Hematopoietic stem-cell transplantation for sickle cell disease: current evidence and opinions

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Abstract: With rapidly expanding evidence of benefit reported by several groups, allogeneic hematopoietic stem-cell transplantation has become an acceptable treatment option for sickle cell disease. It is currently the only curative therapy available. Hematopoietic stem-cell transplantation was offered primarily as a therapeutic option for severe sickle cell disease in the context of myeloablative matched sibling donor transplants over the last two decades and helped to establish the benefits of transplantation for this disorder. While this approach provided proof of principle, the disadvantages and limitations of transplantation became evident along the way. It has been recognized that transplantation for sickle cell disease does not need to adhere strictly to the principles of transplantation for malignant disorders, such as achievement of full donor cell chimerism. As reviewed here, in recent years the transplant community has set out to explore ways to make stem-cell transplantation more available to patients with the disease, define indications and better timing, and offset toxicities with novel approaches to conditioning and better supportive care.

Keywords: hematopoietic stem-cell transplantation, sickle cell disease

Introduction

Sickle cell disease (SCD) is a genetic disorder that results from the substitution of glutamine to valine at the sixth position in the β-globin chain and is a result of a single nucleotide mutation. In the homozygous state, hemoglobin (Hb) SS disease results in significant morbidity in a large percentage of patients while the presence of a trait (Hb AS) renders protection from major manifestations. Disease symptoms and organ damage are also common, with hemoglobin variants such as Hb SC or Hb S-β thalassemia, though the age of onset and symptom progression may vary. Of these variants, Hb SS and $S\beta^0$ thalassemia are traditionally but not exclusively associated with the most severe symptoms. Patients with other Hb S combinations are often not spared and can be similarly affected.

Hemolysis and vascular obstruction due to red cell polymerization and recurrent endothelial damage is initiated by Hb S in deoxygenated states with resultant red cell distortion. Organ damage depends on the location and extent of endothelial injury and is attributed to hypoxia and inflammation resulting from chemokine upregulation and the induction of a hypercoagulable state [Franceschi *et al.* 2011; Hebbel, 2011]. The multifaceted injury makes targeted pharmacologic intervention complicated [Bunn *et al.* 2010]. Despite this, supportive care has advanced significantly, resulting in improvement in conservative management strategies. Management modalities that have made a difference include the use of hydroxyurea, extended phenotyping of transfused donor red cells to reduce alloimmunization risks, erythrocytapheresis to reduce iron overload in the chronic transfusion setting, and oral chelating agents. However, none of these intervention strategies are foolproof and disadvantages include the requirement for lifelong intervention, continued target organ damage despite treatment, and increased morbidity in the second and third decades of life with early mortality. Tracking studies have shown that while survival has significantly improved in childhood years, median survival remains at 40 years with predominantly cardiopulmonary reasons for mortality

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[Fitzhugh *et al*. 2010; Quinn *et al*. 2004, 2010]. In addition, 30% of patients with an initial stroke go on to develop second and even third strokes despite adequate transfusion therapy supporting ongoing vasculopathy not reversed by transfusions [Hulbert *et al*. 2011; Scothorn *et al*. 2002]. The cost and availability of medical resources for lifelong medical care is also to be considered. In a cost analysis review published in 2010, medical expenditure in children with SCD was 6–11 times (US$9,000 to US$13,000) higher per year than in children without SCD for Medicaid and private payers respectively. SCD-attributable medical expenditure in children in 2005 was US$335 million and is only expected to increase with time and age [Amendah *et al*. 2010]. Further, disease progression, organ involvement and sudden death can occur despite adequate supportive care measures.

