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Curative therapies - allogeneic hematopoietic cell transplantation from matched related donors using myeloablative, reduced intensity, and non-myeloablative conditioning in sickle cell disease

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Abstract

Sickle cell disease (SCD) chronically damages multiple organs over the life time of affected individuals. Allogeneic hematopoietic cell transplantation (allo-HCT) is the most studied curative intervention. Fully matched related marrow, peripheral blood derived, or cord blood HCT have the best transplant outcome for symptomatic patients with SCD. For patients with asymptomatic or milder disease who have this donor option available, risks and benefits of HCT should be discussed among the patient, family, treating hematologist, and transplant physician, and decision to proceed to HCT should be individualized. Myeloablative conditioning with busulfan, cyclophosphamide, and ATG has been a commonly employed regimen for children and young adults. Recently, low intensity conditioning with low dose total body irradiation (TBI) and alemtuzumab is emerging as an efficacious and safe regimen for adults, young adults, and possibly children. Mixed donor chimerism (minimum ≥20%), from myeloablative or non-myeloablative conditioning regimen, produces robust normal donor erythropoiesis and is sufficient to provide a clinical cure. The proportion of patients remaining on immunosuppression beyond 2 years post-HCT is likely <10% with either myeloablative or low intensity regimens. Late effects from myeloablative or reduced intensity conditioning, or from several more months of immunosuppression in low intensity conditioning may also be similarly rare. Non-myeloablative approaches with low toxicities should be the focus of future research efforts. Prevention of GVHD is a shared goal in all approaches of allo-HCT in SCD.

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Sickle cell disease (SCD) is a monogenic, autosomal recessive disorder that repeatedly damages multiple organs over the life time of affected individuals. Clinical manifestations from injury to marrow (as vaso-occlusive crisis), spleen, vasculature, and brain parenchyma (stroke) occur in the first decade of life; injury to joints and vital organs (heart, lungs, liver, and kidneys) can be detected as early as in the second decade. While hydroxyurea, red cell transfusion, and iron chelation are the backbone in treating this disorder, allogeneic hematopoietic cell transplantation (allo-HCT) is the most studied curative intervention.

Myeloablative conditioning regimen

The first reported HCT in SCD was performed over 30 years ago in a child who had acute myelogenous leukemia (1, 2). While the HCT was performed for the malignant indication, the child was also cured of her SCD from a matched related donor (MRD) with hemoglobin (Hb) AS. This report demonstrated that SCD could be cured with HCT and that cure was achieved with a sickle trait (HbAS) allograft.

A small series of children and young adults in Belgium published a few years later expanded the literature on MRD allo-HCT, with a description of 12 patients with SCD who had to return to Africa and who would have limited access to optimal supportive care (3, 4). Some patients in this cohort had milder SCD phenotypes; all had MRD, eight of 12 donors had HbAS. Conditioning consisted of myeloablative doses of oral busulfan, intravenous cyclophosphamide, and thoracoabdominal radiation for older recipients. All were cured of their SCD, with one patient requiring a second HCT due to secondary graft failure. No patient had a SCD crisis post-HCT, with Hb electrophoresis levels reflective of donor type. Four of 12 developed grade I-II acute graft-versus-host disease (GVHD). A larger cohort of in Belgian HCT patients was later published with overall (OS) and disease-free survival (DFS) rates of 93 and 85% respectively (5, 6). These reports replicated earlier results indicating that allo-HCT can be curative in SCD and further validated the use of HbAS MRD allografts.

The Multicenter Investigation of Bone Marrow Transplantation for SCD resulted in a landmark publication in 1996, with several follow-up manuscripts describing outcomes of myeloablative MRD HCT in children and adolescents with busulfan, cyclophosphamide, and serotherapy (usually antithymocyte globulin, or ATG) (7, 8). Consensus eligibility criteria were established, many of which are still in use today. The OS and DFS rates were 91 and 73%, respectively. Updates on this cohort with additional subjects indicated OS of 93% and DFS of 85%. Deaths were usually due to GVHD, with 19% developing any GVHD and three deaths attributed to chronic GVHD. Five of the 50 subjects cured of SCD had mixed-donor chimerism, suggesting that full donor chimerism was not required for cure (9). Importantly, all recipients who had donor levels of hemoglobin S (HbS) were free of crises post-HCT and with stable cerebrovascular and pulmonary disease post-HCT.

