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“Hematopoietic Stem Cell Transplantation for Patients with Sickle Cell Disease: Progress and Future Directions”

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Synopsis

Considerable progress has been achieved in allogeneic hematopoietic stem cell transplantation (HSCT) for patients with sickle cell disease. Many studies have solidified matched sibling marrow, cord blood, or mobilized peripheral blood as the best source, with low graft rejection and graft versus host disease (GvHD), and high disease-free survival rates. For transplant eligible patients without HLA-matched sibling donors, fully allelic matched unrelated donor appears to be the next best option, though ongoing studies in sickle cell disease will provide data that are currently lacking. In general, unrelated cord transplant studies reported relatively high GvHD rates and low engraftment rates. Haploidentical transplants have emerged in the last decade to have less GvHD, but improvements are needed to increase the low engraftment rate. As there is no clear preferred choice, the decision to use unrelated cord blood units or haploidentical donors depends on the institutional expertise, and performed in the context of clinical trials. Data regarding 7/8 or lower matched unrelated donors are discouraging. Before routine use of these less matched donor sources, work is needed to improve patient selection, conditioning regimen, and/or GvHD prophylaxis.

Keywords

sickle cell disease; matched sibling donor; cord blood (CB) donor; haploidentical donor; matched unrelated donor

Introduction

The first reported bone marrow transplant for sickle cell disease (SCD) was published in 1984 in a child who had developed acute myeloid leukemia (AML).¹ She was ultimately cured of both and remains alive almost three decades later. This proof-of-principle report paved the way for a series of pilot studies also demonstrating that transplantation from HLA-matched sibling donors (MSD) could cure SCD.^{2–5} Later, the multicenter trial published by Walters et al in 1996 was instrumental in validating transplant as a bonafide treatment.⁶ In this landmark trial, 22 children with very symptomatic SCD underwent MSD marrow transplantation; overall and disease-free survival (DFS) estimates at four years were

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91% and 73%, respectively. Since then, the procedure has become safer and more effective. This success is evidenced by the 95% DFS in 44 patients undergoing refined transplant procedures after January 2000, as described by the French group.⁷

Traditionally, myeloablative conditioning was used in SCD transplants to maximize engraftment. Therefore, patients older than 16 years of age with significant sequelae of SCD, including considerable organ dysfunction, were often excluded. Today, less intense preparative regimens have made curative approaches available to adults. Increased rates of stable mixed chimerism are accepted as part of these less intense regimens because the red cell compartment is replaced with normal donor red cells, and symptoms of SCD resolve with time. The largest report to date of such non-myeloablative (NMA) transplantation was recently described where 30 adults safely underwent matched sibling transplant with an 87% DFS.⁸

Over the last 2 decades, there has been significant progress in transplantation using alternative sources such as umbilical CB units, haploidentical donors, and unrelated donors to make this curative procedure more accessible to those who are eligible.

Indications for Transplantation

Indications for transplant are either directed to patients requiring lifelong transfusion due to an increased risk of recurrent or primary stroke (stroke and elevated transcranial Doppler velocity), a significant impact on quality of life (recurrent vaso-occlusive crises, priapism, acute chest syndrome, osteonecrosis of multiple joints, and symptomatic silent infarct), difficulty maintaining transfusion therapy due to the difficulty in finding compatible units (red cell alloimmunization), or an association with increased mortality (TRV >2.5 m/s, sickle-related liver injury, iron overload, and sickle nephropathy). These indications are summarized in Table 1.

Patient Evaluation Overview

SCD-related complications are important to identify prior to transplant. Not only do they drive the decision for transplant, but they also serve as a baseline for peri- and post-transplant care. Thus in addition to standard transplant-related blood (including renal/liver parameters and transfusion-related infectious pathogens), lung, and cardiac testing, evaluations for SCD related end-organ injury should include the following:

- Brain MRI/MRA to establish the presence and extent of infarcts and vascular abnormalities
- Neurocognitive testing
- Echocardiographic estimate of pulmonary pressure (TRV)
- 6 minute walk test
- Consider right heart catheterization for suspected pulmonary hypertension

