Chapter 12
Matched Sibling Donor Hematopoietic Stem Cell Transplantation for Sickle Cell Disease

Gregory M.T. Guilcher and John T. Horan

Abbreviations

AML	Acute myelogenous leukemia
ATG	Antithymocyte globulin
AUC	Area under the curve
EFS	Event-free survival
GVHD	Graft-versus-host disease
HLA	Human leukocyte antigen
HSCT	Hematopoietic stem cell transplant
HU	Hydroxyurea
MDC	Mixed donor chimerism
MRD	Matched-related donor
MRI	Magnetic resonance imaging
PK	Pharmacokinetics
rATG	Rabbit antithymocyte globulin
SCD	Sickle cell disease
SOS	Sinusoidal obstruction syndrome
STAR	Sickle Transplant Alliance for Research
TBI	Total body irradiation
UCB	Umbilical cord blood

G.M.T. Guilcher (✉)
Departments of Oncology and Paediatrics, Alberta Children's Hospital, University of Calgary, Calgary, AB, Canada
e-mail: greg.guilcher@ahs.ca

J.T. Horan
Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Emory University School of Medicine, Atlanta, GA, USA

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Early Experience with Matched Sibling Donor Hematopoietic Stem Cell Transplantation for Sickle Cell Disease

The first hematopoietic stem cell transplant (HSCT) for sickle cell disease (SCD) was reported in 1984 [1, 2]. An 8-year-old girl with acute myelogenous leukemia (AML) and known HbSS disease received a bone marrow allograft from her 4-year-old brother, who had sickle cell trait (HbAS). The indication for HSCT in this case was AML; she was transplanted in first complete remission as part of a St. Jude Children's Research Hospital clinical trial with myeloablative conditioning prescribed according to the AML study. This patient engrafted on day +12 and did not suffer any further SCD crises. She was successfully treated for acute and chronic graft-versus-host disease (GVHD) as well as *Streptococcal* pneumoniae sepsis. This case served as proof of principle that SCD could be cured with HSCT and that a donor with HbAS is acceptable, provided some clues about the unique supportive care needs of HSCT recipients with sickling syndromes [2].

The first cohort of children and young adults to undergo HSCT specifically for SCD was described by Vermylen et al. in Brussels, Belgium [3]. The 12 patients were returning to Africa, where mortality rates can exceed 50% for children under 5 years of age depending on access to care [4]. It should be noted that some of these children had mild phenotypes; the risks and uncertain efficacy of HSCT in SCD were justified by the authors due to the significant risks of morbidity and mortality of SCD in lower income countries [3]. Myeloablative conditioning consisting of oral busulfan, intravenous cyclophosphamide, and 750 cGy of thoracoabdominal radiation (for recipients over 12 years of age) was given; donors were mostly human leukocyte antigen (HLA)-matched siblings. Four donors had normal hemoglobin electrophoresis analyses, while the remaining eight had sickle cell trait. Eleven of these patients were cured of their SCD, while the remaining patient sustained secondary graft failure (i.e., initial donor hematopoietic engraftment with subsequent graft loss). This child underwent a second HSCT and was also cured. No sickling crises were noted post-HSCT, and hemoglobin electrophoresis levels reflected those of the donors. Only four patients developed grades I–II acute GVHD. The long-term follow-up of this cohort revealed no adverse outcomes secondary to HSCT.

A larger combined experience describing outcomes of 42 young patients in France and Belgium demonstrated sustained donor hematopoietic stem cell engraftment in 36; all those with sustained engraftment were free of ongoing crises due to SCD and achieved donor hemoglobin electrophoresis patterns [5]. All donors but one were matched siblings. One patient died; five had graft rejection, and of these, three had autologous marrow recovery and the other two had successful second HSCTs. The summarized Belgian experience of 50 patients demonstrated overall, event, and disease-free survival rates of 93%, 82%, and 85%, respectively, with the subgroup with milder phenotypes who were returning to Africa faring somewhat better [6].

These encouraging observations led to the era of multicenter clinical trials for matched sibling donor HSCT for SCD from the late 1980s to the present.

Clinical Trials Evaluating Myeloablative Conditioning Regimens for Matched Sibling Donor HSCT for Sickle Cell Disease

Multicenter investigation of hematopoietic stem cell transplantation for sickle cell disease. A landmark collaboration between HSCT centers in Europe, the United States, and Canada provided essential data published in several manuscripts which serves as the foundation of the practice of HSCT for SCD [7–10]. This was a prospective, nonrandomized clinical trial which included a myeloablative conditioning regimen with busulfan (14 mg/kg total over 4 days), cyclophosphamide (200 mg total over 4 days), and serotherapy with either horse antithymocyte globulin (majority) or alemtuzumab. GVHD prophylaxis consisted of methotrexate and cyclosporine. Donors were HLA-identical siblings with HbAA or HbAS.

Eligibility criteria. Patients less than 16 years of age with HbSS, SC, and Sβ thalassemia were considered. Strict inclusion and exclusion criteria were developed at an expert consensus meeting in Seattle in 1990; these criteria have since been used to determine HSCT eligibility for several subsequent clinical trials, as well as for both referring hematologists and consulting HSCT physicians in deciding which children and adolescents should be offered HSCT as part of routine care (see Sect. "Whom Should Be Offered Matched-Related Donor Transplantation?"). The data from this trial are presented here; it should be noted that these results have expanded the practice of HSCT for SCD worldwide.