The Société Française de Greffe de Moelle published results from a national registry in France, which has positioned MRD HCT as standard of care for symptomatic SCD in children and young adults (10, 11). ATG serotherapy was added to myeloabative busulfan and cyclophosphamide, resulting in an EFS of 95% since 2000, and no deaths in the latter 47

consecutive HCTs. Overall GVHD rates for the entire cohort of 87 patients were 20% for acute GVHD grades II-IV and 12.6% for chronic GVHD (2.4% extensive). Table 1 summarizes the experience with myeloablative HCT for children and young adults with SCD.

Matched Related Umbilical Cord Blood Transplantation

The first report using fully matched related umbilical cord hematopoietic cells for SCD was published in 1998 (12). Since then, >50 children have been transplanted using myeloablative conditioning (MAC). The OS was >90%, similar to the outcomes using marrow from MRD, and rates of grade IV acute or severe chronic GVHD were much lower (13, 14). In several children, umbilical cord blood cells were co-infused with marrow, with similarly successful results (15). In contrast, HCT results from unrelated/mismatched umbilical cord products were suboptimal (discussed elsewhere in this journal). The use of this cell source is likely limited, since the cell dose for umbilical cord products is fixed and may be low for larger/older children or adults, and using only fully matched related cord units does not help to expand the donor availability.

MAC with busulfan, cyclophosphamide, and ATG has produced the best HCT outcomes, with marrow or umbilical cord blood cells from MRD. This regimen is commonly employed in children and young adults with acceptably low rates of GVHD and transplant related morbidity.

Reduced intensity and non-myeloablative conditioning regimens

Although MAC HCT achieve high rates of OS and DFS for SCD, acute and late toxicities remain a concern for many patients and physicians. Of particular concern is the risk of infertility with busulfan and the increased risk of toxicities with myeloablation in older recipients (16). International registry data indicated that GVHD-free survival for HCT recipients over 16 years of age with SCD is only 77%, most of whom received MAC. With the already established high rates of cure with MAC in younger patients, fewer toxicities with reduced and low intensity regimens, and the aforementioned data showing mixed chimerism being curative in SCD, recent efforts have focused on HCT with less intensive conditioning protocols.

Several groups have described reduced intensity conditioning (RIC) strategies such as lower dose busulfan (8 mg/kg total) and fludarabine/low dose total body irradiation (TBI). While the former approach cured 6/7 patients, the fludarabine/200 cGy TBI approach was curative in only 1/6 children (17–19). A large series with RIC and MRD allo-HCT included 52 children with hemoglobinopathies, 43 of whom had SCD (20). The conditioning regimen consisted of early (day -21) alemtuzumab, melphalan and fludarabine and almost all recipients received bone marrow infusions, with one related umbilical cord blood allograft. The related cord blood allograft resulted in the only graft failure; rates of OS and EFS for those with SCD were 93 and 91%, respectively. GVHD outcomes were reported for all 52 subjects (including those with thalassemia major), with grade II-IV acute GVHD observed in 23% and extensive chronic GVHD in 13% of patients. All those with extensive chronic

GHVD were over 14 years of age. Three subjects died from GVHD. Of those with SCD and one year of follow-up, 32/46 had full donor chimerism. Additionally, ovarian preservation was reported with this regimen (21). While graft failure rates were low with this approach, rates of GVHD, particularly chronic GVHD in older recipients, could be improved.

The National Institutes of Health (NIH) developed a very low intensity non-myeloablative (NMA) regimen for adults with SCD using alemtuzumab (1 mg/kg total dose), 300 cGy TBI, and longer sirolimus exposure to prevent GVHD (22, 23). The stem cell source was G-CSF mobilized peripheral blood progenitor cells; all donors, including sickle trait donors, experienced expected side effects from G-CSF (24). Major ABO incompatible donations were excluded. One death was seen in a patient with graft failure who died of pre-existing moyamoya disease from SCD; another death occurred in the oldest patient (65 years-old) who developed pancytopenia four years post-HCT. OS and DFS were 94% and 87%, respectively, and there were no reports of acute or chronic GVHD. All had stable mixed donor chimerism, and the majority underwent successful weaning of sirolimus, with no GVHD thereafter. The University of Illinois at Chicago (UIC) replicated the NIH protocol in 13 additional adult patients, including two with major ABO incompatibility to their MRDs (25). All 13 survived with no acute or chronic GVHD. One subject had secondary graft failure with a history of sirolimus non-adherence, and 12/13 had mixed chimerism. This NMA regimen has recently been piloted in a small series of children with similarly encouraging results (26). Fertility preservation was also reported with this regimen (27), as in other NMA regimens (21, 28, 29). There are additional successful reports using other NMA regimen (30), but more data are needed to more accurately understand long-term fertility preservation post-HCT specifically for SCD, particularly with evolving, less intensive conditioning options.