- Quantitative iron assessment including ferritin, liver biopsy (if possible) to assess the extent of inflammation, fibrosis, and quantitative iron, and/or cardiac and/or liver MRI for T2* measurements.
- Creatinine clearance estimation by nuclear GFR (typically in children)
- 24-hour urine collection for creatinine clearance and protein for adults: as patients with SCD often have serum creatinine of 0.6mg/dL or less, higher levels may indicate subtle or overt renal injury.
- Red cell phenotyping of the recipients and donors. The transfusion medicine department should be given ample time to store blood for patients who require difficult to match packed red blood cell units. Further, patients should be screened for donor-directed antibodies to minor red blood cell antigens due to the risk of pure red cell aplasia post-transplant, particularly in the NMA setting.⁸
- HLA-antibody testing of the recipients considering alternative donor transplantation. If donor-specific antibodies are detected, another donor may need to be identified due to the increased risk of graft rejection.^{9–11}

HLA-matched Hematopoietic Stem Cell Transplantation

HLA-matched sibling donor – myeloablative

The first transplant for SCD used bone marrow from a MSD for AML.¹ The preparative regimen consisted of cyclophosphamide 120 mg/kg over two days and fractionated total body irradiation (TBI) of 11.5 Gy. Graft-versus-host disease (GvHD) prophylaxis was a short course of methotrexate (MTX) and 28 days of methylprednisolone. The patient was cured of both diseases. At about the same time, thalassemia major had been reported to be cured by MSD bone marrow transplantation (BMT), and myeloablation was achieved using the non-radiation containing regimen of busulfan and cyclophosphamide (BuCy).^{12,13} In the late 1980's and early 1990's, a few case series of SCD patients undergoing myeloablative BuCy MSD BMT were reported, prompted by the successful outcomes using this approach in patients with thalassemia. The multicenter study published by Walters et al in 1996 demonstrated that the myeloablative BuCy approach could reproducibly achieve good outcomes (73% DFS) in severe SCD.⁶ With better supportive care and in a larger cohort of patients, the addition of rabbit ATG reduced the graft rejection rate from 23% (without ATG) to 3% (with ATG), as reported by Bernaudin et al in 2007.⁷ Many studies have now published the MSD BuCy + ATG regimen and overall survival and DFS ranges from 90–100 % and 77–100%, respectively (Table 2).

A few important points of this standard approach should be highlighted. Intravenous busulfan has largely replaced the oral route of administration to reduce the incidence of sinusoidal obstructive syndrome. Busulfan is usually given as 0.8mg/kg/dose for 16 doses over 4 days (or 3.2mg/kg once daily dosing), targeting steady state concentrations of 600–700ng/ml or area under the curve (AUC) of 900–1100 $\mu\text{mol}\cdot\text{min/L}$.^{14,15} Cyclophosphamide (50mg/kg/dose) is given daily for 4 days. Equine ATG (30mg/kg/dose for 3 days within the 4 days prior to transplant) or rabbit ATG (10–20mg/kg divided over 4 days, typically days -6 to -3) is included. GvHD prophylaxis includes cyclosporine for 180 days post-transplant

and a short course of MTX. CNS protective measures include maintaining a platelet count >50,000/uL, hemoglobin 9–11 g/dL, magnesium >1.6 gm/dL, aggressive antihypertensive management, and seizure prophylaxis while receiving busulfan and calcineurin inhibition.⁷

- Myeloablative transplants from MSD are mostly performed in children and young adults.
- Excellent DFS has been achieved through improvements in supportive care, conditioning regimen, and CNS protective measures in this standard transplant approach.
- Although the rates of graft rejection (5%) and mortality (5%) have reduced recently, further optimization to decrease the rate of GvHD can make this standard regimen even more successful.

