

# Curative Treatment for Severe Sickle Cell Disease: Allogeneic Transplantation

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**Abstract:** Sickle cell disease is an inherited hematologic disorder that in its severe form can result in substantial morbidity and early mortality. Patients with this disorder can suffer from severe pain, lung disease, and strokes, resulting in chronic debilitating conditions, end organ dysfunction, and organ failure. The health care costs of caring for these chronically ill patients are substantial. Allogeneic transplantation is a modality that has the potential to cure these patients. To date, matched sibling donor transplantation is widely accepted as a standard of care for pediatric patients. Utilizing alternative donors for transplant is still under investigation, as is transplant for adult patients with sickle cell disease. This review focuses on the most recent data for hematopoietic cell transplantation for patients with sickle cell disease.

## Introduction

Sickle cell disease (SCD) is an inherited hematologic disorder secondary to a point mutation at the sixth position of the  $\beta$  chain of human hemoglobin that results in the transformation of glutamic acid to valine. This recessive genetic condition causes the polymerization of the deoxygenated form of hemoglobin S, leading to a major distortion of red blood cells (sickle-shaped RBCs). The reduced deformability of these sickle-shaped RBCs leads to chronic hemolysis and vaso-occlusion. Acute signs and symptoms of SCD include pain, splenic sequestration, priapism (in males), aplastic crisis, acute chest syndrome, and stroke. In severe disease, patients are at risk for chronic pain, end organ dysfunction or failure, stroke, early mortality, and other complications. An estimated 5000 to 7000 people in the United States have severe SCD.<sup>1</sup>

The only proven curative therapy for patients with SCD is myeloablative conditioning with allogeneic hematopoietic cell transplantation (HCT) from a human leukocyte antigen (HLA)-matched sibling donor. However, as of 2013, only 1238 patients with SCD had undergone bone marrow transplant in Europe and North America. The overall survival (OS) at 2 years for these patients is approximately 94%.<sup>1</sup>

### Keywords

Allogeneic transplantation, sickle cell disease

The situations in which bone marrow transplant should be considered for a patient with severe SCD include:

(1) A clinically significant neurologic event (stroke) or any neurologic deficit lasting longer than 24 hours that is accompanied by an infarct on cerebral magnetic resonance imaging (MRI).

(2) A minimum of 2 episodes of acute chest syndrome in the preceding 2-year period in which the patient has failed to respond to or declined hydroxyurea treatment.

(3) At least 3 painful events in the past 2 years in which pain has occurred in sites typically associated with vaso-occlusive painful events and cannot be explained by causes other than SCD.

(4) Abnormal transcranial Doppler (TCD) study that requires starting on chronic transfusion therapy.

Other conditions that may warrant bone marrow transplant include red cell alloimmunization despite intervention, and pulmonary hypertension.

This review discusses the most recent advances in allogeneic HCT in SCD, including more novel approaches such as reduced toxicity conditioning and the use of alternative allogeneic donors (eg, matched unrelated donor, unrelated donor cord blood transplantation, haploidentical donor).

### Matched Sibling Donors

In 1984, Johnson and colleagues described a young patient with SCD who underwent matched sibling donor HCT with myeloablative conditioning for acute myeloid leukemia. The patient was successfully cured of both the leukemia and SCD, having been converted to the donor's sickle cell trait. Since then, numerous reports have described successful HCT using a matched sibling donor and a myeloablative preparative regimen, with progressive improvements in disease-free survival (DFS) and OS. In an early report, Walters and colleagues described 22 pediatric recipients of matched sibling donor HCT conditioned with myeloablative busulfan and cyclophosphamide in combination with serotherapy (antithymocyte globulin [ATG] or alemtuzumab).<sup>2</sup> Sixteen patients (73%) engrafted with long-term survival, only one of whom developed stable mixed chimerism. Four patients (18%) experienced graft loss, three of whom reconstituted autologous hematopoiesis, and 2 patients suffered transplant-related mortality, resulting in a 4-year event-free survival and OS of 73% and 91%, respectively. This early report supported the efficacy and safety of matched sibling donor HCT with myeloablative conditioning for pediatric patients with severe SCD. It also identified SCD-specific HCT considerations that helped to refine the HCT approach and minimize transplant-related morbidity and mortality. Of the first 7 patients transplanted,

four experienced significant neurologic events, including 2 intracranial hemorrhages. Subsequently, supportive care measures were implemented (prolonged anticonvulsant therapy, strict hypertension control, avoidance of hypomagnesemia, maintenance of hemoglobin between 9 and 11 g/dL, and platelets >50,000/mL), which resulted in a decreased rate of neurologic toxicity and complete avoidance of hemorrhage.

