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Long-Term Outcome and Evaluation of Organ Function in Pediatric Patients Undergoing Haploidentical and Matched Related Hematopoietic Cell Transplantation for Sickle Cell Disease

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Abstract

HLA-matched related donor (MRD) hematopoietic stem cell transplantation (HSCT) is a well-established therapy for patients with sickle cell disease (SCD); however, experience using alternative donors, including haploidentical donors, in HSCT for SCD is limited. We report the long-term outcomes of 22 pediatric patients who underwent related donor HSCT for SCD at St. Jude Children's Research Hospital, either a myeloablative sibling MRD HSCT (n = 14) or reduced-intensity parental haploidentical donor HSCT (n = 8). The median patient age was 11.0 ± 3.9 years in the MRD graft recipients and 9.0 ± 5.0 years in the haploidentical donor graft recipients. The median follow-up was 9.0 ± 2.3 years, with an overall survival (OS) of 93% and a recurrence/graft failure rate of 0%, for the MRD cohort and 7.4 ± 2.4 years, with an OS of 75%, disease-free survival of 38%, and disease recurrence of 38%, for the haploidentical donor cohort. We report the long-term hematologic response and organ function in patients undergoing MRD or haploidentical donor HSCT for severe SCD. Our data demonstrate long-term hematologic improvements after HSCT with sustained engraftment, and confirm that HSCT offers long-term protection from common complications of SCD, including stroke, pulmonary hypertension, acute chest, and nephropathy, regardless of donor source.

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Keywords

Sickle cell disease; Reduced-intensity regimen; Haploidentical donor; Matched sibling donor; Long-term follow-up

INTRODUCTION

Currently allogeneic hematopoietic stem cell transplantation (HSCT) is the sole curative option for sickle cell disease (SCD). The majority of HSCTs performed for SCD involve transplantation of HLA-matched related donor (MRD) grafts after a myeloablative preparative regimen. Several previous studies have reported excellent outcomes in recipients of MRD HSCT for SCD, with >80% disease-free survival (DFS) and >90% overall survival (OS) [1–4]. Moreover, recipients who achieve durable engraftment of donor cells do not experience the continual vaso-occlusive damage related to SCD [3–9].

Although these results are encouraging, 85% of patients with SCD who meet the criteria for an HSCT do not have an appropriate MRD [10]. This lack of MRD availability has been a major barrier to HSCT for patients with severe SCD. Recently, alternative donor sources for HSCT, including cord blood and HLA-haploidentical donors, have been explored for patients with SCD [11,12].

Bolaños-Meade et al. [11] recently reported the outcomes of 14 patients with SCD who underwent haploidentical donor HSCT with a nonmyeloablative conditioning regimen. Eight of the 14 patients engrafted and were asymptomatic at a median follow-up of 2.1 years. Graft failure (43%) remained a major obstacle, but no serious toxicities were reported. These early reports suggest the potential for using a reduced-intensity haploidentical HSCT platform to treat SCD. Further studies on approaches to decreasing graft failure and continual long-term follow-up are needed to establish haploidentical donor HSCT as a safe, effective alternative treatment for SCD.

The effects of MRD HSCT on other organs have been reported through retrospective reviews of available data from large multicenter studies [4–8,13–17]. Although comprehensive neurocognitive studies performed after HSCT have reported stable findings, no prospective evaluations performed both before and after HSCT have been reported to date [7]. Moreover, long-term prospective imaging, neurocognitive, and pulmonary function studies are needed in patients with SCD undergoing reduced-intensity conditioning haploidentical HSCT. Finally, pulmonary hypertension is associated with a high risk of mortality [18,19] and should be followed in patients undergoing MRD HSCT or haploidentical donor HSCT. A comprehensive evaluation of central nervous system, pulmonary, cardiac, renal, endocrine, growth, and gonadal toxicities in patients undergoing haploidentical HSCT for SCD is currently just emerging. Here we report the long-term outcomes of pediatric patients who underwent reduced-intensity haploidentical donor HSCT or myeloablative MRD HSCT, with similar hematologic responses and organ function in patients with durable engraftment.

MATERIALS AND METHODS

Patients

All 22 patients were enrolled in a St Jude Children's Research Hospital Institutional Review Board–approved study (SCALLO or FAMSCT/SCDHAP). Consent was granted in accordance with the Declaration of Helsinki, and each patient or a parent or guardian signed an Institutional Review Board–approved informed consent form before receiving treatment on a Phase II clinical trial registered at ClinicalTrials.gov (NCT00186810 and NCT00152113). For MRD HSCT, patients age ≤21 years with symptomatic SCD genotype SS, SC, or Sβ0 with an MRD or related umbilical cord blood (UCB) donor with hemoglobin genotype AA or AS were considered for HSCT. HLA typing at the molecular level was performed, and all donors were fully matched as described previously [20]. All patients were required to meet the eligibility criteria as reported previously, and any patient with extensive end-organ damage was excluded [21]. An additional eligibility criterion for patients undergoing haploidentical donor HSCT was a previous cerebrovascular accident (CVA).

Donors and Grafts

MRD grafts consisted of fresh harvested bone marrow (BM) with a collection target of 4×10^8 total nucleated cells/kg. Cryopreserved MRD cords blood units could be used as well. For haploidentical grafts, preference was given to donors who were natural killer cell Ig-like receptor–mismatched with recipients. The haploidentical donor grafts consisted of a granulocyte colony-stimulating factor–mobilized apheresis product that was $CD34^+$-selected, cryopreserved, and administered on day 0. The donor also underwent a second cycle of granulocyte colony-stimulating factor–primed apheresis to provide a fresh $CD3^+$-depleted product to reach the $CD34^+$ cell target dose of 5×10^6 cells/kg. Thus, the product consisted of a $CD34^+$-selected product infused on day 0 and a $CD3^+$-depleted product infused on day +1 using the CliniMACS device, as described previously [22,23]. A fixed $CD3^+$ T cell dose of approximately 1.0×10^5 cells/kg was targeted for infusion.

HSCT Conditioning and GVHD Prophylaxis Regimens

For MRD HSCT, patients were conditioned with targeted busulfan, cyclophosphamide (200 mg/kg), and horse antithymocyte globulin (20 mg/kg). Busulfan was given i.v. or orally 4 times daily at a starting dose of 37.5 mg/m^2 for 4 consecutive days. Busulfan concentrations was measured after the first dose, and subsequent doses were adjusted to achieve a targeted systemic exposure with an area under the receiver-operating characteristic curve of 6000 ng/mL/hr, equivalent to approximately 1500 uM. Busulfan concentration was monitored daily throughout the course of therapy.

GVHD prophylaxis included cyclosporine beginning on day −2 and methotrexate at 15 mg/m^2 on days +1, +3, and +6 and 10 mg/m^2 on day +11. Patients receiving a UCB graft were given cyclosporine without methotrexate. In patients who developed GVHD, methylprednisolone was added at an initial dose of 1 mg/kg and increased in the event of persistent or progressive GVHD.