Table 2 summarizes select RIC and NMA allo-HCT trials. These regimens with MRD have outcomes comparable to MAC. Recent replications of these successful results have garnered its acceptance not just in adults with substantial comorbidities, but also in younger patients with fewer SCD complications. The NIH regimen is emerging as an accepted regimen for adults or those with significant co-morbidities (31).

The general consensus amongst investigators studying HCT for children and adults with SCD, including the recently formed Sickle Transplant Alliance for Research, is that future research efforts should be aimed at reducing rates of GVHD while allowing for fertility preservation and long-term stability of donor chimerism with low toxicity conditioning approaches.

Indications for Transplant

The decision to proceed to MRD HCT for SCD must be carefully considered for each individual patient since the clinical course can be highly variable, even among affected siblings in the same family. The ability to predict an individual patient’s clinical course over time has proven difficult, as the presence or absence of clinical symptoms in the first few years of life do not predict outcome in the later years (32). Similar to other non-malignant conditions, the benefits and risk of HCT must be cautiously weighed against the alternative,

which is ongoing organ insult despite lifelong medical management. Risks and long-term complications of HCT have decreased over time but the median age of death for adult individuals with SCD has remained in the 4th to 5th decade of life (33, 34), and the comparative risk ratio vis-à-vis medical management has gradually shifted in favor of HCT. Along with advances in conditioning regimens, GVHD prophylaxis, and supportive care, all factors which contribute to the success and safety of HCT, indications for HCT have also evolved over time (Table 3). However, the risk-benefit ratio for each patient may need to be reassessed when long-term data from newer sickle-specific treatments become available.

In the early period of HCT for SCD, only patients with the most severe disease phenotypes were selected using well-defined organ-based criteria. Patient selection was meant to identify those at highest risk of complications, similar to HCT for β-thalassemia major where risk factors for severity of disease were developed and shown to predict outcome by the Pesaro group (35). In the absence of a uniform classification for disease severity in SCD, the Multicenter Investigation of Bone Marrow Transplantation for SCD published indications for transplant which included the presence of major complications such as stroke, recurrent acute chest syndrome, and recurrent painful vaso-occlusive crises (VOC). Other organ- based criteria included impaired neuropsychological function, sickle lung disease, sickle nephropathy, bilateral proliferative retinopathy, osteonecrosis of multiple joints and presence of at least 2 or more red cell allo-antibodies (7, 8). Many of these traditional criteria for HCT in SCD remain in use (36–38); other indications have been added to reflect the increased mortality with liver and pulmonary injury from SCD (Table 3). However, patients with extensive organ damage were often excluded from clinical trials.

As hydroxyurea (HU) emerged as an effective first-line treatment, a lack of clinical response to HU was incorporated as an indication (10), and remains a common selection criteria used in the present day (23). Multiple imaging modalities have also shown the ability to predict end organ damage, such as stroke and pulmonary hypertension, which have led to imaging-based criteria such as elevated transcranial Doppler (TCD) velocities, cerebral stenosis demonstrated on MRA, and elevated tricuspid regurgitant jet velocity (39, 40). Additionally, the transplant group in Cleveland, Ohio, analyzed their local cohort and a contemporary multi-center cohort of patients with SCD, and have proposed a risk stratification incorporating additional laboratory parameters (41, 42). Patient risk-factors include fetal hemoglobin (HbF) levels and genetic variants that modify HbF levels, such as *BCL11A*, which have been found to predict the clinical course in thalassemia and SCD to varying degrees and may be potential targets for assessing disease severity in future studies (43, 44).

When is the optimal timing for HCT?