HLA-matched sibling – reduced toxicity and non-myeloablative

As outcomes have been excellent with the myeloablative approach, investigators have attempted to offer transplant to previously excluded adult patients with SCD by using reduced toxicity (RTC) or NMA conditioning. Part of the premise is that achieving complete donor chimerism is not necessary as many patients have been reported to have SCD symptom resolution with a stable mixed chimeric state, an expected scenario with RTC and NMA regimens.¹⁶ Additionally, patients undergoing transplant may benefit from less intense conditioning, potentially leading to decreased problems with fertility and other transplant-related organ dysfunction. However, earlier RTC and NMA experiences utilized transplant regimens from hematologic malignant transplants, and their results showed excessive GvHD leading to death in one series, and graft rejection in another.^{17,18} These initial discouraging results prompted re-design of the conditioning regimen in SCD.

One such regimen was tested in 30 adult patients undergoing MSD peripheral blood stem cell (PBSC) transplants, conditioned with alemtuzumab, low dose TBI (300 cGy), and sirolimus.⁸ In this approach, alemtuzumab was chosen for in vivo T-cell depletion to prevent GvHD and rejection, TBI was increased to 300 cGy over the traditional 200 cGy to increase myelosuppression, and sirolimus was used for tolerance induction. Twenty-six of the 30 patients retained their graft resulting in normalization of their hemoglobin level and most importantly, the approach was well-tolerated without any GvHD. One patient died of intracranial hemorrhage after graft rejection. Although no patient achieved 100% donor chimerism in both T- and myeloid cells, sirolimus was discontinued in 15 of 26 engrafted patients. Promising studies of HLA-matched RTC/NMA transplant for SCD are summarized in Table 2. It is noteworthy that alemtuzumab was commonly included in several recent studies, and may contribute to the almost absent GvHD, mortality, and rejection rates. Further, high CD34 cell counts may help overcome the host versus graft barrier. The relatively small numbers and mixed chimeric state do warrant larger trials with extended follow-up. Longer follow-up would also allow exploration regarding whether RTC/NMA regimens are associated with less infertility and organ toxicity, compared to myeloablative transplants.

- Although the collective experience of RTC/NMA transplants is less robust than myeloablative transplants, their results have dramatically improved recently.
- RTC/NMA transplantation is gaining acceptance as a standard option for older adults or those with organ damage.
- As with MSD myeloablative transplants, T-cell depletion is an essential component of the RTC/NMA conditioning regimen.

Related umbilical cord blood transplantation

The largest CB transplant (CBT) study was reported by the Eurocord and European Blood and Marrow Transplantation (EBMT) group in 2013.¹⁹ Of 160 patients with SCD who underwent HLA-identical CBT or BMT, 30 received CBT. The 6-year DFS was 90% after CBT and 92% after BMT. Of all patients transplanted, those who received a CBT had significantly longer time to neutrophil and platelet engraftment as compared to those who underwent BMT ($p < 0.005$). However, no patients who received CBT developed grade IV acute GvHD as compared to 8 (2%) who received BM cells, and none of the CBT recipients experienced chronic extensive GvHD as compared to 5% of the BMT patients.

Studies have shown that MTX affected outcome in patients with SCD and thalassemia major who undergo related CBT.^{19,20} Patients who did not versus did receive MTX had DFS of 90% versus 60%, respectively ($p < 0.001$). Patients who received thiotepe also did better, though thiotepe did not influence outcome in multivariate analysis. The total nucleated cell (TNC) dose infused did not affect outcome in patients that received CBT, though median TNC count was adequate at 3.9×10^7 cells/kg.

Recent studies have reported a more robust neutrophil (17 versus 25 days, $p = 0.013$) and platelet (29 versus 48 days, $p = 0.009$) recovery in subjects who received CB along with bone marrow as compared to CB alone.²¹ Further, all 13 patients who received CB co-infused with bone marrow remained engrafted with a median follow-up > 5 years, with no acute grade 2 GvHD or chronic GvHD. A second study revealed long-term engraftment in all patients who received hydroxyurea prior to Bu, Cy, and ATG.²² Therefore, CB and bone marrow co-infusion as well as hydroxyurea treatment prior to conditioning appear to be viable options to explore further in young patients with HLA-MSD.