The first 3 haploidentical HSCT recipients received fludarabine (150–200 mg/m^2), thiotepa (10 mg/kg), targeted busulfan (900 ng/mL for 4 days), rabbit antithymocyte globulin (10 mg/kg for 3 days), and muromonab-CD3 (Orthoclone OKT3; 0.1 mg/kg maximum over days +1 to +20). The next 5 patients received hydroxyurea and azathioprine approximately 3 months before HSCT, followed by busulfan (900 ng/mL for 4 days), thiotepa (10 mg/kg), cyclophosphamide (200 mg/kg), and OKT3 (0.1 mg/kg maximum on days −10 to +17), as well as mycophenolate mofetil for GVHD prophylaxis.

Supportive Therapy

Patients who were not receiving long-term transfusion therapy underwent a partial exchange transfusion to achieve a hemoglobin S fraction ≤30% before HSCT. Strategies to prevent neurologic complications included anticonvulsant prophylaxis with phenytoin during busulfan administration and continuing for 6 months after HSCT, along with strict control of hypertension and magnesium levels. Hemoglobin concentration was maintained at 9–11 g/dL, and platelet count was maintained at ≥50,000/μL. Before HSCT, patients were started and maintained on oral penicillin V-K. Oral trimethoprim and sulfamethoxazole was provided for *Pneumocystis jiroveci* prophylaxis. Cytomegalovirus (CMV)-seropositive patients or patients with a CMV-seropositive donor received acyclovir prophylaxis on day +1 to day +120. Viral reactivation of CMV and Epstein-Barr virus were monitored weekly for detection of DNA copy number by PCR. CMV reactivation was treated with gancyclovir or foscarnet. Epstein-Barr virus reactivation and lymphoproliferative disorder were treated with monoclonal anti-CD20 antibody.

Engraftment and Donor Chimerism

Engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count (ANC) ≥500/μL. Hematopoietic cell chimerism was identified by studies of restriction fragment-length polymorphisms or variable number tandem repeats (VNTRs) in DNA. BM aspirates were obtained at the time of engraftment or around day +21. Peripheral blood samples for VNTR analysis were obtained starting at the appearance of signs of ANC recovery or by day +21, whichever occurred first. Thereafter, VNTR analysis was performed weekly up to day +120, then monthly up to 1 year, and then annually. After engraftment, patients with stable donor chimerism who subsequently developed aplasia, cytopenia, or an ANC <500/mm^3 were eligible to receive an additional CD34$^+$ stem cell “boost” of 5×10^6 CD34$^+$ cells/kg. In addition, patients with declining donor chimerism without aplasia or cytopenia were eligible to receive up to 3 donor lymphocyte infusions (DLIs) at 2.5×10^4 CD3$^+$ cells/kg/dose in accordance with protocol.

Assessment of Disease Response and Organ Function

Before HSCT, patients underwent a complete blood count (CBC) with WBC differential, platelet count, reticulocyte count, hemoglobin electrophoresis, and quantification of hemoglobin F, A1, and S, ferritin, and iron. CBC with WBC differential was performed a minimum of 3 times per week until the first hospital discharge after HSCT. Reticulocyte count, hemoglobin electrophoresis, and quantification of hemoglobin F, A1, and S were obtained yearly thereafter. Ferritin and iron levels were measured every 3 months and then

annually after the patient had been transfusion-independent for 1 year. Patients with evidence of iron overload and persistent elevated ferritin levels after successful HSCT were considered for phlebotomy and/or chelation therapy.

Transcranial Doppler (TCD) was performed before and at 6, 12, and 24 months after HSCT. Prospective magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), neuropsychological testing, and neurologic examinations were performed on all patients before and at day +180 after HSCT, and yearly thereafter. Patients were imaged using sagittal T1-, axial inversion recovery T2-, and FLAIR-weighted sequences on a 1.5-T imager. Comprehensive neuropsychological evaluations were obtained before and at 1, 3, and 5 years after HSCT. Neuropsychiatric evaluation included age-appropriate assessment of intelligence or developmental quotient for all patients. For patients of school age and older, comprehensive assessment of academic achievement, attention, memory, visual-motor, and visual-perceptual skills was performed.

All patients underwent organ function studies before HSCT. Pulmonary function tests (PFTs), including total lung capacity, forced vital capacity (FVC), and diffusion capacity of the lung for carbon monoxide (DLCO), were performed yearly. Cardiac function was evaluated by echocardiography and electrocardiography (ECG) annually. Renal function was assessed by 24-hour urine protein and creatinine clearance (CrCl) and/or technetium 99m-labeled diethylenetriamine penta-acetic acid ($Tc99^{m}$ DPTA) plasma clearance at approximately day +120 and annually thereafter. Liver biopsy analysis, including measurement of liver iron content, was performed if the ferritin level was >1000 mg/mL. Liver-spleen scans were performed at approximately 3, 12, and 24 months after HSCT. Endocrine function tests, including thyroid function tests and measurement of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, and testosterone, were performed annually after HSCT. Bone age films were obtained annually until maturation. All patients underwent annual imaging studies by MRI and/or plain film of the hips to assess the risk of osteonecrosis. Bone mineral density (BMD) and BMD *z*-score of the whole body and lumbar spine were monitored yearly with computed tomography bone density and dual-energy X-ray absorptiometry scans.

Statistical Analysis

Statistical analyses were performed to summarize results for the MRD cohort. Descriptive results are provided for patients who underwent haploidentical HSCT. The Kaplan-Meier method was used to estimate OS and DFS; events studied included death, graft rejection, and recurrence of SCD. The Student *t*-test was applied to each of variables to evaluate for any significant changes after HSCT. Descriptive statistics were computed for each function variable.

RESULTS

Patients

Twenty-two patients with SCD underwent related donor HSCT at St. Jude Children's Research Hospital, including 14 recipients of a sibling MRD graft and 8 recipients of a

parental haploidentical donor graft (Table 1). Eighteen patients had SCD-SS, 2 had SCD-SC, and 2 had SCD-SB. The MRD cohort had a median age of 11.0 ± 3.9 years (range, 5.4–17.4 years) and included 3 females and 11 males. The indications for HSCT included a history of stroke (9 patients), recurrent acute chest syndrome (8 patients), and recurrent painful episodes (6 patients), with most patients having multiple indications. The haploidentical cohort had a median age of 7 ± 5 years (range, 4 to 17 years) and included 3 females and 5 males. All the patients had a history of symptomatic SCD and documented CVA. The infused donor products had a mean total nucleated cell count of 450 ± 680 × 10^6 cells/kg (range, 10–1890 × 10^6/kg), a $CD34^+$ cell count of 25.4 ± 16.3 × 10^6/kg (range, 6–57 × 10^6/kg), and a $CD3^+$ cell count of 0.07 ± 0.07 × 10^6/kg (range, 0.006–0.168 × 10^6/kg) (Table 1).

Outcome

After a median of 9.0 ± 2.3 years (range, 5.9 to 12.3 years), 13 of the 14 patients in the MRD cohort were alive, at a median age of 21 ± 6.2 years (range, 12 to 33 years). One patient died at 15 months post-HSCT from complications related to chronic GVHD (cGVHD). Kaplan-Meier estimates of OS and DFS were both 93%, and there were no cases of graft failure/disease recurrence (Figure 1A).