Results. The outcomes for the first 22 subjects were reported in 1996 in the New England Journal of Medicine. With a median follow-up of 24 months, 20 subjects were alive with 16 demonstrating stable donor hematopoietic cell engraftment [7]. Three of the four with failed engraftment had autologous reconstitution; one subject had marrow aplasia. Stable mixed donor chimerisms (MDCs) were noted in one of the 16 survivors. Notably, stability of preexisting cerebrovascular and pulmonary disease was noted.

Updates on this cohort were published in 1997, 2000, and 2001 [8–10]. The most recent publication reports data for 59 subjects with a median follow-up of 42 months [10]. There are 55 survivors, with 50 cured of their SCD. Thirteen of the 50 children and adolescents cured of their sickle phenotype have stable MDCs (90–99% donor), while five had lower levels of MDCs ranging from 11% to 74%. Interestingly, four of these five recipients with low donor chimerisms had HbS levels reflective of their donor, while the subject with only 11% donor chimerisms had only 7% HbS with a donor with a normal hemoglobin phenotype. These important data support the investigation of reduced intensity approaches to HSCT, proving that full donor chimerisms are not required to cure SCD and that even 10% stable MDCs can be sufficient (see Sect. "Clinical Trials Evaluating Reduced-Intensity and Non-myeloablative Conditioning Regimens for Matched Sibling Donor HSCT for Sickle Cell Disease").

None of the 50 subjects who maintained donor engraftment have had SCD-related crises post-HSCT. In ten subjects with a history of stroke and stable donor engraftment with at least 2 years of follow-up, cerebral magnetic resonance imaging

(MRI) was improved or stable post-HSCT [10]. Of the 59 total subjects, 11 (19%) developed GVHD with three deaths due to complications of its therapy. No subject with stable MDCs experienced acute or chronic GVHD. Of the 26 subjects with follow-up of 2 years or longer, three developed grades I–III acute GVHD and two had chronic GVHD.

Supportive care lessons learned. While supportive care is discussed in detail in Chap. 8, it is important to emphasize that four of the first seven subjects had neurologic events, two of whom had intracranial hemorrhages (one fatal) [7]. The risk of intracranial hemorrhage, seizures, and posterior-reversible encephalopathy syndrome led to the development of updated supportive care guidelines in 1993. These included anticonvulsant prophylaxis during busulfan *and* for the duration of cyclosporine administration, maintenance of normal magnesium levels, maintenance of platelet counts greater than 50×10^9/L and Hb between 90 and 110 g/L, and control of hypertension [7, 10].

Other clinical trials of MRD HSCT for SCD. Data from single-institution experiences or registry-based reports complete the summary of existing literature with myeloablative HSCT for SCD. Many of these publications are listed in Table 12.1.

Table 12.1 Myeloablative hematopoietic stem cell transplantation for sickle cell disease

Authors	*N*	Median age (years)	Conditioning	OS	Graft rejection	DFS	cGVHD	TRM
Walters et al. (2000) [10]	50	9.4	Bu-Cy-ATG	94%	10%	84% at 3 years	12%	6%
Bernaudin et al. (2010) [46]	144	9	Bu-Cy-ATG	95%	<2%	93% at 3 years	10%	7%
Dedeken et al. (2014) [12]	50	8.3	Bu-Cy-ATG	94%	8%	86% at 8 years	20%	<5%
Lucarelli et al. (2014) [47]	40	12	Bu-Cy-ATG ± Flu	91%	–	91% at 5 years	5%	9%
McPherson et al. (2011) [15]	27	8.6	Bu-Cy-ATG	96%	0%	96% at 5 years	<5%	<5%
Vermylen et al. (1998) [6]	50	–	Bu-Cy ± TLI ± ATG	93%	10%	85% at 11 years	20%	2%
Bhatia et al. (2014) [17]	18	8.9	Bu-Flu-Alemtuzumab	100%	0%	100% at 2 years	11%	0%

OS overall survival, *DFS* disease-free survival, *cGVHD* chronic graft-versus-host disease, *TRM* transplant-related mortality, *Bu* busulfan, *Cy* cyclophosphamide, *ATG* antithymocyte globulin, *Flu* fludarabine, *TLI* total lymphoid irradiation

Importance of Serotherapy

French experience with antithymocyte globulin. The Société Française de Greffe de Moelle established a consensus approach to HSCT in major transplant centers in France in 1988 [18]. All young patients with severe SCD were recommended HSCT. Severe SCD was initially defined as having a history of stroke, three or more vaso-occlusive and/or acute chest crises per year, multiple sites of avascular necrosis, or red cell alloimmunization (two or more alloantibodies). After 1992, incomplete disease control with hydroxyrurea (HU) was required to meet the vaso-occlusive/acute chest crises criteria. Later, patients with elevated transcranial Doppler velocities or MRI angiographic evidence of cerebral stenoses despite chronic transfusion were also eligible. Results for HSCT for 87 consecutive patients ages 2–22 from 1988 to 2004 who received an HLA-matched sibling donor allograft were described. Conditioning consisted of busulfan and cyclophosphamide, with antithymocyte globulin (ATG) given to patients after 1992 (69/87 received ATG). Rabbit ATG (Thymoglobuline; Genzyme, Saint-Germain en Laye, France) was given at a total dose of 20 mg/kg divided equally and given on days −6 to −3, inclusive. GVHD prophylaxis consisted of cyclosporine and methotrexate in 62 and methotrexate alone in 25. The 5-year cumulative incidence of rejection was 2.9% in those who received ATG serotherapy compared to 22.6% who did not ($p = 0.002$). An increased incidence of mixed but stable donor chimerisms was noted in the ATG group. Improved outcomes since the year 2000 were also reported; only 1/43 patients allografted with ATG after 2000 experienced graft rejection. The event-free survival was 95.3% after January 2000, and no deaths after the 40th HSCT were reported. Rates of acute and chronic GVHD were only reported for the entire cohort; 17/86 (20%) developed grades II–IV acute GVHD, with 5.8% and 2.3% having grades III and IV, respectively. The cumulative incidence of chronic GVHD was 12.6%. Of 83 evaluable patients, 11% had limited, and 2.4% had extensive chronic GVHD.