In 1998, Vermynen and colleagues reported the Belgian experience using matched sibling donor HCT with myeloablative conditioning in 2 groups of patients: 36 patients who met previously established criteria for HCT based on severity of SCD or associated complications, and another 14 patients who underwent HCT before development of severe SCD-related complications because of a desire to return to their home countries where HCT was unavailable.<sup>3</sup> Of those with a history of complications, the DFS and OS at 11 years were 80% and 88%, respectively. The DFS and OS in the less heavily pretreated group were significantly higher, at 93% and 100%, respectively. The difference in outcome was attributable to both impaired engraftment and increased transplant-related mortality in more severely affected patients. This supported the notion that engraftment may be compromised by excessive pre-HCT red cell transfusion exposure leading to potential development of allosensitization, and that HCT is ideally suited for patients prior to the development of SCD-related morbidity.<sup>3</sup>

In a 2007 report of the French experience, Bernaudin and colleagues<sup>4</sup> demonstrated the importance of serotherapy in the conditioning regimen to minimize graft loss. All patients received busulfan-based myeloablative conditioning and a matched sibling donor graft. In the initial cohort, no serotherapy was used and the graft failure rate was 22.6%; after the addition of ATG, this was reduced to 3%. DFS and OS were promising, at 86% and 93%, respectively; of the 44 patients transplanted after 2000, the event-free survival improved to 95%. Neurologic toxicity was again noted to be problematic, with 24% of patients suffering from seizures during the HCT procedure; the authors attributed this to a variety of factors, including hypertension, corticosteroid exposure, and calcineurin-related reversible posterior leukoencephalopathy.<sup>4</sup> A retrospective report from the Center for International Blood and Marrow Transplant Research (CIBMTR) on children with symptomatic SCD from 50 centers undergoing matched sibling donor HCT after myeloablative conditioning documented a 5-year DFS and OS of 85% and 97%, respectively, extending the results from the other studies.<sup>5</sup> Similarly, more contemporary studies of matched sibling donor HCT after myeloablative conditioning report DFS and OS in excess of 90%, suggesting that this approach is a safe modality

to cure SCD patients with severe disease with a low rate of transplant-related mortality and graft loss.<sup>6-8</sup> Moreover, as experience has accrued with matched sibling donor HCT after myeloablative conditioning in this population, rates of neurologic toxicities and other sources of regimen-related morbidity and mortality have declined.

Despite these robust data supporting the safety and efficacy of HCT with myeloablative conditioning using HLA-identical sibling graft sources, this HCT approach is suitable for only a small minority of patients with SCD in need of HCT, for a variety of reasons. First, only a small minority of transplant candidates will have a matched sibling donor<sup>9</sup>—even permitting use of donors with sickle cell trait, which is known not to compromise transplant outcome. Indeed, 85% of children meeting criteria for HCT lack an HLA-identical matched sibling donor.<sup>10</sup> Second, despite low early transplant-related mortality with myeloablative conditioning, late toxicities remain a barrier to acceptance of myeloablative conditioning by both patients and transplant physicians. Third, the intensity of the myeloablative preparative regimen limits applicability to patients with significant SCD-related organ dysfunction. Modifications of the transplant approach to circumvent these issues, including alternative donor graft sources and reduced-intensity conditioning, are discussed in the following sections.

## Alternative Donors

### *Matched Unrelated Donors*

Despite the encouraging progress made in matched sibling donor HCT after myeloablative conditioning in children with SCD, this ideal donor source is not available for the majority of children meeting the criteria for HCT. Unfortunately, the availability of allele-matched volunteer donors is also very limited for African Americans. In a recent study examining the likelihood of identifying an HLA-matched donor based on ethnicity in the US National Marrow Donor Program (NMDP) registry, only 19% of African Americans and 18% of Africans had an 8/8 HLA match available. The probability of identifying a suitable donor increased to 76% for African Americans if 7/8 HLA matches were included, but this increases the risk of graft-versus-host disease (GVHD), transplant-related mortality, and graft loss.<sup>11</sup> Similarly, Dew and colleagues found that only 6% of 50 African American patients requiring HCT for malignant and nonmalignant disease had an HLA-identical donor by molecular typing.<sup>12</sup> For this reason, matched unrelated donor HCT is often not an option for patients with SCD who are candidates for HCT, and experience in the literature for matched unrelated donor HCT is limited. There are ongoing clinical trials evaluating 8/8 matched unrelated donor HCT using a reduced-

intensity conditioning regimen: the SCURT (Sickle Cell Unrelated Donor Transplant) trial (NCT00745420) in children and the STRIDE (Bone Marrow Transplantation in Young Adults With Severe Sickle Cell Disease) trial (NCT01565616) in young adults.