Only successful hematopoietic stem-cell transplantation (HSCT) or gene therapy utilizing transduced autologous hematopoietic stem cells can establish either complete or partial normal erythropoiesis and result in a cure. Since gene therapy is still in the early phases of testing, HSCT is currently the only established curative treatment modality for SCD. HSCT can establish donor-derived erythropoiesis, and more importantly, can stabilize or restore function in affected organs such as the central nervous system (CNS) and lung and prevent further deterioration of function [Walters *et al*. 2010]. Though the benefits of HSCT are well established, complications associated with the procedure beg for continued investigation to make the procedure safer. Priority targets for improvement include HSCT-related organ toxicities, graft *versus* host disease (GVHD), graft rejection (GR) rates and donor availability. These efforts should proceed in parallel with other intervention and conservative supportive care trials to gain maximum benefit against the disease.

Toward expanding donor sources

For over two decades, transplantation was offered only to patients with severe SCD and only if a matched sibling donor was available. Though human leukocyte antigen (HLA) matched sibling donor (MSD) transplants offer the best outcomes for SCD, less than 14% of patients with SCD have such availability [Mentzer *et al*. 1994; Walters *et al*. 2001]. Our opinion is that this small group of patients with normal or trait-positive MSD can and should consider transplantation early in the disease process to optimize successful outcomes. This includes patients who have adequate sibling cord products available to them [Reed *et al*. 2001]. In the event of cord products with low cell dose, a combination of marrow cells from the same donor has been combined with the cord product to optimize engraftment [Walters *et al*. 2005]. This approach supports early HLA typing in patients with SCD and siblings. In the absence of a MSD, donor options include a matched (MUD) or mismatched unrelated donor (mMUD), an umbilical cord blood (UCB) product or a haplo-identical donor from the family. Each of these transplant approaches are associated with complications innate to the graft source and transplant approach used and include GR, GVHD and delayed immune reconstitution, each of which can result in unacceptable outcomes. In this setting, we feel that HSCT should be considered only in the presence of predetermined disease criteria in a study setting wherein toxicities are tracked closely and stopping rules apply if the risks of transplant outweigh the perceived benefits.

Transplant outcomes based on donor source have been described in malignant and nonmalignant disorders and are useful for the consideration of acceptable donor sources for SCD transplants based on outcomes. When transplant mortality and GVHD are used as outcome variables, an 8/8 (A, B, C and DRB1) HLA-matched marrow is comparable to a 5/6 (A, B, DRB1) matched cord. A 6/6 matched cord transplant has better outcomes than a MUD transplant. Cell dose is critical for a successful UCB transplant and engraftment rates and outcomes are better with higher cell doses (total nucleated count $\geq 5 \times 10^7$/kg), especially with UCB products mismatched at more than one locus [Eapen *et al*. 2007; Horan *et al*. 2012; Shaw *et al*. 2010]. Thus, a high-cell dose can trade off with HLA matching to some extent. Though GVHD rates are lower with UCB, GR risks are higher than with marrow or peripheral blood, presumably due to the naïve cells in the product. Center for International Blood and Marrow Transplant Research (CIBMTR) donor registry data suggest that when unrelated donor searches are restricted to high-resolution HLA matches at eight loci (A, B, C and DRB1) for bone marrow and 5–6/6 intermediate typing (class I) and high-resolution (class II) typing, and for cords, coupled with a good cell dose ($>5 \times 10^6$ CD34/kg), only about 30% of searches will be successful in the African population. UCB products are better utilized in the

pediatric age group due to cell dose restrictions [Adamkiewicz *et al*. 2006; Barker *et al*. 2010; Krishnamurti *et al*. 2003]. Based on CIBMTR data, an additional 30–40% of recipients of African origin will find one antigen or allele mismatched marrow donors in the registry. However, less optimum transplant outcomes are to be expected due to mortality and GVHD risks. Further mismatching is not acceptable given the high mortality rates associated with the more mismatched transplants. Minority donors are essential to improve the odds of finding suitable donors in registries for patients with SCD. In the absence of suitable related or unrelated donors, haplo-identical transplantation is emerging as a potential alternative option and is discussed later in this review.