This experience has since been updated with a total of 215 patients who received either (1) no ATG, (2) 10–15 mg/kg, or (3) 20 mg/kg of rabbit ATG [19]. Similar to the earlier report, disease-free survival was 95% with ATG, with the higher dose reducing the risk of chronic GVHD without increasing the risk of viral infection.

These impressive results have led to consideration of HSCT as standard of care for those with a matched sibling donor. Such low rates of morbidity and mortality compare favorably with risks of death and life-threatening and life-limiting complications of SCD with best supportive care practices.

Alemtuzumab. A reduced-toxicity, busulfan-based myeloablative conditioning regimen using alemtuzumab serotherapy resulted in similar rates of acute GVHD (17%, 3/18) compared to ATG-based myeloablative approaches [17]. Alemtuzumab was given days −6 to −2 (total dose 54 mg/m^2). All subjects survived with long-term donor hematopoietic engraftment, with four cases of cytomegalovirus (CMV) reactivation—including one case of CMV disease—and

two cases of respiratory syncytial virus upper respiratory tract infections. The timing and dose of alemtuzumab can greatly impact engraftment, immune reconstitution, and risk of opportunistic viral and fungal infections. While alemtuzumab serotherapy is the focus of many research efforts as a component of reduced-intensity conditioning, the data describing this drug as a component of myeloablative regimens is limited. The impressive French data warrant consideration of ATG serotherapy as the standard when myeloablative conditioning is given.

Role of Pre-HSCT Immune Suppression

Hydroxyurea. HU is used to prevent complications of SCD and is currently routinely recommended for all children and adolescents with HbSS or HbSβ^0 thalassemia 9 months of age and older, regardless of clinical severity [20]. Despite its widespread use as an immunosuppressive agent pre-HSCT (in addition to SCD control), there is scant data to support the use of HU to promote engraftment. While there is theoretical benefit to reduce marrow hypercellularity and in the provision of some degree of immunosuppression pre-HSCT for SCD to promote donor hematopoietic cell engraftment, the data justifying this widespread practice is relatively weak.

The potential benefit of pre-HSCT HU exposure was first described by a Belgian group in 2004 [21]. Routine administration of HU to all children with SCD was not standard practice at the time pioneering HSCTs were performed in children in Belgium between 1988 and 2002. While numbers are small in this report, of five patients who received busulfan (16 mg/kg), cyclophosphamide (200 mg/kg), and ATG, two failed to engraft and a third required donor lymphocyte infusion and steroids for secondary graft rejection. In contrast, none of the 13 patients who received the same conditioning with pre-HSCT HU had failed engraftment or late graft rejection. HU dosing was 20–35 mg/kg/day for a median of 2.16 years pre-HSCT (minimum 0.6 years). It should be noted, however, that the group of five patients who did not receive HU had relatively higher rates of red blood cell alloimmunization, strokes, and acute chest syndrome pre-HSCT. The same group updated their experience in 2014 [12]. They report 97.4% event-free survival (EFS) and no episodes of graft failure since HU was introduced pre-HSCT for all patients; all patients received busulfan, cyclophosphamide, and ATG conditioning since 1991. It should be emphasized that this cohort includes patients transplanted between 1988 and 1991 without ATG, with the SFGM in France having published improved outcomes with ATG (introduced in 1992) and in those patients undergoing HSCT after 2000, thus emphasizing the influence of HSCT-era on outcomes [18].

The optimal duration of HU exposure pre-HSCT is also not clearly defined, and in many studies, its prescription is at the discretion of treating physicians as a disease-modifying therapy for SCD, as opposed to mandated immune suppression prior to transplant [18, 22–24].

Busulfan Dosing and Pharmacokinetics

The practice of busulfan dosing adjustments to achieve targeted area under the curve (AUC) values has become standard practice in most HSCT centers. Levels are targeted to maximize the donor hematopoietic stem cell engraftment while minimizing toxicities, notably sinusoidal obstructive syndrome (SOS), also known as veno-occlusive disease [25]. Busulfan is the myeloablative agent used most commonly in MSD allogeneic HSCT for SCD; targeted dosing has become standard practice whether the drug is administered every 6 h or once a day [26].

McPherson et al. described the Children's Healthcare of Atlanta experience with busulfan pharmacokinetics (PK) between 1993 and 2007 [15]. Of 27 patients to undergo myeloablative MSD HSCT for SCD, 25 had PK measurements. Dosing of busulfan was 0.875 mg/kg/dose for 16 doses, combined with cyclophosphamide and ATG. It should be noted that oral busulfan was administered during the initial study period to 17 subjects. The busulfan area under the curve (AUC) was then calculated after the first dose administered, with adjustments made to target AUCs which varied based on different time periods within the period of study: 585–877 μmol min/L (1996–1999), <1500 μmol min/L with no lower limit (1999–2004), and 900–1100 μmol min/L from 2004 onward. Any subsequent AUC measurements were at the discretion of the treating physician.