### *Unrelated Donor Umbilical Cord Blood*

The probability of identifying a suitable unrelated stem cell source increases if umbilical cord blood is included as a potential graft source. In the aforementioned NMDP study, the likelihoods of identifying a suitable 6/6, 5/6 or greater, or 4/6 or greater HLA-matched umbilical cord blood unit in a young African American patient (probability of adequate cell dose) are 6%, 58%, and 95%, respectively.<sup>11</sup> As umbilical cord blood HCT is generally associated with less GVHD for the same degree of HLA mismatch, this graft source offers the potential to dramatically increase the availability of HCT for African American patients. However, experience with unrelated umbilical cord blood HCT in SCD is limited, and concerns regarding engraftment are limiting widespread implementation at present.

In an early report of 7 children with SCD receiving mismatched (all 4/6 or 5/6) umbilical cord blood grafts, only 3 patients (43%) experienced sustained donor engraftment, all of whom underwent myeloablative conditioning.<sup>13</sup> In a retrospective CIBMTR report of children with hemoglobinopathies undergoing umbilical cord blood HCT, Ruggeri and colleagues reported the outcomes of 16 patients with SCD. Nine patients received myeloablative conditioning—predominately busulfan/cyclophosphamide/ATG—and 7 received a variety of fludarabine-based reduced-intensity conditioning regimens. Most donors (63%) were 4/6 HLA-matched, 25% were 5/6 HLA-matched, and only 13% were HLA-identical, reflecting the NMDP registry data cited above. The median collected and post-thaw infused total nucleated cell (TNC) doses were  $6 \times 10^7$  cells/kg and  $4.9 \times 10^7$  cells/kg, respectively. Nine of 16 (56%) patients engrafted, of whom six received myeloablative conditioning. Overall, engraftment rates were 67% for myeloablative conditioning recipients and 43% for reduced-intensity conditioning recipients. Two-year DFS and OS for the entire SCD cohort were 50% and 94%, respectively. In multivariate analysis, cell dose predicted probability of DFS regardless of underlying disease, with patients receiving TNC doses in excess of  $5 \times 10^7$  cells/kg having significantly improved DFS. Notably, all patients with SCD who experienced graft failure experienced autologous hematopoietic recovery and survived; the 1 death was attributable to severe acute GVHD, but overall rates of grades 2 to 4 acute GVHD (23%) and chronic GVHD (16%) were acceptable, despite the high numbers of mismatched grafts.<sup>14</sup>

The SCURT trial is a phase 2 study of unrelated

donor HCT in children with severe sickle cell disorder, investigating the safety and efficacy of a reduced-intensity conditioning regimen consisting of distal alemtuzumab, fludarabine, and melphalan. As will be discussed below, this immunoablative regimen can serve as a platform to support allografting in HCT for nonmalignant disease, without the excessive early and late toxicity associated with myeloablative conditioning regimens. Unfortunately, the umbilical cord blood arm was closed prematurely owing to excessive rates of graft rejection, despite all grafts being at least 5/6 HLA-matched and providing a minimum of  $3 \times 10^7$  collected TNC/kg, with a median of  $6.4 \times 10^7$  TNC/kg (range,  $3.1$ - $7.6 \times 10^7$  TNC/kg). Of 8 total enrolled patients, 5 experienced graft rejection and autologous hematopoietic recovery for a 1-year DFS of 37.5% and OS of 100%. There was 1 late death due to chronic GVHD, but very few other acute toxicity-related sequelae. The authors concluded that although engraftment rates were disappointing, this reduced-intensity conditioning regimen has the potential to serve as a platform to support umbilical cord blood HCT for SCD. The HCT procedure would require a variety of modifications, however. These potentially include alterations of the conditioning regimen such as the addition of hydroxyurea and/or thiotepa, which has improved engraftment rates in HCT for advanced thalassemia, in addition to higher TNC doses with or without the use of double cord blood units. An effort to facilitate hematopoietic engraftment utilizing coinfusion of third-party mesenchymal stromal cells did not show positive results.<sup>15</sup>