In balancing the need for HCT in non-malignant disorders, timing is a critical factor. There remains a cautious approach in proceeding too quickly when a patient's disease has not manifested itself to justify HCT. Specifically, advocating to postpone HCT in children who have MRD until they reach adult age or become symptomatic has been proposed (47). This is justified by avoiding possible risk of mortality associated with HCT until the disease is more advanced. However, the consequence of delaying allo-HCT in children would result in accumulating end-organ injuries that lead to higher morbidity when undergoing

myeloablative allo-HCT as adults. In other words, the clinical manifestations which eventually qualify a patient for HCT may be the same factors that later compromise a successful outcome. Delaying HCT then contradict the intent for patient selection, which is to identify those at the highest risk of disease progression before end organ damage has already occurred. Ideally, HCT that has no transplant-related mortality could be offered at an earlier stage of disease when the patient is in better condition and has a higher chance of benefit.

There are several advantages of early intervention. The most important is that younger age has been associated with better outcomes in MAC HCT. The aforementioned Belgium group reported a subgroup of children with SCD transplanted early in life due to non-medical reasons, i.e. they had to return to their homes in Africa, and compared them to those who met conventional criteria (6). Patients in the early group were younger (median age of 2 years), had no or minimal symptoms from their SCD, and demonstrated better outcomes in engraftment, relapse, GVHD, and OS. Whether this effect was due to age alone or in combination with the absence of major symptoms was not determined. For many adolescent or young adults from sub-Saharan Africa who may relocate temporarily abroad for work or study purposes, this window of time also provides an opportunity to consider HCT before returning home (48). Separately, a recent analysis of two large databases (Center for International Blood and Marrow Transplant Research, CIBMTR, and Pediatric Health Information System) showed that children with SCD transplanted at <10 years of age utilized the healthcare system less than those transplanted at >10 years of age, with 30 days adjusted inpatient costs of $121,506 vs $128,731 respectively (49). In a contemporary study using pooled transplant data from CIBMTR, older transplant recipients also had worse transplant outcome. The 5-year OS was 81% for patients ≥16 years of age and 95% for patients <16 years; rates of chronic GVHD, 20% and 13%, respectively (16). The most common causes of death were infection, GVHD, toxicity, and hemorrhage – all transplanted related.

Secondly, because asymptomatic individuals often have subtle organ injury, the indications for HCT based on symptoms increase the risk-benefit ratio in patients labeled as ‘not yet transplant eligible’ (50). Vichinsky et al studied 149 adults with SCD and 47 community matched controls. Patients with SCD had poorer cognitive performance that were associated with the anemia and older age, but not related to changes in brain imaging (51, 52). Separately, a recent report from the NIH group showed that pre-HCT chronic pain persisted beyond one year post-HCT (53). These observations support early HCT, before development of irreversible organ damage or chronic pain. It is no surprise that the European Bone Marrow Transplant Working Parties recommended that young patients with symptomatic SCD who have MRD should be transplanted as early as possible, preferably before school age (36). Furthermore, offering allo-HCT to individuals with little or no symptoms from a non-malignant disease is not a major deviation from current practice. Allo-HCT has already been offered to children with asymptomatic or mild SCD. For example, the median age for those that received fully matched umbilical cord HCT was 6 years (13). Similarly, children with β-thalassemia major with little to no symptoms, i.e. Pesaro class I, have routinely undergone HCT using MRD with the understanding that their disease may progress with time (13, 36, 54).

For individuals with asymptomatic or mild disease (and presumed higher OS rate), whether and when to transplant should be discussed in the context of a low risk, highly efficacious allo-HCT regimen. The ethical considerations of such an approach have been explored in children with SCD and found to have clinical equipoise (55). The availability of safer HCT regimens further supports transplanting earlier, especially in children who have a longer horizon for quality of life years gained. For those with moderate or severe disease, the risk-benefit ratio clearly favors MRD HCT sooner. While the use of TBI raises concern for secondary cancer, regimens that use low dose TBI and have no GVHD post-HCT should make this risk very low and acceptable (56, 57).

Mixed chimerism: long term immunosuppression is not necessary for most patients

Mixed chimerism is defined as a state where the lymphohematopoietic system is comprised of a mixture of recipient and donor-derived blood cells after allo-HCT (58). In β-thalassemia major and SCD, stable mixed chimerism is sufficient to resolve disease-related symptoms and improve laboratory parameters (23, 25, 59). Stable mixed chimerism is also associated with lower rates of GVHD compared to full donor chimerism, in both malignant and nonmalignant hematologic diseases.