All patients had donor hematopoietic stem cell engraftment, with full donor chimerisms in 21/25 (84%). AUC was associated with donor chimerisms: AUC of 862 ± 73 μmol min/L for those patients with MDCs compared to 1018 ± 122 μmol min/L for recipients with full donor chimerisms. Eight patients developed SOS (32%); SOS was not associated with busulfan AUC levels. All but one patient is a long-term survivor.

A multicenter experience of myeloablative busulfan-based conditioning by Maheshwari et al. describes a cohort of 16 children and adolescents with SCD who underwent matched-sibling donor HSCT [25]. Conditioning consisted of 0.8–1 mg/kg/dose busulfan (age-based initial dosing) given every 6 h for 16 doses, combined with cyclophosphamide and equine ATG. The first-dose PK analysis was performed to target an AUC of 877–1023 μmol min (steady-state concentration of 600–700 ng/mL). Subsequent dose adjustments were made as required.

Dose adjustments were required for 14/16 (88%) of patients, emphasizing the importance of PK analysis. Nine patients required dose increases, five decreased dosing, and two had no change in dose. The median total dose of busulfan given was 14.7 mg/kg. No patient developed SOS; all had successful long-term engraftment (median 100%, range 80–100) with a 3-year SCD-free survival of 100%.

Myeloablative Reduced-Toxicity Approaches

Fludarabine. Fludarabine, an antimetabolite drug with immunosuppressive properties, can potentiate the effects of alkylating agents such as busulfan and cyclophosphamide when dosed and timed appropriately, yet is associated with lower rates of

toxicity when compared with cyclophosphamide [26]. When combined with busulfan, rates of SOS are lower when fludarabine replaces cyclophosphamide, perhaps due to glutathione-independent metabolism of fludarabine.

The immunosuppressive properties of fludarabine—with comparatively lower rates of toxicity—can be applied synergistically with other immunosuppressing medications and have prompted its study with an aim to reduce doses of alkylating agents [23]. A study of the addition of fludarabine to a myeloablative busulfan-based conditioning regimen with cyclophosphamide and horse ATG in MRD HSCT for SCD aimed to reduce dosing of both busulfan and cyclophosphamide, without compromising day +28 donor hematopoietic cell engraftment. Four dose levels were developed, with initial reduction in cyclophosphamide dosing followed by busulfan dose reductions. Cyclophosphamide dosing was reduced from 200 to 90 mg/kg without adverse impact on donor chimerisms. The trial was stopped when the first two patients to undergo busulfan dose reduction from 12.8 to 9.6 mg/kg had less than 50% donor-derived T-cell engraftment on day +28 post-HSCT (as per study design). All 14 subjects on the trial are alive without SCD, with no reported regimen-related toxicity. These data warrant consideration for future study with the aim of further reducing alkylating agent exposure and their inherent risks of infertility.

With the widespread adoption of myeloablative busulfan, fludarabine, and ATG reduced-toxicity conditioning for hematologic malignancies, this regimen forms the backbone of a current large multicenter trial of MSD HSCT in adolescents and young adults with SCD (clinicaltrials.gov, #NCT02766465).

Treosulfan. This myeloablative alkylating agent with immunosuppressive properties has been of increasing interest due to linear pharmacokinetics, less variability in metabolism between patients, and a favorable side effect profile when compared with busulfan [28]. Notably, the risk of hepatotoxicity- with risks of SOS- has raised concerns regarding busulfan-based conditioning for patients with thalassemia, particularly those with high pre-HSCT iron burden. However, while encouraging results from Italy with a treosulfan-based regimen have been reported, the low rates of hepatotoxicity reported for recipients of busulfan-based regimens for SCD combined with increasing patient and provider interest in reduced-intensity conditioning approaches might limit the interest in a large-scale study of treosulfan for SCD [28].

Clinical Trials Evaluating Reduced-Intensity and Non-myeloablative Conditioning Regimens for Matched Sibling Donor HSCT for Sickle Cell Disease

While rates of successful cure have been high with myeloablative matched-sibling donor HSCT for SCD, there are still short- and long-term toxicities that remain barriers to widespread application of this curative therapy for those with sibling HLA matches. The risk of infertility with myeloablative busulfan, particularly for

adolescent females, is of major concern [29, 30]. In general, outcomes of HSCT are better in younger recipients with notably lower rates of GVHD compared to recipients who are adolescents or young adults [27]. However, younger children cannot participate meaningfully in discussions about risks of infertility weighed against benefits of cure. Decision-making for families and care providers is influenced greatly by risks of end-organ toxicities, GVHD, as well as that of infertility.

With the knowledge that even 10–20% MDCs can result in a cure of the SCD phenotype, the applicability of less intensive conditioning regimens is even more appealing [8, 31]. This principle was applied to the first described non-myeloablative conditioning approaches to cure SCD [31]. However, with this relatively new approach to HSCT, less is known about long-term outcomes, including graft survival and late toxicities [24, 31]. Some of the approaches studied to date are summarized here. Table 12.2 includes the published studies with larger numbers of subjects.

Low-dose busulfan. Doses of busulfan ≥600 mg/m^2 (~20 mg/kg) have been associated with male infertility, and combined with data suggesting adolescent females are vulnerable to busulfan gonadotoxicity and that males with sickle cell disease may already have compromised spermatogenesis, the appeal of dose reduction of busulfan is apparent [33]. Cyclophosphamide, historically commonly administered with busulfan for HSCT for SCD, is also gonadotoxic. Horan et al. described a busulfan dose de-escalation approach to myeloablative, cyclophosphamide-containing conditioning with fertility preservation in mind [23]. Further such efforts include those of Krishnamurti et al., who published a series of seven children and adolescents with severe SCD who received conditioning with lower doses of busulfan (total dose 8 mg/kg) [34]. Minimal regimen-related toxicity was reported, and all patients are alive. Six of seven have long-term donor hematopoietic cell engraftment; two have full donor chimerisms, the remaining with MDCs. One patient had secondary graft failure with autologous hematopoietic reconstitution, with a history of cyclosporine nonadherence.