Clearly, umbilical cord blood HCT offers the potential to augment the available donor pool and offers a rapidly available graft source with acceptable rates of GVHD despite the use of mismatched grafts; however, high rates of graft loss—particularly with reduced-intensity conditioning—preclude widespread application outside of a clinical trial. Although efforts are ongoing to refine the umbilical cord blood HCT approach in nonmalignant disease, alternative donor sources that more effectively achieve hematopoietic engraftment are immediately necessary in order to extend HCT to eligible patients with SCD. In addition, although umbilical cord blood increases the unrelated donor pool for African American patients, donor availability remains an issue, particularly when TNC dose and HLA match requirements are stringent.

### Familial Haploidentical Grafts

Although the aforementioned alternative donor sources (matched unrelated donor and umbilical cord blood) modestly expand the donor pool for patients with SCD lacking an HLA-identical matched sibling donor, major barriers remain, including poor engraftment rates with umbilical

cord blood grafts and higher risk of GVHD with matched unrelated donors, among other issues. The use of familial haploidentical grafts offers the potential to dramatically increase the availability of donors for patients in need of HCT. Familial haploidentical HCT has been used successfully in the treatment of malignant disorders in both adults and children, but literature is limited in the nonmalignant setting.<sup>16</sup> Although familial haploidentical donors are available for the vast majority of patients, this benefit is balanced by the high risk of severe GVHD without significant augmentation of GVHD preventive strategies.

One approach taken to mitigate GVHD risk in the familial haploidentical HCT setting has been ex vivo T-cell depletion either by negatively selecting for potential alloreactive T cells or positively selecting for progenitor cells (CD34+). This produces a graft that is enriched for progenitor cells with the elimination of cells potentially mediating GVHD, and has been successful in the treatment of children with hematologic malignancies.<sup>17</sup> Although this approach can successfully achieve hematopoietic engraftment and mitigate GVHD risk, lymphoid immune reconstitution is impaired, resulting in increased risk of infectious complications. In addition, T-cell depletion requires expertise and resources that allow for sophisticated ex vivo graft manipulation, currently limiting its application to selected centers.

Dallas and colleagues reported the experience at St. Jude Children's Research Hospital with T-cell depletion HCT in children with SCD. Eight patients received grafts from familial haploidentical donors obtained by peripheral blood leukapheresis after granulocyte colony-stimulating factor (G-CSF) stimulation. The grafts were subjected to ex vivo CD34+ selection using the CliniMACS device to obtain a target CD34+ cell dose of  $5 \times 10^6$  cells/kg. A fixed dose of  $1 \times 10^5$  CD3+ cells/kg was infused on the first day after transplant. The preparative regimen for familial haploidentical recipients consisted of either fludarabine, thiotepa, targeted myeloablative busulfan, ATG, and muromonab-CD3, or hydroxyurea and azathioprine for 3 months followed by busulfan, cyclophosphamide, thiotepa, and muromonab-CD3. In addition, patients received mycophenolate mofetil for post-HCT GVHD prophylaxis. Although all 8 patients achieved initial donor neutrophil and platelet engraftment, 4 (50%) subsequently experienced graft loss, one of whom was able to be rescued after additional stem cell infusion. Two of the 4 patients with sustained engraftment developed grade 2 acute GVHD and three developed chronic GVHD, two of whom died from GVHD-related complications. The DFS and OS of this cohort at a median of 9 years of follow-up were 38% and 75%, respectively, which compared unfavorably with a concurrent group of children receiving matched sibling donor HCT after myeloablative

conditioning in which DFS and OS were both 93%.<sup>18</sup> There is experience in the high-risk thalassemia major population with a highly immunosuppressive and myelo-suppressive conditioning regimen consisting of pre-HCT hydroxyurea and azathioprine followed by myeloablative conditioning with busulfan, cyclophosphamide, and fludarabine. This regimen reduced the incidence of graft rejection to 8%, compared with 30% seen in recipients of the same preparative regimen without the inclusion of hydroxyurea, azathioprine, and fludarabine.<sup>19,20</sup> Based on this, a multicenter trial has been developed to investigate a similar conditioning procedure in children with SCD receiving familial haploidentical T-cell depletion grafts with T-cell add back, and the addition of total lymphoid irradiation to augment engraftment potential (NCT01461837).<sup>21</sup> Early results of this study appear promising; however, long-term results will help to define the role of T-cell depletion grafts from familial haploidentical donors for children with SCD. Significant potential for optimization of T-cell depletion remains, including refinements of ex vivo graft manipulation techniques (eg, selective  $\alpha\beta$  T-cell depletion) and efforts to augment post-HCT immune reconstitution.