Mobilized peripheral blood products have a higher risk of chronic GVHD with associated mortality, especially in children. For this reason, transplant protocols for nonmalignant disorders that use unmanipulated stem-cell products have preferred to use bone marrow, accepting the more involved process of obtaining this stem-cell product. Adult patients have had higher mortality following related donor peripheral blood stem-cell transplantation for severe aplastic anemia, and we feel may benefit from marrow as the stem-cell source, especially in nonmalignant disorders [Chu *et al*. 2011].

The course of the disease: defining indications and eligibility for hematopoietic stem-cell transplantation

In the USA, approximately 94% of children with Hb SS or Hb Sβ^0thal will reach 18 years of age. However, stroke-free survival rates decrease to 88.5% by adulthood [Quinn *et al*. 2004]. CNS involvement defined by overt stroke or high transcranial Doppler velocities are definitive indicators of continued risk for recurrent CNS events [Kwiatkowski *et al*. 2011]. The need for lifelong erythrocytapheresis to attempt to offset progression and the uncertainty that it will do so makes this a clear transplant indication. The incidence of overt stroke in SCD is 9% by 14 years of age [Ohene-Frempong *et al*. 1998]. Another 18% develop magnetic resonance imaging (MRI) changes consistent with silent cerebral infarcts by this age, a 27% rate of neurologic complications before adolescence [Kinney *et al*. 1999]. Up to 20% of children with previous strokes and cerebral vasculopathy experience second overt strokes within 5 years, despite adequate transfusion therapy [Scothorn *et al*. 2002]. New onset cerebral infarction (overt or silent) is noted in as many as 45% of chronic blood transfusion therapy recipients, underscoring the need for more effective interventions [Hulbert *et al*. 2011]. The cumulative risk of all cerebral disease by age 14 is 50%, making half the population with SCD neurologically compromised in one way or another by adolescence or early adulthood [Bernaudin *et al*. 2011]. The debilitating recurrent vaso-occlusive episodes are harder to define precisely for a transplant threshold but significantly impair quality of life [Dampier *et al*. 2011]. Other 'severe' disease complications include sickle nephropathy, avascular necrosis/osteonecrosis, silent strokes with cognitive impairment, priapism and red cell alloimmunization, especially in patients with a lifelong need for chronic transfusion therapy.

The average life expectancy despite modernization of supportive care has remained approximately 40 years for men and women with SCD over two decades [Fitzhugh *et al*. 2010; Platt *et al*. 1994]. Cardiopulmonary events, primarily acute chest syndrome (ACS) and pulmonary hypertension, were found in over 50% of the population who eventually died of the disease. Therefore, cardiopulmonary events contributed to comorbidity in high-risk patients [Fitzhugh *et al*. 2010; Gladwin *et al*. 2004]. Tricuspid regurgitation with jet velocities over 2.5 m/s measured as a precursor to pulmonary hypertension was noted in over 20% of children at a mean age of 6.2 years [Colombatti *et al*. 2010]. However, HSCT indications need to be weighed in the context of risk–benefit ratios for each of these indications, and donor availability and patient age (Table 1). Increasing age at transplant as well as suboptimal HLA matching increase risks of organ toxicity, GVHD, morbidity and transplant-related mortality exponentially. This is attributable to established organ dysfunction and comorbidities expected with age. HSCT indications hence remain a fluid paradigm based on the natural history of SCD (for example, the recognition of pulmonary hypertension as a prominent cause of mortality is relatively recent), newer transplant approaches and changing outcomes. With stringent severity criteria (CNS, pulmonary) about 16% of patients would qualify for transplant whereas approximately 38% would fit more extended criteria [Mentzer *et al*. 1994]. Extended criteria and mild disease symptoms may prompt consideration of MSD transplants early while we feel critically stringent criteria should be applied

Table 1. Indications for hematopoietic stem-cell transplantation balanced with donor availability: risk/benefit ratio considerations.