Fludarabine/low-dose total body irradiation. A cohort of six children and young adults with SCD who underwent MSD bone marrow allografting who received

Table 12.2 Reduced intensity conditioning/non-myeloablative conditioning for children, adolescents, and young adults with sickle cell disease

Authors	*N*	Median age (years)	Conditioning	OS	Graft rejection	DFS	cGVHD	TRM
King et al. (2015) [22]	43	13	Flu-Mel-Alemtuzumab	93%	<2%	91%	13%	7%
Hsieh et al. (2014) [24]	29	28.5	TBI-Alemtuzumab	97%	14%	86%	0%	0%
Saraf et al. (2016) [38]	13	30	TBI-Alemtuzumab	100%	8%	92%	0%	0%

OS overall survival, *DFS* disease-free survival, *cGVHD* chronic graft-versus-host disease, *TRM* transplant-related mortality, *Flu* fludarabine, *Mel* melphalan, *TBI* total body irradiation

fludarabine (30 mg/m^2/day), 200 cGy total body irradiation (TBI) with or without equine ATG [35]. Horan et al. also described three patients with SCD who received very low intensity consisting of fludarabine (25 mg/m^2/day × 5 days), rabbit ATG (daily × 4 days), and 200 cGy (TBI) [36]. While toxicities were minimal, all but one patient in these papers had autologous recovery and recurrence of SCD, demonstrating the need for either additional myelosuppression, immunosuppression, or both.

Alemtuzumab/melphalan/fludarabine. A multicenter study included 43 children with symptomatic SCD and nine with thalassemia major who received this combination of conditioning agents and MRD allografts (bone marrow in the majority, with some sibling umbilical cord blood (UCB) products given) [22]. Alemtuzumab was given "early," i.e., days −21 to −19. GVHD prophylaxis varied during the life of the study. The OS and EFS for those children and adolescents with SCD were 93% and 90.7%, respectively, at a median of 3.4 years. Graft rejection occurred in the one recipient who received only sibling UCB. Three deaths due to GVHD occurred in recipients 17–18 years of age. Rates of acute and chronic GVHD for all subjects were 23% and 13%, respectively; all cases of chronic GVHD were extensive and seen in recipients greater than 14 years of age. Of those with SCD and thalassemia who had follow-up of at least 1 year, 36/50 had full donor chimerisms (four with thalassemia). Two patients with SCD required donor lymphocyte infusion, neither of whom developed GVHD nor have evidence of SCD. Of those recipients with MDCs, immune suppression was withdrawn successfully without evidence of GVHD or graft rejection. Delayed lymphocyte recovery was noted, and *Staphylococcus* bacteremia and cytomegalovirus preemptive therapy were noteworthy. While these results are encouraging for successful donor hematopoietic cell engraftment with reduced-intensity conditioning, GVHD rates remain a concern.

National Institutes of Health Protocol. Hsieh et al. presented provocative data in the New England Journal of Medicine describing reduced intensity conditioning in adolescents and adults with symptomatic SCD [37]. Conditioning consisted of "late" alemtuzumab (1 mg/kg total dose) and 300 cGy TBI, followed by prolonged sirolimus exposure for GVHD prophylaxis and to prevent secondary graft failure due to delayed lymphocyte recovery (related to the timing of alemtuzumab). Donor-recipients with major ABO incompatibilities were excluded due to the risk of pure red cell aplasia. The NIH group expanded on their experience in 2014 with an updated description of 29 young adults and adults who received the same conditioning regimen [24]. Of these subjects, 25 (86%) had stable long-term donor engraftment. No acute or chronic GVHD was noted. There was only one death in a subject with recurrence of SCD who died of intracranial hemorrhage. Fifteen of the twenty-six subjects with stable donor engraftment had sirolimus withdrawn successfully with ongoing stable donor chimerisms and no GVHD. This protocol originally mandated 100% donor CD3$^+$ chimerisms prior to sirolimus weaning; since no patients achieved this degree of donor T-cell chimerisms, the study was amended to allow for weaning after 50% donor CD3$^+$ cells were achieved. Adverse events included pain, infections, thyroiditis, and sirolimus toxicities. The toxicities noted were quite acceptable given the SCD comorbidities noted in many subjects at baseline. No malignancies secondary to the radiation therapy have been noted, but longer follow-up is required. Pregnancies have been documented in recipient females.

An additional 13 high-risk young adult and adult patients with SCD have undergone this approach in Chicago, including two cases in which a major ABO incompatibility existed between the donor and recipient [38]. All patients are alive, with 12/13 having stable MDCs. One patient sustained secondary graft failure with a history of sirolimus nonadherence. No acute or chronic GVHD was noted. Four patients have since discontinued sirolimus without graft loss or GVHD. This approach has also been used with success in children and adolescents, with most recipients eligible for weaning of immune suppression at 1-year post-HSCT [39]. Given the absence of reported acute or chronic GVHD with this regimen, the possibility of fertility preservation in addition to high rates of cure of SCD, this regimen warrants further multicenter evaluation. Long-term graft survival data following sirolimus withdrawal will be essential.