An alternative to ex vivo T-cell depletion to mitigate GVHD risk in recipients of familial haploidentical grafts is the use of in vivo augmented GVHD prophylaxis with high-dose posttransplant cyclophosphamide. The general approach of posttransplant cyclophosphamide in familial haploidentical HCT relies on the principle that activated and proliferating alloreactive T lymphocytes are more susceptible to the cytotoxic effects of cyclophosphamide exposure than hematopoietic progenitor cells.<sup>22</sup> Thus, administration of high-dose cyclophosphamide after graft infusion depletes potential mediators of GVHD while preserving cells with engraftment potential. Bolanos-Meade reported the adult and pediatric SCD experience with this approach at Johns Hopkins.<sup>23</sup> Patients were conditioned with cyclophosphamide, fludarabine, total body irradiation (200 cGy), and ATG, received unmanipulated (T-cell replete) bone marrow grafts from familial haploidentical (n=14) and matched sibling (n=3) donors, and subsequently received cyclophosphamide 50 mg/kg per day on the third and fourth day after transplant, along with tacrolimus or sirolimus and mycophenolate mofetil for GVHD prophylaxis. All matched sibling donor recipients engrafted, but 43% of the familial haploidentical graft recipients experienced graft loss (all of whom recovered autologous hematopoiesis). No familial haploidentical graft recipients developed GVHD. The authors concluded that familial haploidentical HCT with posttransplant cyclophosphamide is a feasible approach to expand the donor pool in patients with SCD. Despite the high incidence of graft loss, the authors documented that use of familial

**Table 1.** Comparison of Approaches to Familial Haploidentical Hematopoietic Cell Transplantation

	With Ex Vivo T-Cell Depletion	With High-Dose Cyclophosphamide
Feasibility	Technically difficult	Straightforward
Cost	Expensive	Inexpensive
Safety (transplant-related mortality)	Similar	Similar
GVHD incidence	Less	More
Graft failure/rejection (primary and secondary)	Equal	Equal

GVHD, graft-versus-host disease.

haploidentical grafts allowed 89% of referred patients with SCD to proceed with HCT, with 58% of these achieving long-term DFS. This compares favorably with a report by Hsieh and colleagues, in which only 21% of referred patients were able to proceed with HCT using a matched sibling donor.<sup>24</sup> Although engraftment rates remain suboptimal with familial haploidentical HCT and posttransplant cyclophosphamide, modifications of the protocol such as using G-CSF-primed bone marrow grafts offer the potential for further improvements in this approach.

Both ex vivo T-cell depletion and posttransplant cyclophosphamide are viable approaches to expansion of the donor pool in patients with SCD. Each approach offers a balance of advantages and disadvantages that require careful consideration before either can be adopted into routine practice (Table 1). The process of T-cell depletion requires technical laboratory expertise and is cost-intensive, whereas posttransplant cyclophosphamide is relatively straightforward and inexpensive. The incidence of GVHD appears to be lower with the use of T-cell depletion compared with posttransplant cyclophosphamide. Although the incidence of graft failure is approximately the same, use of G-CSF-stimulated donor bone marrow may be effective in reducing this risk in the posttransplant cyclophosphamide population. Ideally, a randomized trial would compare these innovative HCT strategies head-to-head, but there are significant impediments to the design and implementation of such a study.

### Reduced-Intensity Conditioning

The significant early and late toxicity of myeloablative conditioning remains a barrier to successful implementation of HCT for patients with SCD who have an available donor source. The use of conditioning regimens characterized as minimal-intensity or reduced-intensity offers the potential to ameliorate these toxicities, and make HCT available to patients with organ dysfunction that precludes

the use of fully ablative regimens. However, reduction in the myelosuppressive components of the conditioning regimen to spare toxicity leads to the need to include highly immunosuppressive elements in order to achieve engraftment, thereby increasing infection risk. Moreover, development of mixed chimerism between the donor and the recipient is an additional barrier introduced with this approach. Although there is clear evidence that a state of stable donor-recipient chimerism is adequate to achieve a disease-free state in patients undergoing HCT for hemoglobinopathies, mixed chimerism can be unstable and progress to late graft loss. Moreover, to salvage patients with low levels of donor contribution to hematopoiesis, therapeutic approaches such as rapid withdrawal of immunosuppression or donor lymphocyte infusions may be employed, carrying risks of GVHD. Unlike in HCT for malignant indications, GVHD provides no potential benefit for these patients, and can produce significant morbidity and mortality.