After a median of 7.4 ± 2.7 years (range, 2.8 to 9 years), 6 of the 8 patients (75%) were alive, at a median age of 21 ± 6.2 years (range, 12 to 33 years). Three of the 8 patients (38%) experienced sustained engraftment and remained disease-free. Two patients (25%) died from complications related to chronic GVHD, at 0.9 and 2.3 years after HSCT. Graft failure and SCD recurrence occured in 3 patients (38%). Kaplan-Meier estimates of OS and DFS were 75% and 38%, respectively (Figure 1B).

Engraftment and Chimerism

All MRD HSCT recipients engrafted; the median time to engraftment with an ANC ≥500/μL was 16.0 ± 4.7 days (range, 15 to 32 days), and the median time to a platelet count ≥20,000/μL was 28.0 ± 17.5 days (range, 11 to 40 days). At 5 years post-HSCT, all surviving patients demonstrated sustained engraftment with ≥85% donor-derived blood cells on chimerism tests.

All 8 haploidentical HSCT recipients achieved donor engraftment with 100% donor chimerism, with a median time to engraftment of 12.5 ± 1.7 days (range, 10 to 14 days) and a median time to a platelet count ≥20,000/μL of 19.0 ± 15.4 days (range, 17 to 49 days). Thereafter, 4 patients (50%) developed evidence of graft rejection at a median of 30 days (range, 22 to 44 days) and required additional stem cell infusion. After this infusion, 1 of the 4 patients recovered with sustained 100% donor chimerism, whereas the other 3 patients progressed to graft failure with recurrence of disease. Donor engraftment was sustained in 5 patients (62%), and graft failure occurred in 3 patients (38%).

GVHD

Four MRD HSCT recipients (28%) developed grade II–IV acute GVHD (aGVHD), and 3 patients (21%) developed cGVHD. One patient with extensive or severe cGVHD of the lung

died of this complication; the other patients with GVHD recovered and discontinued immunosuppressive therapy.

Four of the 5 engrafted haploidentical HSCT recipients developed aGVHD. Two patients were limited to grade I aGVHD, and the other 2 had grade II aGVHD. Three of the 4 patients developed cGVHD: 1 with limited skin involvement and the other 2 with extensive severe cGVHD of the lung. The latter 2 patients died from complications of cGVHD (Table 1). One of these 2 patients had received the highest $CD3^+$ dose in the graft, and the other patient developed severe chronic lung GVHD after receiving a DLI.

Hematologic Disease Response

All patients with sustained engraftment became transfusion-independent with evidence of normal erythropoiesis, decreased hemolysis, and iron burden. Hematologic response values after MRD and haploidentical HSCT are presented in Table 1. After HSCT, recipients demonstrated a significant increase in median hemoglobin A_1 levels and decreases in median hemoglobin S and hemoglobin F levels (Figure 2A), along with significant increases in median total hemoglobin and hematocrit levels (Figure 2B). Furthermore, there was a decline in the indices of hemolysis after HSCT. Compared with initial studies, there were significant decreases in median bilirubin, reticulocyte, and lactate dehydrogenase levels (Figure 2C), along with a significant decrease in iron load and a nonsignificant decrease in mean ferritin level (Figure 2D).

Central Nervous System

Prospective MRI/MRA, TCD, neuropsychological testing, and neurologic examinations were performed before and then annually after HSCT to evaluate the effect of HSCT on neurologic status in children with SCD (Table 2). Neuroimaging before HSCT revealed evidence of cerebral infarction and vasculopathy in the patients with documented CVA. Four patients experienced seizure activity during the first year after HSCT, including 1 patient with a history of seizure. One patient sustained a subarachnoid hemorrhage on day +16 after HSCT that resolved without complications. MRI/MRA results confirmed a previous finding that parenchymal changes can continue despite normal erythropoiesis during the first 3 years after HSCT. By 5 years after HSCT, no patient with sustained engraftment exhibited any clinical evidence of CVA or progression on imaging studies. MRI showed improvement in white matter changes, and MRA revealed stable or even improved vessel abnormalities (Table 3). TCD studies performed before and after MRD HSCT showed a significant decrease in maximal velocity, from 170 ± 16 cm/s to 81 ± 18 cm/s (P = .001) (Table 1). All TCD studies were normal at the last evaluation. Comprehensive neuropsychiatric evaluations were performed in 11 of the 13 patients before and at 1, 3, and 5 years after HSCT. (Testing was limited in 2 patients in whom English was not their first language.) The results confirm stable cognitive function after HSCT, with no significant decreases in full, performance, or verbal IQ scores (Table 1 and Figure 3A).

Renal and Cardiac Function

The mean CrCl value was 158 ± 55.7 mL/min/1.73 m^2 (range, 120 to 320 mL/min/1.73 m^2) in the MRD cohort and 98 ± 33 mL/min/1.73 m^2 in the haploidentical HSCT. At the most

recent evaluation, the mean CrCl in the MRD cohort was 103.5 ± 24 mL/min/1.73 m^2 (range, 57 to 131 mL/min/1.73 m^2), for a significant difference of 60 ± 55 mL/min/1.73 m^2 (P = .004) (Table 1). In 2 MRD HSCT recipients, renal function values decreased to below-normal levels (Figure 3B). At the last evaluation, all patients had normal urinanalysis results, with no proteinuria or hematuria. Before undergoing HSCT, all patients had normal cardiac function, with a median shortening fraction of 41% ± 5% (range, 34% to 51%), and at the most recent evaluations the median shortening fraction was 37.5% ± 4% (range, 28% to 44%), demonstrating a significant difference between the 2 time points (P = .001). No haploidentical HSCT recipient exhibited a change in shortening fraction (Figure 3C). Three patients had mild tricuspid insufficiency, and 1 patient had trace pulmonary insufficiency, but no patient had evidence of pulmonary hypertension.

Pulmonary Function

Among the 16 patients treated successfully for SCD, 12 were age >6 years at the time of HSCT and had baseline PFT data available. The other 4 patients underwent PFTs when able to perform the studies. Three patients underwent PFTs at 1 year after HSCT and 1 patient did so at 3 years after HSCT. There was no significance difference in the mean predicted FVC, FEV_1, and FEV_1/FVC ratio between baseline studies and the most recent evaluation (Table 2); however, in the MRD cohort, the mean DLCO declined from 99% ± 6% to 77% ± 7% (P = .02) after HSCT (Table 2 and Figure 4). Before HSCT, 6 patients had normal PFT values, 5 had a restrictive pattern, and 1 had a combined restrictive/obstructive pattern. Three of the 4 patients who underwent PFTs performed after HSCT exhibited a restrictive pattern, whereas the other patient had normal values. The 7 patients with normal initial PFT values maintained normal lung function after HSCT. Among the 9 patients who had restrictive disease at the initial examination, 1 patient had improved function, 4 patients had persistent restrictive changes, and 4 patients developed a combined restrictive/obstructive pattern, as documented by decreased FEV_1, FVC, and FEV_1/FVC ratio values.

Liver and Spleen Function

Liver and spleen scans were performed in 12 patients. The 3 patients with documented splenectomy did not undergo these studies. Three patients who had minimal splenic uptake before HSCT demonstrated improved splenic uptake/regeneration after HSCT. One patient with no splenic uptake before HSCT exhibited increased splenic function, with evidence of splenic regeneration at day +160 and 1 year after HSCT. The other patients with no splenic uptake did not recover any function. Nine patients who had a normal liver scan before HSCT also had a normal scan at the last evaluation. The 3 patients with documented mild to moderate hepatomegaly before HSCT also had a normal liver scan after HSCT (Table 4).