Matched sibling donor	Matched unrelated donor or minimally mismatched good quality cord product	Mismatched marrow donor, haploidentical donor
Stroke Elevated TCD velocity Acute chest syndrome VOE Pulmonary hypertension/ Tricuspid regurgitation jet velocity >2.5 m/s Osteonecrosis/AVN Red cell alloimmunization Silent stroke especially with cognitive impairment Recurrent priapism Sickle nephropathy	Stroke Elevated TCD velocity Recurrent acute chest syndrome despite supportive care Recurrent severe VOE despite supportive care Red cell alloimmunization despite intervention plus established indication for chronic transfusion therapy Pulmonary hypertension	Recurrent stroke despite adequate chronic transfusion therapy Inability to tolerate supportive care though strongly indicated, e.g. red cell alloimmunization, severe VOE and inability to tolerate hydroxyurea

AVN, avascular necrosis; TCD, transcranial Doppler; VOE, veno-occlusive episodes.

to high-risk transplants such as with mismatched or unrelated donors and with adult recipients. Since the validity of expanding HSCT indications are defined by outcomes to define risk–benefit ratios, in our opinion, expansion of transplant indications and donor options from the sibling to the unrelated/alternative donor should only be undertaken in a trial setting with careful follow up.

A caveat to the above argument is that HSCT has the best outcome when the recipient is at a good functional baseline prior to irreversible organ damage. This is at variance with the need to wait for the disease to declare itself in severity (i.e. consider transplant after organ damage is established), thus modifying transplant outcomes negatively. The dilemma faced with SCD is the absence of a good marker that predicts disease severity prior to established symptoms and the clinical variability in the time of onset and the eventual degree of morbidity from the disease. Attempts at defining early predictors of future severity using markers such as leukocytosis or clinical symptoms have proved largely inaccurate [Quinn *et al.* 2008]. This poses a unique problem in defining eligibility and ideal timing for HSCT. Currently, HSCT is often considered only after damaging symptoms are established, even in the MSD setting.

It is perhaps intuitive that the acceptability of transplant increases with patient age and with previous family experience with severe disease, as the travails of the disease are better known and influence decisionmaking. It is difficult for families to grasp the nature of transplant complications and this begs for multiple meetings and information sessions regarding disease and transplant options. When parents of children with SCD completed a questionnaire, 37% of parents were willing to accept HSCT as a treatment modality given a 15% mortality risk. Acceptance was only 13% if the 15% mortality risk was layered on a 15% GVHD risk [Kodish *et al.* 1991; van Besien *et al.* 2001]. In contrast, 63% of adult patients with SCD were willing to accept a mortality risk of over 10% and 20% were even willing to accept chronic GVHD over SCD manifestations while only 50% would accept infertility [Chakrabarti and Bareford, 2007].

Transplant trials: the evolution of hematopoietic stem-cell transplantation for sickle cell disease

Though the SCD population in the USA is over 72,000, only about 500 transplant procedures were reported in the CIBMTR database by 2011, over a span of 15 years. Of these, 85% were MSD transplants and 80% were in children less than 16 years of age. HSCT options have often remained below the radar due to anticipated complications and mortality. Patients with SCD receiving transplantation also have unique complications that need preventive measures, vigilant monitoring and timely intervention. Some of these include hypertension, hemorrhagic or ischemic strokes driven by vasculopathy, a lowered seizure threshold,

sinusoidal obstruction syndrome and progressive renal or pulmonary dysfunction.