- Related CBT with mostly 6/6 matched units resulted in similar overall and disease-free survival but lower incidence of chronic GvHD, compared to HLA-MSD BMT (Table 2).
- Specific pre- and peri-transplant treatment used (e.g. hydroxyurea or MTX) affects CBT outcome.
- Co-infusion of CB and bone marrow may shorten duration of bone marrow recovery and improve CBT outcome.

Alternative Donor Transplantation

Donor availability

While MSD transplants are safer, there remains the inherent problem of donor availability. The likelihood of two siblings being HLA-identical is only 25%, and some siblings will have SCD, further limiting the chance of having a suitable donor. Therefore, the field has moved to investigate alternative donor sources. Improved outcomes for malignancy and immunodeficiency have already been described with matched unrelated donor (MUD), umbilical CB, and haploidentical transplantation techniques in the last two decades.^{23–26}

In one report from 2003 that evaluated searches done by the National Marrow Donor Program (NMDP), the chance of finding a potential 6/6 HLA MUD for a patient with SCD was approximately 60%.²⁷ In the same report, the chances of finding a 5/6 or 6/6 HLA-matched CB donor were approximately 62% and 30%, respectively. However, this matching was done at the serological level for HLA-A and -B and at the potential allelic level for -DRB1. A recent study with detailed matching demonstrated that the chances of finding a potential allelic 8/8 HLA-A,-B,-C and -DRB1 MUD was only 19%.²⁸ Combining 5/6 and 6/6 HLA-matched cords (HLA-A,-B antigen; DRB1 potential allele) with higher cell doses as needed for hemoglobin disorders (TNC count of at least 5×10^7 cells/kg) could increase the alternative donor option. When this was examined, the probability of a potential 8/8 MUD, 5/6 or 6/6 unrelated cord in SCD improved the chances, but they remained relatively low at 45%.²⁸

Matched unrelated donor transplantation

Due to the low chance of finding appropriate donors, MUD marrow transplants have not been performed in a sufficient number of patients with SCD. One report from Germany included 2 children who received fully matched MUD marrow transplant successfully.²⁹ Another report included 2 patients with 7/8 MUD and 4 patients with 4–5/6 matched unrelated CB units. Only 3 patients engrafted; 4 died of transplant-related complications, and the 2 patients that remained living had return of SCD.³⁰ The Sickle Cell Unrelated Transplant (SCURT) trial (BMT CTN 0601, NCT00745420) combined 8/8 MUD and myeloablative conditioning in children. The study has been open since 2008, and recently reached target accrual. Another study, Sickle Cell Transplantation to Prevent Disease Exacerbation (STRIDE, NCT01565616), has initiated accrual and will also evaluate 8/8 MUD marrow and myeloablative conditioning, but in adults age 16 to 40 years. These study results will provide useful information about this donor option for patients with SCD. In thalassemia major, earlier reports of MUD marrow transplants from 10/10 matched donors showed that patients with Pesaro Class 3 (higher severity) had a DFS rate of 55%, lower than 80% in less severe patients.^{31,32} A recent large study described in mostly Pesaro Class 2 patients, but allowed 1 allele HLA-mismatch donors, showed DFS rate of 96%, with 8% acute GvHD.³³ Having more Class 2 patients, using reduced doses of cyclophosphamide, and employing more current supportive care contributed to the better results reported in this recent cohort.

- DFS in MUD transplants for thalassemia major has improved recently, and the data from corresponding studies (SCURT and STRIDE) for SCD will be available soon.

- It may be reasonable to extrapolate the good DFS rate in 8/8 MUD transplants from thalassemia to SCD, but such donors are rare for patients with SCD.
- There are insufficient data in less than 8/8 MUD transplants; priority should be given to other donor options.

Unrelated umbilical cord blood transplantation

In contrast to the results in the related setting, unrelated CBT has been much less successful. The largest study includes 16 patients with SCD.³⁴ Nine of them received myeloablative regimens while 7 underwent RTC. While the overall survival was 94%, DFS was only 50%. The incidence of GvHD in the entire cohort of patients with SCD and thalassemia was reported as 22% acute grade 2–4 GvHD and 3% chronic extensive GvHD. There were additional reports that included small numbers of patients, and the results combined 6/6 with lower HLA matches. Some reports showed favorable results, but others had high rates of GvHD with low rates of engraftment (Table 2). Therefore, unrelated CBT for patients with SCD, even among recent reports, remains suboptimal and needs improvement.