Early reports of reduced-intensity conditioning HCT for SCD produced mixed results. Although a case report of successful engraftment of a single patient receiving peripheral blood stem cells from a matched sibling donor after conditioning with fludarabine and cyclophosphamide alone was encouraging,<sup>25</sup> many subsequent single- and multi-institution studies have achieved limited success. One early report of 7 patients with hemoglobinopathies (6 with SCD) receiving matched sibling donor HCT after fludarabine, ATG, and 200 cGy of total body irradiation, provided an early indication of the complexity of the post-HCT management of these patients. Although 6 of these 7 patients achieved initial donor engraftment, this was followed by a state of mixed donor-recipient chimerism that eventually resulted in graft loss and autologous hematopoietic reconstitution in all patients.<sup>26</sup> Graft loss in these patients coincided with the taper of immunosuppression (consisting of a calcineurin inhibitor in all patients), suggesting a dynamic interplay between pharmacologic immunosuppression and donor/recipient lymphocytes. In a separate report, 2 of 3 patients with SCD receiving matched sibling donor HCT after a similar conditioning and GVHD prophylaxis regimen experienced graft loss.<sup>27</sup> A study of 10 adults with SCD receiving G-CSF–mobilized peripheral blood stem cells from a matched sibling donor after conditioning with alemtuzumab and 300 cGy of total lymphoid irradiation achieved engraftment in 9 of 10 patients with no GVHD.<sup>24</sup> Notably, GVHD prophylaxis consisted of sirolimus, with ongoing immunosuppression in all patients at the time of publication. The successful engraftment of the vast majority of adult patients—many of whom had multiple transfusion exposures—with this minimally intensive regimen is notable. The effect of sirolimus on

the post-HCT immunologic milieu is difficult to evaluate given a lack of a comparison group. However, given that similar regimens have failed to produce reliable engraftment in pediatric studies,<sup>26,27</sup> the choices of serotherapy and post-HCT immunosuppression likely have profound implications for successful allografting. A recent report of the long-term follow-up of these initial 10 patients, with 20 additional patients, supports that this conditioning approach can achieve engraftment rates comparable to myeloablative conditioning regimens (87%). In this extension study, the protocol was amended to permit discontinuation of immunosuppression in patients with T-cell chimerism below 50%, with persistence of mixed donor-recipient chimerism and no late graft failures or GVHD. This suggests that there is induction of tolerance between donor and recipient T cells.<sup>28</sup>

Inclusion of a stem-cell toxin—even at submyeloablative dosing—also influences engraftment potential. Using a busulfan-based regimen with fludarabine, ATG, and total lymphoid irradiation, with cyclosporine and mycophenolate mofetil as GVHD prophylaxis, 6 of 7 patients with SCD receiving matched sibling donor bone marrow transplant achieved stable long-term engraftment.<sup>29</sup> Similarly, Bhatia and colleagues reported 100% engraftment in 18 pediatric recipients of matched sibling donor grafts with a busulfan (myeloablative dosing), fludarabine, and alemtuzumab conditioning regimen.<sup>30</sup> The desire to eliminate busulfan as a component of the regimen to avoid the neurologic and hepatic toxicity seen with HCT after myeloablative conditioning has prompted the use of the alkylating agent melphalan in many contemporary protocols. In addition, the highly immunosuppressive serotherapy agent alemtuzumab provides protection against graft rejection and GVHD, and has been incorporated into multiple reduced-intensity conditioning regimens for nonmalignant disorders in general and SCD specifically.<sup>31,32</sup>

In a study evaluating 8 patients with SCD receiving either matched sibling donor bone marrow (n=7) or umbilical cord blood (n=1) grafts, patients were conditioned with a fludarabine and melphalan backbone plus either thiotepea or total lymphoid irradiation, and ATG or alemtuzumab. All patients converted to donor erythropoiesis, and three had stable leukocyte chimerism, with minimal regimen-related toxicity.<sup>33</sup> The success of this approach has led to the use of fludarabine, melphalan, and alemtuzumab in the ongoing Blood and Marrow Transplant Clinical Trial Network study of alternative donor HCT for SCD.