Hypothalamic-Pituitary (Adrenal, Thyroid, and Gonadal) Function

Endocrine function was monitored in all survivors after HSCT. All patients were age ≥12 years at the last evaluation. The median age was 20.3 ± 7.1 years (range, 12 to 33 years) for the 9 males (69%) and 18.3 ± 3.3 years (range, 15 to 22 years) for the 4 females (31%). Five of the 9 males exhibited normal gonadal function, with normal LH, FSH, and testosterone levels. Three males had evidence of hypogonadism, with elevated gonadotropin, LH, and

FSH levels but normal testosterone levels. One patient developed primary hypogonadism and was started on testosterone therapy. Two of the 4 females developed ovarian failure with elevated gonadotropin and low estradiol levels requiring replacement therapy. The other 2 females had normal laboratory results and menstrual cycles, and 1 of the women was 5 months pregnant at her last evaluation.

Growth and Bone

Growth was monitored based on skeletal bone age, growth velocity, and somatomedin C or insulin-like growth factor 1 levels. All 13 of the surviving patients underwent annual skeletal bone age studies until skeletal maturation was complete. Seven of the 13 patients (54%) had no evidence of abnormal skeletal development detected on initial or follow-up studies. Five of the 13 patients with delayed bone age on the initial study exhibited normal bone age by 2 years after HSCT. One patient with cGVHD who had normal bone age before HSCT exhibited delayed bone age and low/normal insulin-like growth factor 1 levels and developed severe osteoporosis after HSCT. No survivor demonstrated hypothyroidism or adrenal insufficiency at the last evaluation. All patients had normal thyroid-stimulating hormone, thyroxine, and free thyroxine before and after HSCT. At the last evaluation, cortisol levels were normal in all patients screened for adrenal insufficiency (n = 10). Adrenocorticotropic hormone and metyrpone stimulation studies were normal in patients considered at increased risk for insufficiency (n = 7).

All patients underwent imaging studies (MRI or radiography) to evaluate the risk of osteonecrosis. Before HSCT, 3 patients had evidence of avascular necrosis (AVN) at common sites, including the femoral head, knee, and/or sacrum; these patients had stable findings by 3 years after HSCT, (Table 5). Two patients developed AVN (1 knee and 1 hip) at 2 years after HSCT. By 5 years after HSCT, all patients with AVN had stable lesions, and no additional lesions were detected.

Osteoporosis was monitored yearly with computed tomography bone density and dual-energy X-ray absorptiometry scans (Figure 5). The median whole-body BMD values were 151 ± 41 (range, 72 to 210) and 151 ± 22 (range, 128 to 200), and median lumbar spine BMD values were 0.70 ± 0.16 (range, 0.35–0.86) and 0.79 ± 0.96 (range, 0.61 to 1.0). Median BMD *z*-scores were −1.5 ± 1.0 (range, −2.21 to 1.1) and −1.3 ± 1.5 (range, −4.6 to 1.6) for whole body and −2.2 ± 2.0 (range, −5.9 to 2.0) and −2.0 ± 1.6 (range, −3.5 to 2.3) for lumbar spine.

DISCUSSION

This study is the first comprehensive evaluation of quality of survival after successful related-donor (haploidentical or MSD) HSCT for SCD. Hansbury et al. [24] previously described our institutional experience of finding an unaffected MRD (7%) for patients with severe SCD, and the use of haploidentical donors expands the pool of patients eligible for HSCT. Here we report the long-term follow-up results of routine assessments of organ function, particularly of the brain, lung, heart, liver, spleen, kidney, bone, and endocrine system.

Recipients of haploidentical HSCT had a much higher and significant risk for graft rejection compared with MRD HSCT recipients. However, their risk of rejection was similar to that of patients who underwent reduced-intensity conditioning haploidentical HSCT reported by Bolaños-Meade et al. [11]. Unfortunately, we found a greater risk for GVHD, particularly extensive cGVHD, which led to increased mortality in our study. Our haploidentical grafts were based on $CD3^+$ depletion and $CD34^+$ selection. Patients who received high doses of $CD3^+$ T cells or DLI were at significant risk for increased mortality. Although the small number of patients in both studies limit conclusive results, the findings suggest that a preparative regimen with post-transplantation cyclophosphamide may be more effective than T cell depletion in preventing GVHD.

In this study, patients who successfully engrafted after haploidentical HSCT had beneficial outcomes similar to those seen in our MRD HSCT recipients. Our findings confirm that children with CVA are protected from further CVA after successful haploidentical HSCT. A previous report suggested that early progressive imaging changes noted after HSCT may be due to the natural history of neurovascular injury, including reactive gliosis related to the initial event [17]. It was hypothesized that these early changes were not new findings, but rather reflected the evolution of cerebrovascular disease that existed before HSCT. Our study supports these findings, with long-term follow-up demonstrating improvement and stabilization of cerebral lacunae or leukoencephaly by 5 years after HSCT in both the MRD and haploidentical donor cohorts. Furthermore, we confirmed that persistent brain MRI changes were not associated with progressive neurocognitive deficits. The routine neuropsychologic testing showed stable neurocognitive function with no appreciable change in IQ after HSCT. In the series reported here, individuals with silent cerebral infarction were protected from progressive changes on brain MRI, and some patients experienced resolution of abnormalities documented before HSCT. Improvements in vessel abnormalities documented on MRI/MRA were noted after HSCT, with 2 patients demonstrating diminished vessel disease; all patients with abnormal TCD velocities before HSCT had normal velocities after HSCT.

Previous studies have reported no significant decline in pulmonary function after HSCT [7,13]. Here we found a significant decline in DLCO in our MRD cohort. We assume that this decline is associated with busulfan toxicity rather than with progression of vascular damage from SCD, civen the lack of evidence of other vascular occlusive damage in the lungs. Some patients developed decreased FEV_1 level and FEV_1/FVC ratio, consistent with obstructive disease. Although obstructive changes observed after HSCT may be associated with the use of busulfan in the conditioning regimen [5], a growing body of evidence suggests that the progressive pulmonary toxicity of SCD may be restrictive or obstructive pulmonary disease [25,26]. The available data strongly suggest that the decline in pulmonary function due to SCD vasculopathy is halted by the establishment of normal erythropoiesis, regardless of donor source.

Our HSCT recipients demonstrated significant declines in renal function after transplantation, as demonstrated by decreased CrCl values. Although our cohort’s median CrCl value after HSCT was in the normal range, 2 patients had values clearly below the normal range. Furthermore, there was significant difference in the median CrCl values

before HSCT and that measured at the last evaluation; however, no patient had evidence of proteinuria or hematuria on urinanalysis.

Although some patients had evidence of mild tricuspid regurgitation, their jet velocities were normal, with no clinical impact on cardiac function. We found no evidence of pulmonary hypertension in any of our patients. Of the 16 patients treated successfully (median age, 20 years), 85% were past late adolescence (>17 years), and 70% were age >20 years. This suggests that the abrogation of hemolysis by successful HSCT decreases the risk of developing pulmonary hypertension in patients with SCD.