Stable mixed chimerism has been observed in 12-37% of SCD patients undergoing MAC allo-HCT with busulfan or treosulfan-based regimens (5, 9, 60). Younger age (<10 years-old) (9), the use of ATG (10), and using cord blood versus bone marrow as the graft source (13) were associated with more SCD patients achieving mixed chimerism after HCT. In these MAC regimens, donor chimerism values as low as 10–20% were sufficient to improve hemoglobin levels, HbS%, and SCD-related complications. Furthermore, no GVHD was observed in patients with mixed chimerism, compared to in 19% with full donor chimerism. In RIC or NMA regimens, developed to minimize HCT-related toxicity, mixed chimerism has been more commonly observed, and has been sufficient to improve the laboratory and clinical phenotype of SCD (17, 19, 20). An early concern was that the level of donor engraftment would decrease upon withdrawal of immunosuppression. This was observed in one study, in which five of six SCD patients were treated with a NMA regimen, and initially engrafted with donor chimerism values ranging from 25–85% at two months post-HCT. Improvements in Hb levels, HbS%, and SCD-related complications were observed during this period of mixed chimerism. However, when the immunosuppression was withdrawn (median day of withdrawal 120 days; range, 60–209 days), all patients had secondary graft failure (18). More recent regimens using a RIC approach have demonstrated stable mixed chimerism in 27–57% of SCD patients in which immunosuppression was successfully withdrawn after six months (17, 20). Erythroid lineage specific chimerism, determined by β-globin RNA pyrosequencing, was predominantly of donor origin and there was no evidence of SCD by the HbS% (17). Donor lymphocytes infused in three SCD patients, allowed one patient to reach full donor chimerism; none of the three patients developed GVHD (20). Consistent with the clinical data showing benefits with less-intense conditioning regimens, sickle transgenic mice treated with low-dose busulfan and co-stimulatory blockade (anti-CD40L or CTLA4-Ig) demonstrated stable mean donor white cell chimerism of 45% at 150

days post-HCT, red cell chimerism reaching 100%, and a phenotypic cure without histologic evidence of GVHD (61).

Other NMA HCT regimens have been developed for SCD patients to further reduce the HCT-related toxicity while taking advantage of the clinical benefits of stable mixed chimerism. Two adults undergoing HCT with a NMA fludarabine-busulfan based regimen had stable mixed chimerism with values of 26% and 47% at three months post-HCT. Both patients demonstrated donor levels of HbS% and the donor β- globin RNA values were 66% and 100%, respectively, consistent with high levels of donor-derived erythropoiesis (62). The NIH alemtuzumab-low dose TBI regimen has been utilized in three independent centers and demonstrated stable mixed chimerism in most patients (87–100%). Improved Hb concentrations, HbS%, markers of hemolysis, and cardiopulmonary function, were reported (23, 25). The UIC study also demonstrated improvement in many quality of life indicators starting from the first month after transplant. By 12 months, patients had achieved significantly higher scores in SF-36 parameters, including bodily pain, general health, vitality and social functioning. In all three centers, immunosuppression was administered for 12 months and tapered when the T-cell chimerism was >50%. To date, none of the SCD patients treated with the NIH regimen have experienced acute or chronic GVHD. A recent analysis and mathematical modeling of the minimal donor chimerism necessary to prevent return of SCD related complication showed the cutoff to be about 20% donor myeloid chimerism (63, 64). These observations of low donor chimerism being sufficient to improve the SCD phenotype were corroborated in murine studies. In lethally irradiated mice transplanted with varying ratios of donor transgenic and normal marrow, a myeloid chimerism >25% from the normal marrow was sufficient to restore the hemoglobin content to >90% normal (65).

When weighing the risks and benefits of allo-HCT, age, disease severity, toxicities of the conditioning regimen, expected rates of transplant related complications (including mortality), and expected rates of successful outcomes should be carefully considered (Table 4). In MAC regimens, the duration of immunosuppression was usually short, 3-6 months, except in 10-15% with GVHD. All received full doses of chemotherapy (e.g. busulfan and cyclophosphamide) with very low risk of secondary malignancy. In RIC regimens, one study reported 35% of patients with GVHD receiving immunosuppression ranging from 6 to 24 months, indicating more patients with longer exposure to immunosuppression (20). With NMA regimens (e.g. the NIH regimen,) no patients had GVHD, tapering immunosuppression began at 1- year post-HCT, and was discontinued in most patients (up to 88%). Taken together, the proportion of patients remaining on immunosuppression beyond 2 years post-HCT is likely <10% with myeloablative or low intensity regimens. Late effects (e.g. secondary cancer) from MAC, RIC, or from longer immunosuppression in NMA may also be similarly rare (57, 66, 67). The low-intensity regimens are then poised at reducing the duration of immunosuppression in the next iteration of studies.