Myeloablative transplant outcomes are best in the young (<16 years), especially with MSD transplants (marrow or cord stem-cell sources), likely due to the absence of comorbid conditions and organ decompensation [Bernaudin *et al*. 2007; Locatelli *et al*. 2003; Vermylen *et al*. 1998; Walters *et al*. 2001]. Conditioning has included busulfan-based myeloablative preparative regimens [such as busulfan, cyclophosphamide, with or without antithymocyte globulin, or antilymphocyte globulin with or without total lymphoid radiation (TLI)], avoiding radiation. Disease-free survival was over 80% and GR rates were low at 10% or less. More importantly, as disease parameters were followed long-term (2 or more years after transplant), most patients were relieved of pain, had no further strokes or ACS, had stabilized pulmonary function, and had stable neurologic and cognitive evaluations [Walters *et al*. 2010].

Though highly successful in achieving donor engraftment in children under ideal conditions, subsequent studies have sought to minimize transplant-related toxicities to be able to offer this intervention to larger numbers of patients, and utilize alternative donor sources in the absence of a sibling donor. Transplants in older patients and transplants with alternative stem-cell sources have had less success with a myeloablative transplant approach [Hoppe and Walters, 2001; Ruggeri *et al*. 2011]. The upper age bar could potentially be pushed into the second decade with reduced intensity conditioning if better tolerated and successful in the presence of disease-related organ toxicity. Even in the young, on cerebral imaging early post-transplant, new magnetic resonance angiography (MRA)/MRI changes were noted, especially in patients with previous MRI abnormalities (lacunae/infarcts). Patients with SCD were also more prone to develop CNS toxicity early post-transplant. Seizures, cognitive impairment and intracranial hemorrhage were common CNS toxicities (described in 23–50%), especially in the presence of pretransplant CNS involvement such as stroke [Fitzhugh *et al*. 2008; Kalinyak *et al*. 1995; Walters *et al*. 1995; Woodard *et al*. 2005]. If underlying vasculopathy is to blame, additional stressors such as toxicities from the conditioning and other medications, cytokine storm and engraftment syndrome, hemodynamic changes of HSCT and GVHD related complications add to the complex physiology. These effects are expected to be worse in alternative donor or mismatched transplants. Late effects of myeloablation, especially in the young, include growth failure, sterility, ovarian failure, poor spermatogenesis, poor performance, organ dysfunction and second cancers [Hingorani *et al*. 2008; Parsons *et al*. 2012; Rizzo *et al*. 2009]. Similar to advances in supportive care measures for SCD, transplant efforts targeting newer interventions are directed at improving safety and efficacy of HSCT, minimizing areas of risk, and making a curative intervention available to more patients.

Trials with minimal (nonablative) conditioning to offset toxicities were met with high rates of graft failure and recurrence of disease symptoms, though they were tolerated well [Horan *et al*. 2005; Iannone *et al*. 2003; Jacobsohn *et al*. 2004]. Since then, it has become apparent both in SCD and thalassemia that achieving stable mixed donor–host chimerism is able to establish a cure and predominantly donor-derived erythropoiesis can support a disease-free state even when other lineages are predominantly host derived [Hsieh *et al*. 2011; Krishnamurti *et al*. 2008]. Donor chimerism levels can vary over wide amplitude and can be as low as 11% [Walters *et al*. 2001]. In addition to chimerism status, the level of circulating Hb S is also determined by donor genotype. Recipients of HSCT from donors with sickle trait who had mixed chimerism (25% donor) had higher Hb S levels (36%) compared with those receiving transplants from normal donors (11% donor chimerism with Hb S levels of 7%). In both cases, however, the recipients were cured of the disease [Walters *et al*. 2001]. In thalassemia transplants, though mixed chimerism was noted in 74% and 34% of recipients at 1 and 6 months respectively, the incidence of secondary (late) GR at 1 year post-transplant was only 8% [Lisini *et al*. 2008]. The current era of transplant for SCD is exploring the following: reduced intensity conditioning to achieve stable donor engraftment with pretransplant immune suppression, for which mixed chimerism is considered acceptable [the Bone Marrow Transplant Clinical Trials Network Sickle Cell Unrelated Donor Transplant Trial (BMT CTN SCURT)]; infusing high doses of stem cells to achieve engraftment with minimal conditioning and inducing tolerance with rapamycin; post-transplant cyclophosphamide to offset GVHD for mismatched/haplo-identical transplants [Bolaños-Meade *et al*. 2012; Hsieh *et al*. 2009; Shenoy, 2011; Shenoy *et al*. 2005].