Patients with SCD are at increased risk for AVN and osteoporosis [27]. Most of our patients had significant osteoporosis with very low BMD values before HSCT. Patients with documented AVN before HSCT demonstrated some improvement after HSCT, but although BMD and BMD *z*-score values increased after HSCT, these patients remained at high risk for osteoporosis. Furthermore, females with hypogonadism had significant osteoporosis unless treated with hormone therapy. Hip MRI performed before HSCT documented abnormal marrow intensity associated with SCD. These findings were all normalized after HSCT. In summary, we observed improvement of AVN with modest increase in BMD after both MRD and haploidentical donor HSCT.

Our patients with delayed bone growth all demonstrated normalized growth after HSCT, if not complicated by cGVHD. Endocrine function studies showed no increased risk for thyroid or adrenal insufficiency; however, a significant proportion of patients (30%) developed gonadal insufficiency after HSCT and required treatment with hormone replacement therapy. Taken together, these observations tend to confirm the gonadal toxicity associated with exposure to myeloablative doses of busulfan [6].

In summary, HSCT offers long-term protection from clinical and subclinical vaso-occlusion associated with SCD, regardless of donor source. Complications that commonly develop in patients with SCD, including stroke, pulmonary hypertension, acute chest, proteinuria, and hematuria, were not observed in our patients after successful HSCT; however, the patients who underwent myeloablative MRD HSCT demonstrated progressive declines in renal, pulmonary, and cardiac function over time that have not been reported previously. Our data suggest that the declining organ function is likely due to the conditioning regimens rather than to complications of SCD. Whether patients with SCD are at greater risk for declining organ function, and whether reduced-intensity conditioning regimens may offer better outcomes after HSCT, require additional investigation. Although our study was limited by number of patients, 100% of the patients underwent extensive pre- and post-HSCT evaluation. This might have facilitated the better detection of declining organ function compared with large retrospective multi-institutional studies. We hope that this report encourages further long-term evaluations in patients undergoing reduced-intensity haploidentical HSCT for SCD to examine whether organ function is better preserved with this modality compared with conventional MRD HSCT.

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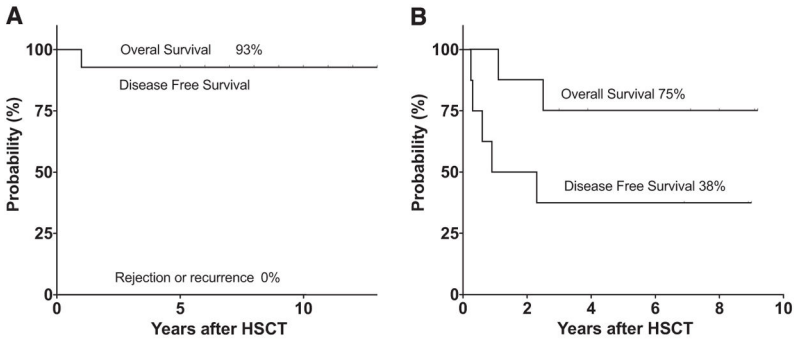

Figure 1.

Kaplan-Meier estimates of OS and DFS after MRD HSCT and haploidentical HSCT. OS and DFS were determined with events defined as death, graft rejection, or recurrence of SCD after MRD HSCT (A) or haploidentical HSCT (B). Tick marks represent surviving patients and indicate the duration of follow-up after transplantation. The percentages above each curve indicate the estimates of OS, DFS, and cumulative incidence of graft rejection or recurrence of disease for the entire cohort.

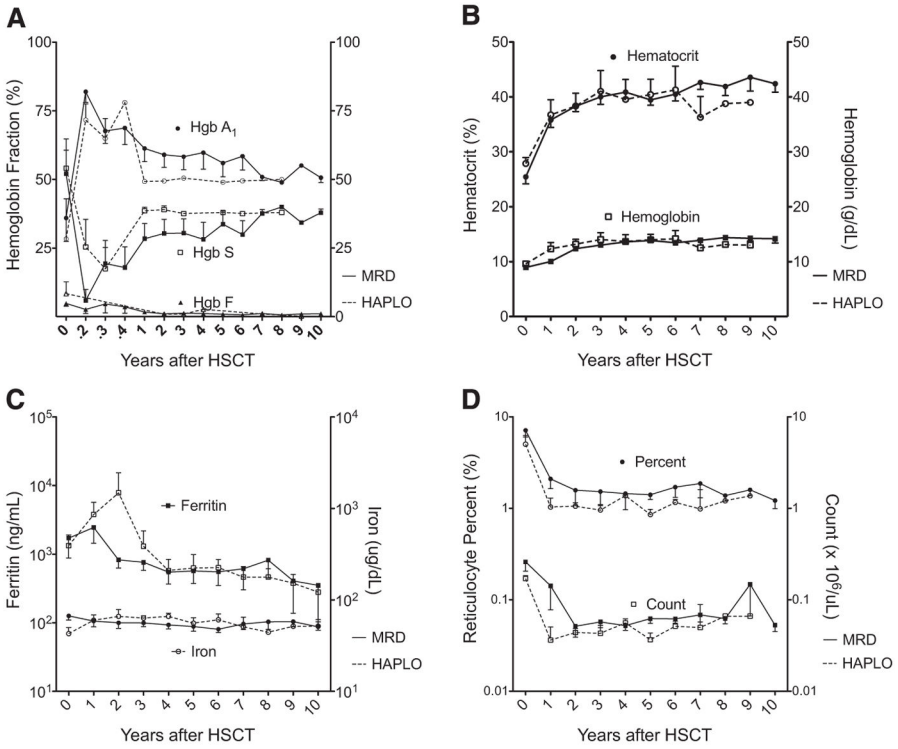

Figure 2.

Disease response after MRD HSCT (solid lines) and haploidentical HSCT (dashed lines) for SCD. Mean ± SEM values are plotted over time after MRD HSCT and haploidentical HSCT for hemoglobin and hematocrit (A), hemoglobin fractions (B), reticulocyte index and percent (C), and iron and ferritin levels (D).