Preventing GVHD in SCD is a shared goal

A recent HCT study reported results from 30 patients with matched unrelated donors (discussed in another section). At initial glance, the 1- and 2-year OS appeared acceptable at

86% and 79%; however, DFS were only 76% and 69%, respectively. Both acute and chronic GVHD were chiefly responsible for these low rates, with 23% mortality directly attributed to GVHD and additional transplant related toxicities (68). These results have had a sobering effect among patients, hematologists, and transplant physicians alike, and fueled an ongoing national debate about the true benefits of HCT in SCD. Prior experience using other MAC regimens had 15-20% GVHD (17, 69). In another study, the negative effects of GVHD showed a decrease in performance status below 90 post-HCT with a hazard ratio 1.74 (0.75-4.01) for acute GVHD and 1.67 (0.91-3.06) for chronic GvHD (49). These collective data predict a high likelihood of transplant related toxicities or mortality replacing SCD complications, and thereby worsen quality of life post allo-HCT.

There are ongoing studies comparing outcomes of allo-HCT to non-transplant best supportive care. Since adults undergoing any allo-HCT are more likely to develop GVHD, many patients and hematologists would easily conclude from these studies that HCT would lead to an inferior outcome and quality of life. This generalization omits the real culprit - myeloablative conditioning and GVHD being the key contributors of HCT related morbidities and mortalities. If a low intensity regimen with virtually no GVHD rate was chosen instead, the true benefit of HCT would be better represented, especially when reduction in GVHD has been demonstrated in NMA regimens with MRD. For matched unrelated or haploidentical HCT, clinical trials using NMA regimens are still warranted. Regardless of donor source or conditioning regimen, prevention of GVHD remains an essential goal in allo-HCT for SCD.

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Summary

1. Fully matched related marrow, peripheral blood derived, or cord blood HCT have the best transplant outcome for symptomatic patients with SCD. For patients with asymptomatic or milder disease who have this donor option available, risks and benefits of HCT should be discussed among the patient, family, treating hematologist, and transplant physician, and decision to proceed to HCT should be individualized.
2. Myeloablative conditioning with busulfan, cyclophosphamide, and ATG remains the most commonly employed regimen for children and young adults. RIC and NMA approaches should be the focus of future research efforts. Low intensity conditioning with low dose TBI and alemtuzumab is emerging as an efficacious and safe regimen for adults, young adults, and possibly children.
3. Conditioning and immunosuppression regimens with matched unrelated donor, mismatched umbilical cord blood, or mismatched family donor HCT should be studied in clinical trials because of the potential morbidity and mortality from GVHD and other transplant related complications (discussed separately in this journal).
4. Mixed donor chimerism (minimum of about 20% from donor myeloid cells), from myeloablative or non-myeloablative HCT, produces robust normal donor erythropoiesis and is sufficient to provide a clinical cure.
5. The proportion of patients remaining on immunosuppression beyond 2 years post-HCT is likely <10% in myeloablative or low intensity regimens. The late effects from MAC or RIC, or from longer immunosuppression in NMA conditioning may also be similarly rare.
6. Since MAC regimens are more toxic, and adults undergoing MRD HCT are more likely to develop GVHD, many patients and hematologists would generalize that MRD HCT leads to an inferior outcome and quality of life, compared to non-HCT best supportive care. Low intensity regimen with very low GVHD rates (<10%) would better capture the true benefit of allo-HCT in SCD.