Since transplant trials in patients with SCD have demonstrated a fine balance between intensity of conditioning, stem-cell source and post-transplant immune suppression, fine tuning these aspects to achieve the right balance without increasing toxicity (death, GVHD, rejection) is work in progress and current transplant protocols are focused on styling treatment strategies to suit stem-cell sources. Regimens targeting immune ablation without myeloablation using combinations of alemtuzumab, fludarabine, melphalan or low-dose busulfan, TLI and cyclophosphamide have been successful in ameliorating disease [Krishnamurti *et al*. 2008; Shenoy *et al*. 2005]. A preliminary experience with 14 patients treated in a multicenter trial with a combination of alemtuzumab, fludarabine and melphalan (related or unrelated donor marrow) had an overall survival of 95% and an event-free survival of 79% in patients who were assessed at least 6 months post-transplant, with GR rates of 11% (S. Shenoy, personal communication, August 2012). This experience paved the way for a national trial supported by the National Heart, Lung, and Blood Institute (BMT CTN SCURT). This is a reduced intensity transplant trial of unrelated donor marrow transplantation for SCD in children less than 20 years of age with severe SCD. This trial accepts only fully (8/8 at A, B, C and DRB1) matched marrow donors to optimize outcomes, with strict stopping rules for death, GVHD and GR, and is designed to determine the benefits of unrelated donor HSCT for SCD. Many centers, including ours, offer this same treatment strategy to patients with matched related donors in a trial setting. The trial was closed to unrelated cord transplant recipients due to increased GR [Kamani *et al*. 2012]. Since cord transplants require higher intensity conditioning than bone marrow, patients with severe disease and unrelated well matched (5–6/6 antigens) cords (with an adequate cell dose which is critical) or allele mismatched marrow are being enrolled on an experimental protocol of reduced intensity conditioning (RIC), albeit more intensified. There is experience with this approach in a national study of unrelated donor transplantation for thalassemia using cord or marrow as the stem-cell source (the unrelated transplant for thalassemia trial [URTH] trial). Recently, total colony forming units have been identified a useful predictor of cord engraftment and may become the standard assessment of the future [Page *et al*. 2011]. Emerging data on double cord transplants may open yet another avenue of circumventing engraftment barriers with cords [Jiang *et al*. 2007]. *Ex vivo* cord cell expansion trials in myeloablative umbilical cord blood transplantation (UCBT) for SCD are underway and such manipulation may be a routine reality in the near future.

At the National Institutes for Health, a study using mobilized peripheral blood CD34+ stem cells from HLA MSDs has supported mixed chimerism after nonablative alemtuzumab and low-dose TBI-based conditioning with prolonged rapamycin post-transplant to induce tolerance in predominantly adult recipients (16–45 years), most importantly without transplant-related mortality [Hsieh *et al*. 2009]. Continued immune suppression was able to maintain mixed lymphoid chimerism status and a delayed rapamycin wean was planned only with full T-cell donor chimerism. Other trials of marrow transplants in adult patients are in early stages of exploration (L. Krishnamurti, personal communication, July 2012).