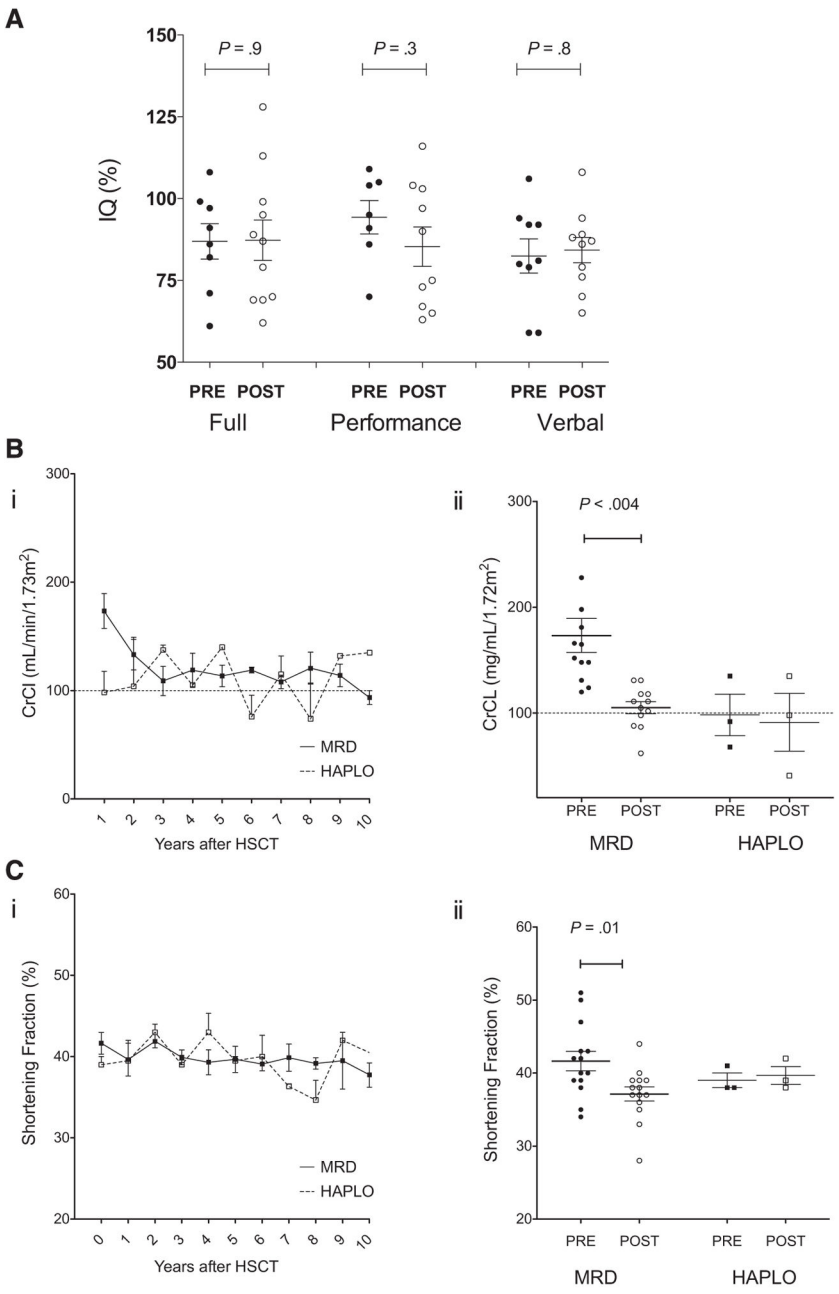

Figure 3.

IQ, renal function, and cardiac function before and after HSCT. IQ (A), renal function (B), and cardiac function (C) were monitored before (solid symbols) and yearly after (open symbols) MRD (●, ○) and haploidentical (HAPLO) (■, □) HSCT. Mean ± SEM values are plotted over time after HSCT for CrCl (Bi) and shortening fraction (Ci), and median and SEM values for CrCl (Bii) and shortening fraction (Cii) before HSCT are compared with the values measured at the most recent evaluation.

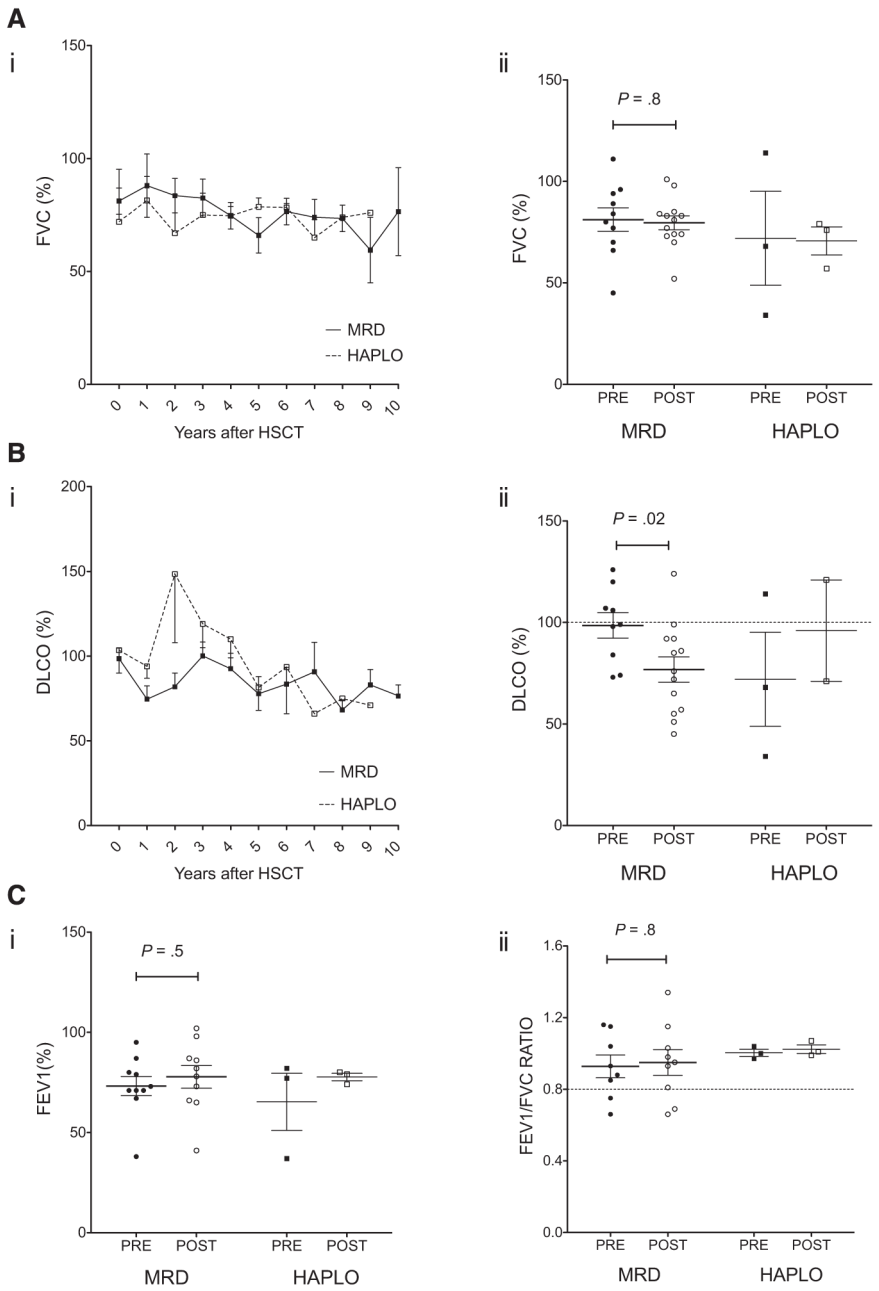

Figure 4.

Pulmonary function before and after HSCT. PFTs, including FVC (A), DLCO (B), FEV_1 (C), and FEV_1/FVC ratio (D), were monitored before (solid symbols) and yearly after (open symbols) HSCT. Mean ± SEM values are plotted over time after MRD (●, ○) and haploidentical (HAPLO) (■, □) HSCT for FVC (Ai) and DLCO (Bi). The median ± SEM values before HSCT or first available values (closed symbols) are compared with the most recent value (open symbol) for FVC (Aii), DLCO (Bii), FEV_1 (Ci), and FEV_1/FVC ratio (Cii).