Summary of Key Matched Sibling Donor HSCT Clinical Trials for SCD

Myeloablative conditioning regimens remain the most studied and most commonly prescribed for MSD allogeneic HSCT for SCD [27]. With the high rates of EFS and OS with busulfan, cyclophosphamide, and ATG conditioning, this regimen is widely considered the standard of practice [18, 19]. Fludarabine has been increasingly used to replace cyclophosphamide [17]. Efforts to reduce long-term toxicities—particularly infertility—are ongoing, with reduced-intensity conditioning regimens the focus of ongoing investigation. However, sustained donor engraftment and graft-versus-host disease remain barriers to their widespread implementation [22].

Impact of Hematopoietic Stem Cell Source

While bone marrow is the most common hematopoietic stem cell source used in MRD transplantation of children, UCB has shown to be a viable alternative for many children [40]. Because of their association with chronic GVHD and mortality, the use of peripheral blood stem cells have been avoided in transplantation for pediatric SCD [41].

Most of what we know regarding the suitability of UCB in MRD transplantation for pediatric SCD comes from registry studies of patients with thalassemia or SCD performed by Eurocord. In 2003, this group reported on outcomes in 44 patients (33 with thalassemia, 11 with SCD) [32]. In 2013, Eurocord published the results of larger study in patients with hemoglobinopathies comparing bone marrow and cord blood [40]. This study included 485 patients, 130 with SCD. Cord blood grafts were given to 96 of the 485 recipients. The distribution of patients with SCD between the two groups was similar. The cord blood recipients were significantly younger (5.9 vs 8.1 years, $p = 0.02$). Various forms of myeloablative, busulfan-based conditioning were used in all cases. In cord blood recipients, the infused cell dose was ample (median = 3.9×10^7 nucleated cells/kg recipient weight).

There were no differences in the incidence of graft failure between the two groups. Recovery of neutrophil and platelet counts was slower in UCB transplant recipients. Acute and chronic GVHD were more common in the marrow transplant group. Remarkably, no extensive chronic GVHD was observed in the cord blood transplant recipient group. Disease-free survival, event-free survival (defined as the absence of graft failure, extensive chronic GVHD, and death), and overall survival did not differ (Fig. 12.1).

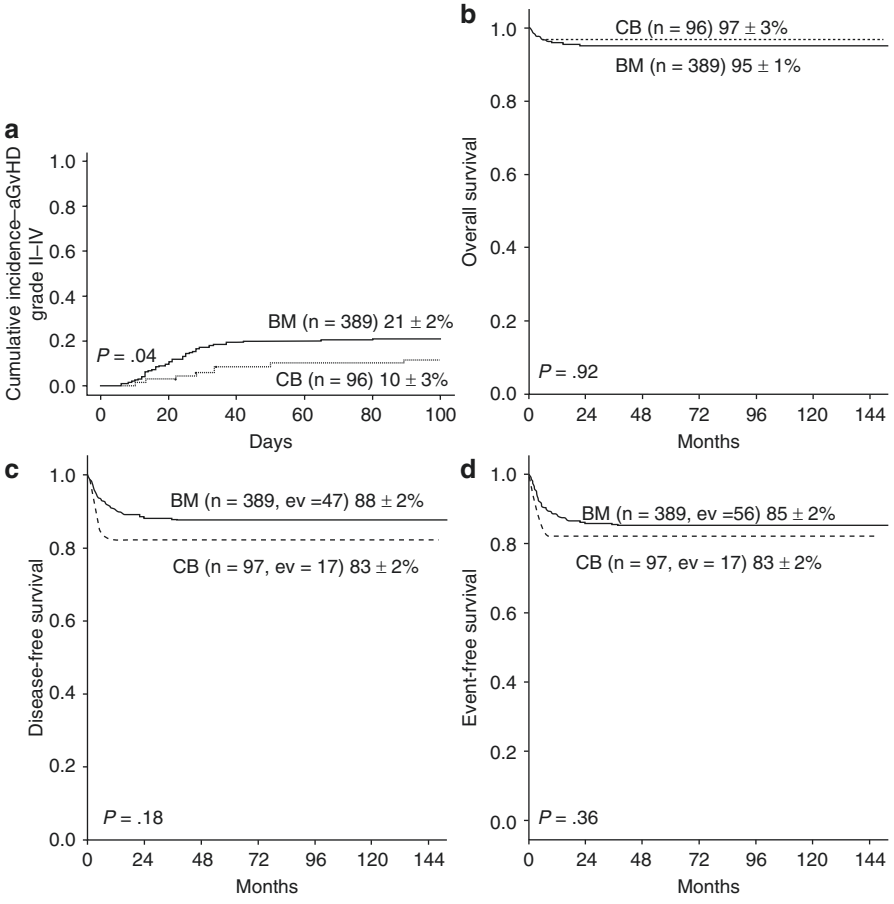

Fig. 12.1 Cumulative incidence of grade II–IV acute GVHD and Kaplan–Meier estimates of OS, DFS, and EFS. (**a**) Cumulative incidence of grade II–IV acute GVHD (aGVHD) for patients given BM and CB transplantation. (**b**) Kaplan–Meier estimate of OS for patients given BM and CB transplantation. (**c**) Kaplan–Meier estimate of DFS for patients given BM and CB transplantation. In the calculation of DFS, both death and graft failure were considered events. (**d**) Kaplan–Meier estimate of EFS for patients given BM and CB transplantation. In the calculation of EFS, death, graft failure, and extensive chronic GVHD were considered events. *BM* bone marrow, *CB* cord blood, *DFS* disease-free survival, *EFS* event-free survival, *GVHD* graft-versus-host disease, *OS* overall survival. © 2013 by The American Society of Hematology. Used with permission

One limitation of this study from the perspective of transplantation for SCD is that the patient sample was comprised predominantly of patients with thalassemia. The investigators did, however, perform a multivariate analysis of disease-free survival, examining the influence of graft type, recipient age, diagnosis, and year of transplant. Those with SCD were less likely to experience treatment failure (graft failure or death, HR = 0.52, 95% CI 0.28–0.97, $p = 0.04$).