The development of reduced-intensity conditioning approaches to HCT for SCD holds promise for successful engraftment while avoiding many of the early and late toxicities of myeloablative conditioning. However, concern remains regarding the highly immunosuppressive

nature of many reduced-intensity conditioning regimens. These regimens carry the risk of infectious complications, as well as the development of unstable mixed chimerism that may progress to graft loss. In addition, the experience with reduced-intensity conditioning regimens is limited, and there has been considerable heterogeneity in the agents employed. HCT using myeloablative conditioning regimens has documented excellent outcomes in a large number of patients with SCD, with DFS rates in excess of 90%. Whether the better toxicity profiles seen in reduced-intensity conditioning regimens offset the risk of graft failure remains an area of controversy. Progress in approaches to salvage of patients with unstable chimerism and management of regimen-related toxicities will continue to influence decisions regarding the appropriate preparative regimens in these patients. As the role of HCT evolves and is increasingly considered in patients with less severe forms of SCD, there will be a growing emphasis on minimizing long-term toxicities, allowing a wider patient population to access this curative approach to SCD management.

### Late Effects of HCT in Patients With SCD

Clearly, undergoing HCT will result in secondary effects from the HCT. Walters and colleagues<sup>34</sup> reported on late effects of matched sibling donor HCT with myeloablative conditioning in children with severe SCD who underwent transplant. After HCT, patients with stroke who had stable engraftment of donor cells experienced no subsequent stroke events after HCT, and brain MRI scans demonstrated stable or improved results. After transplant, most patients also had unchanged or improved pulmonary function. There was, however, significant gonadal toxicity after HCT, particularly among female recipients.

Bodas and colleagues<sup>35</sup> recently performed a literature review for neurologic outcomes following myeloablative conditioning and HCT in patients with SCD. Eighty-one of the 196 (41%) patients transplanted with a matched sibling donor graft for SCD had a history of cerebrovascular abnormalities on imaging prior to HCT. Two patients in this cohort experienced transient ischemic attacks during or after transplant. Of the 45 patients who had post-HCT imaging, 71% had stable findings, 13% had improvements, and 16% showed progressive neurovascular abnormalities after HCT.<sup>35</sup> Patients who underwent neurocognitive testing showed a statistically nonsignificant trend toward improvement in IQ. The authors concluded that future studies looking at neurologic morbidity after HCT are warranted. However, the majority of patients had improvement or stabilization of their neurologic disease after HCT.

Dallas and colleagues<sup>18</sup> recently reported on patients who underwent matched sibling donor or haploidentical HCT at St. Jude Children's Research Hospital. By 5 years after HCT, no patient with sustained engraftment exhibited any clinical evidence of a stroke or progression on imaging studies. MRI showed improvement in white matter changes, and magnetic resonance angiography revealed stability of or even improvement in vessel abnormalities. TCD studies performed before and after matched related donor HCT showed a significant decrease in maximal velocity, from  $170 \pm 16$  cm per second to  $81 \pm 18$  cm per second ( $P=.001$ ). In addition, all TCD studies were normal at the last evaluation. Comprehensive neuropsychiatric evaluations were performed before and at 1, 3, and 5 years after HCT. The results confirm stable cognitive function after HCT, with no significant decreases in full, performance, or verbal IQ scores.<sup>36</sup>

HCT in general seems to limit the progression of organ toxicity from the natural course of severe SCD. However, future studies are needed to evaluate larger cohorts of patients in a systemized fashion.

### Summary

SCD can result in significant morbidity and early mortality for patients who have severe disease. This article summarizes the experience to date of curative approaches using allogeneic transplantation. The data are clear that matched sibling donor allogeneic HCT after myeloablative conditioning offers a cure for this disease and is accepted as standard of care. This modality should be offered to all patients with severe SCD prior to developing severe end organ dysfunction. Utilizing an alternative donor for transplantation and/or reduced-intensity conditioning for this disease is still under investigation. We must continue to perform clinical trials to optimize the best treatment for these patients. However, to date a minority of patients affected have been offered this opportunity.

### Disclosures

*The authors have declared no financial conflicts of interest.*

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