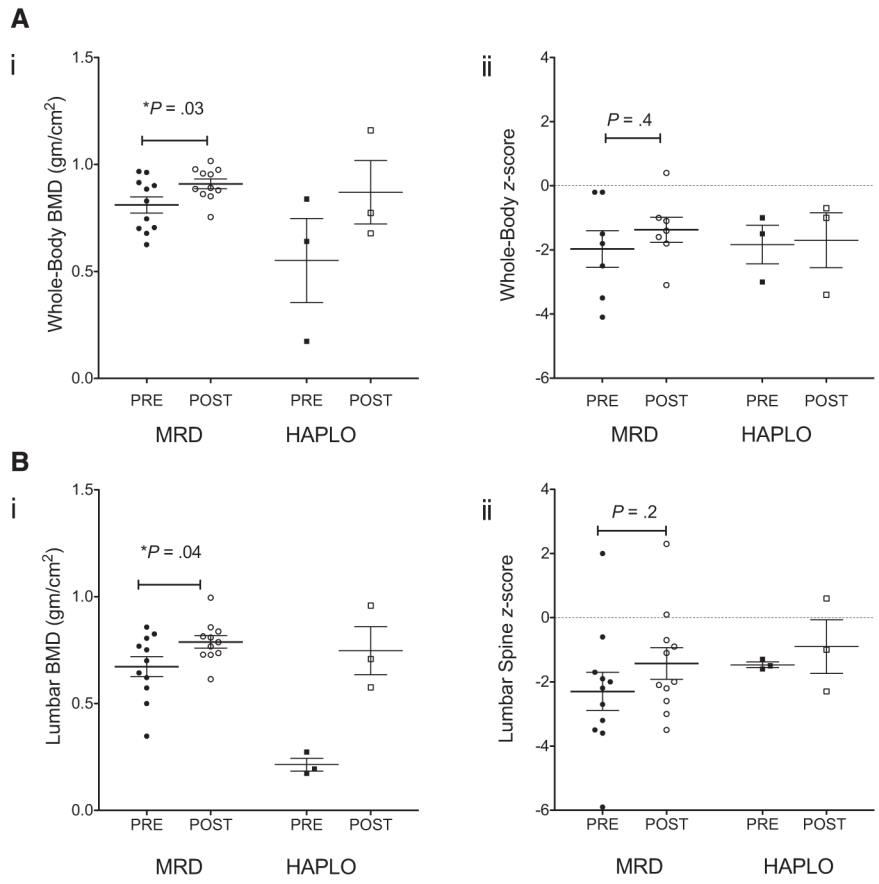

Figure 5.

Bone density before and after HSCT. Whole-body (A) and vertebral body (B) BMD (i) and BMD *z*-scores (ii) were monitored before (solid symbols) and after (open symbols) HSCT. Median ± SEM values for the MRD (●, ○) and haploidentical (HAPLO) (■, □) recipients are compared with those measured at the most recent evaluation.

Table 1

Patient and Graft Characteristics, Engraftment, GVHD, and Follow-Up

Patient	Age, yr	Sex	Diagnosis	Donor	Indication	HLA Match	TNC, × 10^8/kg	CD3, × 10^6/kg	ANC, Days	Graft	aGVHD	cGVHD	Status	Follow-Up, yr
1	14.6	M	SCD-SS	MRD BM	CVA/AC	6/6	4.64		12	Stable	Grade III	Severe lung	Expired	(1.2)
2	14.5	M	SCD-SB	MRD BM	CVA/AC	6/6	3.20		16	Stable	Grade II	Moderate GI	Alive	7.3
3	9.2	F	SCD-SS	MRD BM	CVA/AC	6/6	3.23		17	Stable	None	None	Alive	12.3
4	6	M	SCD-SS	MRD BM	AC	6/6	5.75		19	Stable	Grade I	None	Alive	6.1
5	10.5	M	SCD-SS	MRD BM	TCD	6/6	2.14		15	Stable	None	None	Alive	5.2
6	14.3	M	SCD-SS	MRD BM	AC	6/6	2.85		24	Stable	None	None	Alive	10.9
7	14.6	F	SCD-SS	MRD BM	AC/TCD	6/6	3.29		15	Stable	None	None	Alive	9.3
8	5.8	M	SCD-SC	MRD BM	TCD	6/6	3.31		14	Stable	None	None	Alive	5.9
9	5.4	M	SCD-SS	MRD BM	CVA	6/6	3.94		28	Stable	None	None	Alive	11.0
10	8.8	M	SCD-SS	MRD BM	CVA	6/6	3.00		16	Stable	None	None	Alive	12.2
11	13.7	M	SCD-SS	MRD BM	CVA	6/6	3.21		23	Stable	None	None	Alive	7.9
12	17.4	M	SCD-SS	MRD BM	CVA/AC	6/6	3.29		14	Stable	Grade II	Moderate GI	Alive	8.8
13	8.5	F	SCD-SB	MRD cord blood	CVA/AC	6/6	0.45		23	Stable	Grade I	None	Alive	6.0
14	11.5	F	SCD-SS	MRD BM	TCD/AC	6/6	4.71		15	Stable	Grade III	None	Alive	10.0
15	8.5	F	SCD-SS	Haplo; father	CVA	3/6	0.32	0.009	12	Stable; DLI on day +107	None	None	Alive	8.9
16	6.9	M	SCD-SS	Haplo; father	CVA	3/6	0.18	0.010	12	Rejection; CD34 boost	None	—	Alive with SCD	7.8
17	13.4	M	SCD-SB	Haplo; father	CVA	3/6	0.18	0.013	13	Stable after rejection; CD34 boost	Grade I	None	Alive	9.0
18	17.1	F	SCD-SS	Haplo; father	CVA	3/6	4.52	0.168	11	Stable	Grade I	Extensive; severe lung	Expired	(0.9)
19	4.2	M	SCD-SS	Haplo; mother	CVA	3/6	10.16	0.149	13	Stable	Grade II	Limited; mild skin	Alive	6.9
20	16.9	M	SCD-SB	Haplo; mother	CVA	3/6	1.541	0.100	14	Rejection; DLI on day +51; CD34 boost	None	—	Alive with SCD	3.7
21	5.8	M	SCD-SS	Haplo; father	CVA	4/6	18.90	0.100	16	Rejection; auto-HSCT	None	—	Alive with SCD	2.8
22	9.5	F	SCD-SS	Haplo; mother	CVA	4/6	0.14	0.006	11	Stable; DLI on day +70	Grade II	Extensive; severe lung	Expired	(2.3)

AC indicates acute chest; Haplo, haploidentical; TNC, total nucleated cells; $CD34^+$ boost, 5×10^6–10^8 cells/kg; DLI dose, 0.025×10^6 $CD3^+$ cells/kg.