This experience indicates that matched-related cord blood grafts are an excellent option for children with SCD. Transplant providers, however, should be careful in applying this experience to their own patients, being mindful of the ample cell dose received by most and myeloablative conditioning received by all recipients. We believe that matched-related cord blood transplantation is a good option when the cryopreserved cell dose is at least 3.9×10^7 nucleated cells/kg recipient weight and myeloablative conditioning is appropriate.

Whom Should Be Offered Matched-Related Donor Transplantation?

The eligibility criteria utilized in the international trial of MRD transplantation for SCD conducted in the 1990s [7, 10] have long guided the determination of whom should be offered transplantation. The consensus eligibility criteria (disease and patient) have been widely adopted for subsequent clinical trials as well as for patients offered transplantation as routine care.

This trial restricted enrollment to children who were severely affected by their SCD, utilizing nine disease-based criteria. Of the nine, three—clinical stroke, recurrent vaso-occlusive pain, and recurrent acute chest syndrome—accounted for nearly all the enrollment to the trial; clinical stroke accounted for over half. Patient-related criteria were designed to exclude patients more likely to suffer transplant-related complications, such as GVHD and SOS of the liver. Eligibility was limited to patients under the age of 16 years with a Lansky performance status of at least 70. Patients with bridging portal fibrosis/cirrhosis, significant renal insufficiency, and other organ dysfunction were excluded [7].

Since this study opened in 1991, there have been a myriad of changes in the care of patients with SCD as well as in the field of transplantation. While the consensus criteria developed for this trial remain relevant, they have been modified and supplemented in an effort to keep pace with advances in care. The most prominent changes in the care of children with SCD relate to the early detection of cerebrovascular disease and the widespread adoption of hydroxyurea. Cerebrovascular disease is now routinely identified before children suffer clinical stroke through transcranial Doppler ultrasound screening and the detection of silent cerebral infarcts by MRI scanning. Chronic transfusion therapy, in turn, is used to prevent the occurrence of clinical stroke and additional silent ischemic injury [11, 13]. Hydroxyurea is widely used to lessen the frequency of vaso-occlusive pain and

acute chest syndrome [14]. It is also now increasingly being initiated early in childhood to prevent disease-related complications [16, 20]. Elevated transcranial Doppler velocities and severe or progressive silent cerebral infarcts are now being recognized by some groups as indications for transplantation [22, 23]. Similarly, some have broadened criteria relating to vaso-occlusive pain and acute chest syndrome to offer transplantation to severely affected children who experience incomplete relief with hydroxyurea [23].

The Sickle Transplant Alliance for Research consortium (STAR, curesicklenow.org) employs a set of criteria to define severe disease that have been updated to account for advances in the field of SCD. These are shown in Table 12.3.

One of the chief advances in the field of transplantation since the Multicenter Investigation of Bone Marrow Transplantation for Sickle Cell Disease has been the development less intensive and safer forms of conditioning. With reduced intensity conditioning now having been studied successfully for MRD transplantation for SCD, it has made it possible to offer transplantation to some patients who would have been ineligible for the international trial, which used myeloablative conditioning. For example, in a multicenter trial of alemtuzumab, fludarabine, and melphalan, the lower limit for performance status was dropped from 70 to 40 [22].

Table 12.3 Indications for matched-related transplantation: updated criteria for defining severe disease

Previous clinical stroke, as evidenced by a neurological deficit lasting longer than 24 h, which is accompanied by radiographic evidence of ischemic brain injury and cerebral vasculopathy
Asymptomatic cerebrovascular disease, as evidenced by one the following:
Progressive silent cerebral infarction, as evidenced by serial MRI scans that demonstrate the development of a succession of lesions (at least two temporally discreet lesions, each measuring at least 3 mm in greatest dimension on the most recent scan) or the enlargement of a single lesion, initially measuring at least 3 mm. Lesions must be visible on T2-weighted MRI sequences
Cerebral arteriopathy, as evidenced by abnormal TCD testing (confirmed elevated velocities in any single vessel of TAMMV ≥200 cm/s for non-imaging TCD) *or* by significant vasculopathy on MRA (greater than 50% stenosis of ≥2 arterial segments or complete occlusion of any single arterial segment)
Frequent (≥3 per year for preceding 2 years) painful vaso-occlusive episodes (defined as episode lasting ≥4 h and requiring hospitalization or outpatient treatment with parenteral opioids). If patient is on hydroxyurea and its use has been associated with a decrease in the frequency of episodes, the frequency should be gauged from the 2 years prior to the start of this drug
Recurrent (≥3 in lifetime) acute chest syndrome events which have necessitated erythrocyte transfusion therapy
Any combination of ≥3 acute chest syndrome episodes and vaso-occlusive pain episodes (defined as above) yearly for 3 years. If patient is on hydroxyurea and its use has been associated with a decrease in the frequency of episodes, the frequency should be gauged from the 3 years prior to the start of this drug

TCD transcranial Doppler ultrasound, *TAMMV* time average mean of the maximal velocity

Future Directions

As more experience with MRD HSCT for SCD is garnered, it has become increasingly clear that outcomes are better in children compared to adolescents [27]. This recognition, we believe, presents both an opportunity and a challenge—an opportunity to expand the use of transplantation by extending it to children who are less severely affected by their disease and a challenge to improve outcomes in adolescent patients.