Table 1

Myeloablative conditioning HCT for SCD

Authors	N	Median Age (years)	Conditioning	OS	Graft Rejection	DFS	cGVHD	TRM
Walters *et al* (2000)	50	9.4	Bu-Cy-ATG	94%	10%	84% @ 3 years	12%	6%
Bernaudin *et al* (2010)	144	9	Bu-Cy-ATG	95%	<2%	93% @ 3 years	10%	7%
Dedeken *et al* (2014)	50	8.3	Bu-Cy-ATG	94%	8%	86% @ 8 years	20%	<5%
Locatelli *et al* (2013)	160	–	Bu-Cy ± Thiotepa	–	<2%	90% @ 6 years	–	13%
Lucarelli *et al* (2014)	40	12	Bu-Cy-ATG ± Flu	91%	–	91% @ 9 years	<5%	7.5%
McPherson *et al* (2011)	27	8.6	Bu-Cy-ATG	96%	0%	96% @ 5 years	<5%	<5%
Vermylen *et al* (1998)	50	–	Bu-Cy ± TLI	93%	10%	85% @ 5 years	20%	–
Bhatia *et al* (2014)	18	8.9	Bu-Flu-Alemtuzumab	100%	0%	100% @ 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

Table 2

Reduced or Low Intensity Conditioning HCT for SCD

Authors	N	Median Age (years)	Conditioning	OS	Graft Rejection	DFS	cGVHD	TRM
King *et al* (2015)	43	13	Flu-Mel- Alemtuzumab	93%	<2%	91% @ 3 years	13%	7%
Hsieh *et al* (2014) and updated	52	29	TBI (300 cGy)- Alemtuzumab	94%	11.5%	88.5%	0%	0%
Saraf *et al* (2016)	13	30	TBI (300 cGy)- Alemtuzumab	100%	8%	92%	0%	0%
Ozdogu *et al* (2018)	20	33	Flu - Bu - Cy - ATG - TBI (200 cGy)	100%	0%	100%	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; Bu, busulfan; Cy, cyclophosphamide; ATG, anti-thymocyte globulin

Table 3

Commonly accepted indications for HCT in SCD

Each indication below has been associated with increased mortality, thus eligible for any types of HCT (with moderate to high risk of HCT related complications)
• Stroke or clinically significant neurologic event or deficit lasting >24 hr • 2 or more episodes of ACS in the 2-year period preceding HCT, despite supportive care (ie. asthma therapy, HU, and/or regular transfusion program) • 2 or more VOC per year in the 2-year period preceding HCT, despite supportive care (ie, HU, pain management plan, and/or regular transfusion program) • tricuspid regurgitant jet velocity ≥2.7 m/s on echo • regular RBC transfusion therapy (≥8 transfusions per year for ≥ 1 yr) to prevent vaso-occlusive complications (ie, VOC, stroke, abnormal TCD, or ACS)
Each indication below has been associated with substantial morbidity, thus eligible for low risk HCT. If 2 or more indications, then eligible for moderate risk HCT in the context of clinical trials
• Impaired neuropsychological function with abnormal cerebral MRI and angiography, Walters *et al* (2016)[38] • Sickle nephropathy (moderate or severe proteinuria, glomerular filtration rate 30 to 50% of the predicted normal value, or serum creatinine ≥1.5 times the upper limit of normal), Powars *et al* (1993)[45] • Sickle liver disease (direct bilirubin >0.4 mg/dL or ferritin >1000 ng/L), Feld *et al* (2015)[46] • Osteonecrosis of multiple joints • Red-cell alloimmunization during long-term transfusion therapy
Indications that have been largely replaced by the above criteria
• Bilateral proliferative retinopathy with major visual impairment in at least one eye • Stage I or II sickle lung disease

HU, hydroxyurea; RBC, red blood cell; VOC, vaso-occlusive crisis; ACD, acute chest syndrome; TCD, transcranial Doppler testing

Table 4

Risks and benefits of high to low intensity conditioning regimen with MRD

Myeloablative (e.g. Bu-Cy-ATG)	**Reduced Intensity/Toxicity**	**Low Intensity (e.g. 300 rads TBIalemtuzumab)**
• Full doses of 2 or more chemo combination • Mild to moderate disease • Children and young adults • Gonadal toxicity; infertility in all • 10-15% GVHD, 5-10% mortality • Mixed chimerism uncommon • Shortest course (<6 months) immunosuppression	• Reduced doses of 2 or more chemo combination • Mild to moderate disease • Children and young adults • Less gonadal toxicity; infertility in most • 10-15%GVHD, 5-10% mortality • Mixed chimerism uncommon • Shorter course (about 6-12months) immunosuppression	• Low dose chemo, antibody, and/or TBI combination • Any disease • Any age • Most potential for fertility preservation • 0% GVHD, 5-10% mortality • Mixed chimerism in majority • Longer course (about 12 months) immunosuppression