There are additional considerations in unrelated CBT. Since TNC count is important, this source is better suited for children. Fully matched unrelated cord blood units are also rare for patients with SCD. Delayed platelet engraftment is typical with CBT and may lead to excessive morbidity due to the potential risk of bleeding in patients with red cell alloimmunization who require difficult to match red blood cell units or CNS vasculopathy with the risk of intracranial hemorrhage in the setting of prolonged thrombocytopenia.

- At this time, unrelated CBT has about 50% DFS, 20% acute GvHD, and 15% mortality (Table 2).
- Further studies exploring fully vs. less well matched CB, better chemotherapy combinations and/or improvement in GvHD prophylaxis are indicated to enhance outcome for unrelated CBT in patients with SCD.

Haploidentical donor transplantation

Since fully matched CB units are rare, and haploidentical donors are more accessible, a novel approach of using post-transplant administration of cyclophosphamide in haploidentical transplantation was first explored in preclinical models, and later tested in the hematologic malignant setting.^{35–37} Post-transplant cyclophosphamide, when given a few days after donor cell infusion, was shown to preferentially target and remove proliferating T-cells, which include alloreactive donor cells that lead to GvHD and host cells that mediate graft rejection. The largest study to date was reported by the Johns Hopkins group in 2012 where 14 patients, mostly adults, were transplanted.³⁸ While the rate of graft rejection was expectedly high in the setting of haploidentical donors, the sickle phenotype was completely reversed in 7 of the 14 patients. Additionally, one other patient exhibited a mixture of donor and recipient erythroid cells with severe anemia and sickle hemoglobin elevated more than would be expected in a subject with sickle cell trait. Six of the patients with complete donor chimerism have stopped immunosuppressive therapy, consisting most recently of sirolimus and a short course of mycophenolate. Amazingly, none of the patients developed acute or chronic GvHD, and all of the patients are living. In contrast, a pediatric study involving 8

patients using ex vivo T-cell depletion reported an overall survival of 75% and DFS of 38%.³⁹ Two patients developed grade 2 acute GvHD, and 2 patients died from chronic extensive GvHD.

- Similar to unrelated CBT, haploidentical transplantation has 43% DFS, 9% acute GvHD, and 9% mortality (Table 2).
- Post-transplant cyclophosphamide has dramatically improved the safety of haploidentical transplantation by lowering GvHD rate and transplant-related mortality.
- The addition of sirolimus in haploidentical transplants in recent reports is credited to the tolerance induction achieved in patients.

Timing and Preparation for Transplantation

Overall and SCD-free survival rates approaching 90% have prompted physicians to reconsider the methods and timing of treatment. The concept of transplantation earlier in the disease course was already being considered in the 1980's, as reported by investigators in Belgium.⁴⁰ In this study, 50 transplanted patients belonged to one of two groups: permanent residents of a European country who had already developed a severe sickle cell phenotype before transplant, or visiting patients who were transplanted much earlier in the disease course due to a desire to return to their country of origin. The combined rate of non-engraftment, mixed chimerism, and death was significantly higher in the more diseased group (25% vs. 7%, $p < 0.001$). While transplanting patients earlier in their disease course was controversial in the 1980's, current understanding of the devastating nature of SCD has led providers to accept early transplant in less severe patients, such as those with an elevated transcranial Doppler velocity.

In general, transplantation can proceed when patient's medical condition has stabilized, or sufficient time for recovery has elapsed to meet inclusion criteria (Karnofsky score, pulmonary function, etc.). Fertility potential after transplantation should be discussed, and sufficient time allowed for consultation with fertility specialists for testing and cryopreservation of oocytes or spermatocytes. For patients undergoing NMA transplantation, pre-conditioning with hydroxyurea for at least several weeks may be important to reduce recipient hematopoiesis to improve transplant outcome. Pre-conditioning is less of a concern for patients undergoing myeloablative transplants. All patients should undergo simple or exchange red cell transfusions to target HbS of 30% within 1 week of starting the conditioning regimen to minimize sickle-related complications peri-transplant.