Another area of investigation has been haplo-identical HSCT from a family member. Though almost all patients with SCD are likely have a haploidentical donor, such studies in SCD have been lacking due to the risk of GVHD, rejection and poor immune reconstitution. Classic haplo-identical transplant protocols following marrow ablation based on the haplo-identical transplant experience for thalassemia has developed into a SCD transplant trial (M. Cairo, personal communication, October 2012). Another novel approach used haploidentical granulocyte colony-stimulating factor mobilized marrow as a stem-cell source and reduced intensity rabbit antithymocyte globulin, fludarabine, cyclophosphamide and low-dose TBI with higher dose cyclophosphamide post-transplant as GVHD prophylaxis. This approach has had early success, with engraftment in approximately half the patients transplanted, mainly adults (15–42 years), most importantly without mortality or GVHD [Bolaños-Meade *et al*. 2012]. This success in transplanting older patients with SCD contrasts with previous experience when SCD transplantation in adults was associated with high mortality [van Besien *et al*. 2000]. Reduced intensity HSCT with immunoablation now has the potential to extend this intervention to larger numbers of patients and it is our opinion that the risk of GR in this setting is more acceptable than mortality risks associated with more intense conditioning regimens. Transplant outcomes based on different transplant approaches are summarized in Table 2.

Table 2. Summary of transplant outcomes.

	Nonablative (MSD) [Horan *et al*. 2005; Iannone *et al*. 2003]	Nonablative (MSD) [Hsieh *et al*. 2009]	Reduced intensity (MSD + URD) [Krishnamurti *et al*. 2001; Shenoy *et al*. 2005]*	Myeloablative (MSD) [Bernaudin *et al*. 2007; Vermylen *et al*. 1998; Walters *et al*. 2001]	Cord blood (MSD) [Locatelli *et al*. 2003]	Cord blood (URD) [Adamkiewicz *et al*. 2004; Ruggeri *et al*. 2011]	Haploidentical [Bolaños-Meade *et al*. 2012]
Number	9	10	39	179	11	16	14
Age (years)	3.8–30	16–45	0.9–45	0.3–22	1–20	3–12	15–42
Stem-cell source	Marrow or PBSC	CD34 selected PBSC	Marrow	Marrow	UCB	UCB	Marrow
Conditioning agents	Flu, TBI, ATG	TBI, Al; Prolonged ongoing IS	Bu, Flu, Al, Mel, ATG, Cy	Bu, Cy, ATG/ALG, TLI/ alemtuzumab	Bu, Cy, Flu, TT	Bu, Cy, ATG/ALG, Flu, TLI/Al, TBI	Flu, Cy, TBI; post-transplant Cy
OS	9	10	38	90–100%	11	15	14
EFS	1	9	34	79–92%	10	9	8 (6 off IS)
Graft rejection	8	1	4	2–10%	1	7	6
Cause of death	–	–	Cerebral thrombosis	GVHD, infection, organ failure, CNS hemorrhage	–	GVHD	–

*Updated numbers.
Al, alemtuzumab; ALG, antilymphocyte globulin; ATG, antithymocyte globulin; Bu, busulfan; CNS, central nervous system; Cy, cyclophosphamide; EFS, event-free survival; Flu, fludarabine; GVHD, graft *versus* host disease; IS, immune suppression; Mel, melphalan; MSD, matched sibling donor; OS, overall survival; PBSC, peripheral blood stem-cell; TBI, total body radiation; TLI, total lymphoid radiation; TT, thiotepa; UCB, umbilical cord blood; URD, unrelated donor.

Future directions

Multiple efforts are underway to optimize transplant efforts for SCD. Improving HSCT outcomes and expanding transplant methods will widen the use of transplant for SCD and more patients can benefit from this intervention. A single transplant approach will not fit all. HSCT studies will require taking host factors (disease severity), age and donor selection process into consideration, with twin goals of safety and success in mind. The acceptability of adverse outcomes such as treatment-related mortality, GR and GVHD will continue to vary between groups, depending on the above variables. It is important from outcome and safety perspectives to perform SCD transplants and expand applicability in a trial setting. A multicenter team approach as opposed to individual centers pursuing different transplant methods is ideal. At individual centers, hematologists, healthcare staff, transplant teams, and patients/families need to work together to utilize transplant in a timely fashion in those who might benefit from this intervention.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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