrabarti S, Bareford D. A survey on patient perception of reduced-intensity transplantation in adults with sickle cell disease. *Bone Marrow Transplant.* 2007;39:447–451.
- van Besien K, Koshy M, Anderson-Shaw L, et al. Allogeneic stem cell transplantation for sickle cell disease. A study of patients' decisions. *Bone Marrow Transplant.* 2001;28:545–549.
- Kodish E, Lantos J, Stocking C, Singer PA, Siegler M, Johnson FL. Bone marrow transplantation for sickle cell disease. A study of parents' decisions. *N Engl J Med.* 1991;325:1349–1353.
- Roth M, Krystal J, Manwani D, Driscoll C, Ricafort R. Stem cell transplant for children with sickle cell anemia: parent and patient interest. *Biol Blood Marrow Transplant.* 2012;18:1709–1715.
- Ribeil JA, Hacein-Bey-Abina S, Payen E, et al. Gene therapy in a patient with sickle cell disease. *N Engl J Med.* 2017;376:848–855.
- de Montalembert M, Brousse V, Chakravorty S, et al. Are the risks of treatment to cure a child with severe sickle cell disease too high? *BMJ.* 2017;359:j5250.

27. Fitzhugh CD, Hsieh MM, Bolan CD, Saenz C, Tisdale JF. Granulocyte colony-stimulating factor (G-CSF) administration in individuals with sickle cell disease: time for a moratorium? *Cytotherapy*. 2009;11:464–471.
28. King AA, Kamani N, Bunin N, et al. Successful matched sibling donor marrow transplantation following reduced intensity conditioning in children with hemoglobinopathies. *Am J Hematol*. 2015;90:1093–1098.
29. Lagresle-Peyrou C, Lefrere F, Magrin E, et al. Plerixafor enables the safe, rapid, efficient mobilization of haematopoietic stem cells in sickle cell disease patients after exchange transfusion. *Haematologica*. 2018;103:778–786.



Eltrombopag for the Treatment of Refractory Pure RBC Aplasia after Major ABO Incompatible Hematopoietic Stem Cell Transplantation

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Pure RBC aplasia (PRCS) is a well-recognized complication after allogeneic hematopoietic stem cell transplantation (HSCT). Many therapeutic options are available to treat this condition, including erythropoietin, rituximab, bortezomib, plasma exchange, immunoadsorption, donor lymphocyte infusion, mesenchymal stem cells, antithymocyte globulin, and high-dose steroids; however, treatment outcomes are often variable and can sometimes lead to disappointing results. In this brief article we report our experience with 2 patients with PRCA after major ABO-incompatible HSCT who were resistant to multiple therapeutic interventions and who eventually benefited from treatment with eltrombopag, a thrombopoietin mimetic approved by the US Food and Drug Administration for the treatment of patients with immune thrombocytopenic purpura or severe aplastic anemia refractory to immunosuppressive agents or not eligible for HSCT. Data from these 2 patients show that eltrombopag was effective in treating erythroid aplasia and transfusion dependence after HSCT in patients who did not benefit from multiple previous treatments. Moreover, eltrombopag was well tolerated, with only a transient thrombocytosis requiring dose adjustment and no evidence of clonal evolution. Based on the positive results obtained in these 2 patients, we suggest that eltrombopag may have a favorable effect on unilineage cytopenias such as PRCA. Further studies in a large proportion of patients are mandatory to confirm these preliminary results.

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INTRODUCTION

Pure RBC aplasia (PRCA) is an uncommon complication of ABO major mismatched allogeneic hematopoietic stem cell transplantation (HSCT), occurring in 7.5% to 16% of patients [1–4]. PRCA has been considered as the result of B lymphocytes of recipient origin producing isohemoagglutinins, which can interfere with the engraftment of donor erythroid cells, and is characterized by delayed RBC recovery after transplantation, anemia, and reticulocytopenia [5].

The diagnosis is confirmed by the absence of erythroblasts from otherwise morphologically normal bone marrow, once other causes, for instance viral infections and drug toxicity, have been excluded. A number of risk factors have been associated with the development of PRCA, including anti-A isoagglutinins, the use of reduced-intensity conditioning,

cyclosporine-based graft-versus-host disease (GVHD) prophylaxis, the absence of GVHD, and grafts from matched sibling donors [3–5].

Although several patients may recover spontaneously, others need more aggressive treatment strategies to avoid extensive RBC transfusions and related iron overload [6]. Rapid tapering of immunosuppressive agents, erythropoietin (recombinant human erythropoietin [rHuEPO]), rituximab, bortezomib, plasma exchange (PEX), immunoadsorption, donor lymphocyte infusion, mesenchymal stem cells, antithymocyte globulin, and high-dose steroids have been used for treatment of PRCA; however, results reported in the literature with these therapeutic options are largely variable or even disappointing in many cases [3,6–18].

Eltrombopag is an oral thrombopoietic receptor agonist that is approved by the US Food and Drug Administration for the treatment of patients with immune thrombocytopenic purpura [19,20] and severe aplastic anemia (SAA) refractory to immunosuppressive treatments or not eligible for HSCT [21–23]. We hypothesized that eltrombopag might have activity in patients with PRCA based on the favorable multilineage responses observed in patients with SAA, particularly with extended therapy [22]. Here we report our experience with the use of eltrombopag for the treatment

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