Novel Therapies and Their Integration in Transplantation

Based on the combined studies thus far, active research is most necessary for unrelated CB and haploidentical transplantation to improve outcome. While the data in unrelated CBT have remained the same recently, results from the Hopkins group in haploidentical transplant showed no GvHD or mortality, giving enthusiasm for that donor source. The

major obstacle with both approaches remains graft failure, and there are efforts to optimize the transplant regimens.

In the haploidentical transplants, reduction of donor-specific HLA antibodies (DSA) is actively being investigated to improve engraftment.⁴¹ Their desensitization methods of plasmapheresis, IVIg, tacrolimus, and mycophenolate mofetil, starting 1 to 2 weeks before transplant conditioning, appears to be promising.⁴² Other strategies include rituximab and bortezomib.⁴³ Further, another ongoing study is evaluating whether tolerance induction using alemtuzumab and sirolimus as a backbone with escalating doses of post-transplant cyclophosphamide may decrease the risk of graft rejection in the haploidentical setting (NCT00977691).

Double cord transplantation is also being studied in hemoglobin disorders. The currently open trial (NCT00920972), which evaluates alemtuzumab, fludarabine, and melphalan conditioning, has strata dedicated to single and double cord transplants.

A limiting factor for CBT is cord size/cell dose. A study published from the Eurocord Registry, the Center for International Blood and Marrow Transplant Research (CIBMTR), and the New York Blood Center describing outcomes of unrelated cord transplants for hemoglobin disorders recommended a TNC count of at least 5×10^7 cells/kg for single cord transplants to maximize engraftment.³⁴ Such high cell doses can restrict cord options for patients, especially for adults. In the last few years a bevy of approaches expanded hematopoietic stem cells (HSCs) in the basic science lab and translated to clinical practice. The most impressive report to date described 31 adults with hematologic malignancy who received unrelated double umbilical cord transplants.⁴⁴ In this trial, one cord was co-cultured ex vivo with mesenchymal stromal cells prior to infusion, resulting in a 12-fold increase in TNC count and a 30-fold increase in CD34+ cell content. Neutrophil engraftment rate by day 42 improved in patients who received the expanded cord as part of their transplant (96%), compared to two separate control cohorts receiving unmanipulated double cords (83% and 78%). While the expanded cord contributed to hematopoiesis early on, the predominant donor-derived chimerism was from the unmanipulated unit in the majority of the patients at 1 year. This finding questions whether expanded units, despite having increased numerical cell doses, behave functionally similar to unmanipulated grafts of similar size and are capable of life-long engraftment. Preliminary data in transplants for malignancy have supported the NiCord® trial for SCD (NCT01590628), which is evaluating the use of double cord transplantation after myeloablative conditioning where one of the cord units is expanded ex-vivo with cytokines and nicotinamide.⁴⁵ The study is estimated to complete in 2015.

Gene Therapy

Autologous transplantation for hemoglobin disorders has only been considered in gene therapy trials. Clinical trials using lentiviral vectors to correct autologous HSCs have begun in France (NCT02151526) and New York City (Memorial Sloan Kettering Cancer Center, NCT01639690) for patients with thalassemia. Patients typically received close to myeloablative doses of busulfan to enhance the engraftment of genetically modified cells.

Patients achieving transfusion-independence have been reported.⁴⁶ A gene therapy trial for SCD is expected to begin enrollment soon.

Summary

Substantial progress in allogeneic HSCT has been made (Figure 1). These transplant studies can be summarized into the following key points, and applied to children and adults (Figure 2).