Extending Transplantation to Less Severely Affected Children

One of the chief advantages of performing transplantation prior to adolescence is a markedly lower risk of graft-versus-host disease. While it is unclear in MRD transplantation—where recipient and donor ages are closely correlated—whether it is the age of the recipient, the donor, or both that matter, studies in transplantation for pediatric leukemia clearly demonstrate that children are at lower risk for acute and chronic GVHD [42, 43].

While this issue has not been rigorously examined in HSCT for pediatric SCD, the published experience in SCD is consistent with that in leukemia. In the aforementioned multicenter trial of alemtuzumab, fludarabine, and melphalan conditioning, for example, there were three transplant related deaths, all in adolescent patients due to chronic GVHD. Furthermore, no chronic GVHD was observed in patients less than 14 years [22].

The safety afforded by earlier transplantation during childhood, coupled with the recognition that SCD produces significant suffering in most adults and greatly reduces life expectancy, provides a basis for extending MRD to less severely affected children. Experience from three STAR centers suggests that MSD HSCT could be a safe and effective treatment for these patients. This series included 25 patients with a median age of 5.3 years, most transplanted after 2010. Twenty-two had HbSS, and three patients had HbSC. While none of the patients met the criteria for severe disease listed in Table 12.3, most had a history of recurrent vaso-occlusive pain or acute chest syndrome. Most of these patients received myeloablative conditioning and a marrow allograft. One patient developed acute GVHD (grade III), one chronic GVHD, and one patient developed posterior-reversible encephalopathic syndrome. With a median follow-up of 28 (range 12–142) months, all 25 patients are off immune suppression and free of SCD. These findings must be confirmed by larger, prospective clinical trials. To this end, STAR recently developed a multicenter trial of HLA-matched MSD HSCT for children with less severe disease. This trial will be open to children who are moderately affected by SCD. To minimize the risk of GVHD, only patients less than 10 years with donors less than 10 years are eligible.

Providers need to be mindful that the decision to offer transplantation to less severely affected children is ethically more ambiguous than the decision to offer transplantation to those with severe complications. The benefits are less certain and less immediate, and while the risks for graft-versus-host disease and transplant related mortality are low, they still exist. Moreover, myeloablative conditioning carries a high risk of gonadal failure [29, 30]; and while the risk of gonadal failure with reduced intensity conditioning is likely to be lower, it remains poorly defined [22]. Finally, by limiting transplantation for less severe disease to children (excluding adolescents)—which we believe is a reasonable approach at this time—patient participation in the decision-making process is largely or completely precluded, depending on the age and capacity of the recipient. Given this ambiguity, it is imperative that painstaking care is taken by transplant providers to thoroughly inform families of the risks of transplantation and by hematologists to thoroughly inform them of alternatives to transplantation.

Improving Outcomes in Adolescents by More Effectively Preventing Graft-Versus-Host Disease

While the need for more effective approaches to preventing graft-versus-host disease in unrelated donor transplantation for SCD is widely recognized, the need for more effective strategies in adolescents with related donors also deserves greater attention. Future trials of GVHD prophylaxis in this age group are needed.

One strategy that merits consideration is pretransplant administration of higher-dose rabbit antithymocyte globulin (rATG, Thymoglobulin®). In a retrospective review of 236 MRD transplants (median age = 9.7 years) performed in France, using high dose busulfan and cyclophosphamide and varying doses of rATG for conditioning, the investigators demonstrated that the incidence of chronic GVHD was inversely related to rATG dose. Patients receiving the highest total dose 20 mg/kg (n = 160) had a very low incidence of chronic GVHD (6.4%). Higher rATG dose was associated with mixed donor chimerisms, but not rejection or serious infections [19]. Given the strong association of high-dose rATG (15 mg/kg) with infectious mortality in a randomized controlled trial in adults receiving unrelated donor transplants for hematologic malignancies, however, underscores the need for this to be examined in the context of a carefully conducted clinical trial [44].

STAR is currently investigating another strategy, the use of the co-stimulation blocking agent abatacept (CTLA4-Ig), an agent that has shown promise in early phase trials in mismatched unrelated donor transplantation for hematologic malignancies [45]. The STAR trial (NCT02867800) is open to patients receiving MRD transplants who are at least 10 years or whose donor is at least 10 years. It is also open to patients of all ages undergoing matched unrelated donor transplants. Patients receive IV abatacept on days −1, +5, +14, and +28 in addition to standard GVHD prophylaxis with a calcineurin inhibitor and methotrexate.

Conclusion

Matched sibling HSCT for SCD has evolved in the last three decades from being considered an experimental treatment for the sickest patients to now being viewed as a therapeutic option which should be considered early in the disease course to prevent the development of SCD-related organ injury. The field now focuses on reducing the intensity of the conditioning regimen with the hope of reducing HSCT toxicites, thereby making transplantation more acceptable to patients and families. Low toxicity HSCT approaches also allow adults with SCD who had been previously ineligible for HSCT due to concerns of exacerbating preexisting organ injury to now consider this curative treatment. With the impressive outcomes of non-myeloablative matched-sibling donor HSCT, notably the absence of any GVHD or significant toxicities, patients in the future with available donors may routinely undergo this curative treatment before the development of any complications of SCD.

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