Table 2

Characteristics of Patients before and after HSCT

		Pre-HCST		Post-HSCT		Difference	
		Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	*P* Value
Age, yr	MRD	11.1 ± 4.7	5.4–17.4	21.5 ± 8.1	12–32		
	Haploidentical	10.3 ± 5	4.2–17.1				
Hemoglobin, g/dL	MRD	7.8 ± 1.0	6–10	14.2 ± 1.5	11.5–17	6.3 ± 1.0	<.0001
	Haploidentical	9.6 ± 0.6	9–10	13.6 ± 2.9	11–16		
Hematocrit, %	MRD	26 ± 5	19–32	42 ± 5	33–48	16 ± 6	<.0001
	Haploidentical	28 ± 1.9	26–30	40 ± 8.3	32–49		
Hemoglobin A, %	MRD	33 ± 28	0–64	59 ± 15	47–90	26 ± 33	.0055
	Haploidentical	38 ± 38	0–77	50.2 ± 1	50–51		
Hemoglobin S, %	MRD	53 ± 27	21–97	29 ± 16	0–40	24 ± 32	.0087
	Haploidentical	45.4 ± 30.8	13–75	37 ± 1	37–38		
Hemoglobin F, %	MRD	6.6 ± 5.6	1.6–22	0.4 ± 0.6	0–1.4	6.2 ± 5.5	.0004
	Haploidentical	9.7 ± 5.8	2.1–16	1.2 ± 1.4	0–2.7		
Reticulocytes, × 10^3/mL	MRD	293 ± 211	104–706	90 ± 114	29–471	168 ± 245	.0049
	Haploidentical	170 ± 240	156–198	45 ± 30	11–66		
Bilirubin, mg/dL	MRD	4.5 ± 4.6	1.1–19.3	0.4 ± 0.3	0.2–1.2	4.1 ± 4.6	.0025
	Haploidentical	3.2 ± 1.3	1.7–4.1	0.3 ± 0.3	0.1–0.6		
Lactate dehydrogenase, IU/L	MRD	1249 ± 538	455–2138	181 ± 46	129–290	1068 ± 565	<.0001
	Haploidentical	1630 ± 708	1065–2424	220 ± 48	188–276		
Ferritin, ng/mL	MRD	1722 ± 3068	46–12,239	462 ± 602	56–1720	1259 ± 3121	.15
	Haploidentical	1334 ± 1001	644–2480	331 ± 152	230–507		
Iron, ng/mL	MRD	132 ± 63	44–214	91 ± 41	34–171	35 ± 65	.03
	Haploidentical	70 ± 27	42–96	90 ± 38	51–128		
CrCl, mL/min/1.73 m^2	MRD	173 ± 56	120–320	101 ± 24	57–131	60 ± 54	.004
	Haploidentical	98 ± 33	68–135	91 ± 47	41–135		
TCD, cm/s	MRD	170 ± 16	125–222	89 ± 9	65–118	81 ± 18	.001
	Haploidentical	127 ± 17	115–139	88	—		
Shortening fraction, %	MRD	42 ± 5	34–51	37 ± 4	28–44	37 ± 4	.01

		Pre-HCST		Post-HSCT		Difference	
		Mean ± SD	**Range**	**Mean ± SD**	**Range**	**Mean ± SD**	***P* Value**
	Haploidentical	39 ± 2	38–41	40 ± 2	38–42		
FVC, %	MRD	80 ± 18	45–111	80 ± 12	52–101	3 ± 12	.80
	Haploidentical	72 ± 40	34–114	71 ± 12	57–80		
DLCO	MRD	99 ± 6	73–126	77 ± 6	45–124	22 ± 9	.02
	Haploidentical	72 ± 23	34–114	96 ± 25	71–121		
FEV_1	MRD	73 ± 5	36–95	78 ± 6	41–102	5 ± 7	.50
	Haploidentical	65 ± 14	37–82	78 ± 2	74–80		
FEV_1/FVC	MRD	0.93 ± 0.18	0.66–1.16	0.95 ± 0.21	0.66–1.34	0.02 ± 0.09	.80
	Haploidentical	0.97 ± 1.04	0.66–1.34	1.02 ± 0.4	0.99–1.07		
Full IQ	MRD	87 ± 5	61–108	87 ± 6	62–128	0.4 ± 8	.90
Performance IQ	MRD	94 ± 5	70–109	85 ± 6	63–116	9 ± 8	.30
Verbal IQ	MRD	85 ± 6	59–106	84 ± 4	65–108	2 ± 6	.70

Table 3

CNS Evaluation before and after HSCT

Clinical		MRI/MRA	
Pre-HSCT	**Post-HSCT**	**Pre-HSCT**	**Post-HSCT**
MRD			
CVA	Normal	Encephalomalacia; significant stenosis	Stable; normal MRA
CVA	Normal	Multiple lacunar infarcts, circle of Willis occlusion	Stable
CVA	Normal	Lacunar infarcts; moyamoya disease; severe arterio-occlusive disease	Stable
CVA	Normal	Small lacune; intracranial tortuosity	Stable
CVA	Normal	Perivascular demyelination; mild tortuosity	Stable
CVA	Seizure	Lacunar infarcts; significant stenosis	Stable
CVA	Seizure	Multiple lacunar infarctions; abnormal MRA	Stable
Normal	Seizure	Leukoenchephalopathy; normal MRA	Stable
Normal	Subarachnoid hemorrhage	Normal brain; intracranial vessel tortuosity	Stable
Normal	Normal	Normal brain; intracranial vessel tortuosity	Stable
Normal	Normal	Mild leukoencephalopathy; normal MRA	Normal brain; normal MRA
Normal	Normal	Punctate lacune; mild stenosis	Improved leukomalacia; normal MRA
Haploidentical			
CVA	Normal	Encephalomalacia; significant stenosis	Stable
CVA	Normal	Multiple lacunar infarctions; abnormal MRA	Stable
CVA	Normal	Encephalomalacia; significant stenosis	Stable

Table 4

Results of Liver Spleen Scans before and after HSCT

	Age Pre-HSCT, y	Spleen		Liver	
		Pre-HSCT	Post-HSCT	Pre-HSCT	Post-HSCT
MRD	14.6	Normal	Normal	Normal	Normal
MRD	5.8	Normal	Normal	Normal	Normal
MRD	9.2	Minimal uptake	Recovered	Normal	Normal
MRD	5.4	Minimal uptake	Mild regeneration	Normal	Normal
MRD	6.0	None	Mild regeneration	Normal	Normal
MRD	14.3	None	None	Normal	Normal
MRD	8.8	None	None	Hepatomegaly	Normal
MRD	10.5	None	None	Hepatomegaly	Normal
MRD	14.5	None	None	Hepatomegaly	Normal
Haplo	8.5	None	None	Normal	Normal
Haplo	13.4	None	None	Normal	Normal
Haplo	4.2	Minimal uptake	Mild regeneration	Normal	Normal

Haplo indicates haploidentical.

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Table 5

Osteonecrosis and BMD before and after HSCT

MRI AVN		BMD		Clinical
Pre-HSCT	**Post-HSCT**	**Pre-HSCT**	**Post-HSCT**	
Normal	Normal	Normal	Normal	
Normal	Normal	Mild	Normal	
Normal	Normal	Mild	Normal	
Normal	Normal	Mild	Mild	
Normal	Normal	Mild	Mild	
Normal	Normal	Mild	Moderate	
Normal	Normal	Moderate	Normal	
Normal	Normal	Moderate	Mild	Fracture
Normal	Normal	Severe BMD	Moderate	Osteoporosis
Knee	Stable	Moderate	Moderate	
Femoral head	Normal	Moderate	Moderate improved	Osteoporosis
Femoral head	Normal	Moderate	Moderate improved	
Sacrum and knee	Knee	Severe	Severe	Osteoporosis and fracture