- Marrow, peripheral blood-derived, or cord blood progenitor cells from matched sibling/related donors offer the best results of transplantation.
- Fully matched unrelated marrow (8/8 or 10/10 allelic match) would likely be the next best option, as described in patients with thalassemia from 2 reasonably sized studies in different populations.^{32,33} There are insufficient data in SCD thus far, but the results from the SCURT trial (NCT00745420) should be available soon. This donor source is rare for patients with SCD.
- While fully matched unrelated cord blood units would appear to be the next reasonable option, no study directly compared fully to less well matched units.
- Haploidentical (or mismatched related) donors have emerged as a reasonable alternative. The data from a recent series showed better survival and lower GvHD rates.³⁸
- At this time, unrelated cord blood units are not clearly more preferable than haploidentical donors. The institutional expertise would dictate which source is better suited, and transplantation in the context of clinical trials would be preferable.
- Mismatched unrelated marrow (7/8 or less) in SCD to date is disappointing. This donor source should be studied only in the context of innovative clinical trials.

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Key Points

- Progenitor cells (BM, CB, or PBSC) from matched sibling/related donors offer the best results of transplantation.
- Although there are insufficient data in SCD, fully matched unrelated marrow would likely be the next best option. This donor source is rare for patients with SCD.
- No study directly compared fully to less well matched unrelated CB transplants. The combined data showed 50% disease-free survival, 20% acute GvHD, and 15% mortality.
- The data from haploidentical (or mismatched related) transplants have 43% disease-free survival, 9% acute GvHD, and 9% mortality. The institutional expertise would dictate whether haploidentical or unrelated CB is better suited; both should be performed in the context of clinical trials.
- Mismatched unrelated marrow (7/8 or less) in SCD to date is disappointing. This donor source should be studied only in the context of innovative clinical trials.

Figure 1.

Summary of allogeneic HSCT for SCD. Data for matched unrelated donor transplantation are currently not available. Acute GvHD includes grade 2–4, and chronic GvHD includes only extensive.

Figure 2.

Suggested priority in decision-making among transplant options.

Table 1

Indications for allogeneic HSCT in SCD.

Established indications	Potential indications for consideration
<ol style="list-style-type: none"> 1 Clinically overt stroke 2 Elevated transcranial Doppler velocity (>200m/s) 3 Frequent vaso-occlusive crises (2 hospital admissions requiring parenteral narcotics while on a therapeutic dose of hydroxyurea) 4 Recurrent priapism requiring medical therapy 5 Acute chest syndrome (1 episode while on a therapeutic dose of hydroxyurea) 6 Red cell alloimmunization (typically in MSD transplant) 7 Osteonecrosis of 2 or more joints (typically in MSD transplant) 	<ol style="list-style-type: none"> 1 Silent infarct with severe anemia and/or neurocognitive dysfunction 2 TRV >2.5 m/s 3 Sickle-related liver injury and/or iron overload (typically in NMA transplant) 4 Renal insufficiency (requiring dialysis, nephrotic syndrome, or biopsy proven sickle nephropathy; typically in NMA transplant)

Table 2

Summary of transplant studies to date

References	Donor source	Conditioning regimen	HLA match	Number of patients (age range)*	Disease free survival*	Acute GvHD (gr 2-4)*	Chronic GvHD (extensive)*	Number of deaths (%)*
7,14-16,22,39,47-49	Matched sibling**	Myeloablative	8/8 or 10/10	334 (1.2-27)	87% (290 patients)	17%	3%	5%
8,50-53	Matched sibling***	RTC and NMA	8/8 or 10/10	65 (1.8-65)	92% (60 patients)	5%	0%	2%
19,22,52,54-57	Related cord	Mostly myeloablative	Mostly 6/6	89 (1.8-20)	90% (80 patients)	8%	0%	9%
34,58-62	Unrelated cord	RTC and myeloablative	Mostly 4/6 and 5/6	41 (1-22)	49% (20 patients)	20%	7%	15%
38,39,63	Haplo	Mixed	Haplo-identical	23 (4.2-42)	43% (10 patients)	9%	9%	9%

* Disease free survival is an average of the total number of patients from all studies that were alive and without disease. The median follow-up time may be different across studies. Many references include subjects with SCD and thalassemia, matched sibling and cord blood sources. Rates of GvHD and death were estimated with the assumption that rates were the same for hemoglobin disorder type or graft source.

** Studies published after 2000

*** Studies published after 2005

RTC, reduced toxicity conditioning; NMA, non-myeloablative conditioning.