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Blood and marrow transplantation for sickle cell disease: Is less more?

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Abstract

Blood and marrow transplantation is a curative therapy for patients with sickle cell disease yet this is option seldom used. Clinical studies have shown however that children transplanted for this condition can achieve excellent results. In children with sickle cell disease transplanted following conditioning with busulfan, cyclophosphamide, and anti-thymocyte globulin, cure rates in excess of 80% can be obtained when an HLA-matched sibling is used as the donor. However, the large majority of patients with sickle cell disease will not have such a donor, or will not be able to tolerate high dose conditioning regimens. Therefore novel approaches such as non-myeloablative regimes, and alternative donors such as haploidentical, unrelated, or cord blood grafts are currently being explored in clinical trials. Recent reports on non-myeloablative conditioning (HLA-matched or haploidentical donors) highlight the safety and efficacy of these approaches with low mortality and high efficacy suggesting that in the near future non-myeloablation could be the preferred type of conditioning and donor availability will not be a barrier anymore to proceed to transplant. This review will focus on the results obtained when bone marrow transplants are used to treat sickle cell disease and will discuss the results obtained with these novel approaches.

Keywords

Sickle cell disease; bone marrow transplant; graft-versus-host disease; alternative donors

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Conflict of Interest

None.

Introduction

Sickle cell disease (SCD) kills nearly half a million people annually. In 2010 there were more than 300,000 newborns with SCD (1). In the United States, SCD is the most common inherited blood disease affecting nearly 100,000 children and adults. The annual cost for medical care for SCD patients in the United States exceeds 1 billion dollars. For adults with SCD the average annual cost of medical care exceeds 35,000.00 US dollars per year (2). Survival of patients with SCD has improved in developed countries due to the improved supportive care, judicious use of blood transfusions, prophylactic antibiotics, and drug therapy with hydroxyurea. Despite these advancements, most adults and many children develop a chronic debilitating condition, with over 30% of adults on disability and over 50% of patients unemployed (3). Median survival is shortened by more than two decades and quality of life is severely impacted due to complications of chronic pain, narcotic dependence, stroke, renal failure, thrombosis, pulmonary hypertension, blindness, priapism, and infection.

Allogeneic blood and marrow transplantation (BMT) can cure SCD; however, BMT is seldom used for these patients due to perceived toxicity and lack of suitable donors. As of 2013, there were 1238 BMT for SCD reported to the CIBMTR and EBMT-Eurocord (4). In 1984, Johnson et al., reported a successful bone marrow transplant (BMT) of a child with leukemia and SCD who was cured of both disorders (5). This was followed by several reports of myeloablative allogeneic BMT from matched sibling donors for children in SCD (6;7). These data firmly established that SCD is a potentially curative disease following myeloablative allogeneic BMT from a healthy HLA matched sibling donor. Unfortunately, BMT is only available in developed countries. Even in these countries, there are numerous obstacles such as donor availability, transplant related morbidity and mortality, and engraftment difficulty in patients with SCD, that limit the availability of BMT to only small percentage patients (8;9). The past decade has witnessed dramatic improvements in improving safety and expanding the donor pool for patients in need of BMT. This review will focus on the indications, the outcomes, and recent in advances for expanding donor pool for patients with SCD.

Indications for BMT

Indications for BMT in patients with SCD continue to evolve and clearly there is no consensus about these (Table 1)(10). The majority of the published series report on highly symptomatic SCD with advanced disease (7;8;11;12). Until recently, virtually all BMT in SCD was performed in children using myeloablative conditioning and matched related sibling donors. This meant that parents of patients with SCD were often put in the difficult position of making the final decision. Now that non-myeloablative conditioning regimens and HLA-haploidentical donors are showing success in children and adults with SCD, the indications continue to evolve and adult patients are now able to sign consent forms (9;13). Most pediatric hematologist agree that stroke or silent cerebral infarction is an absolute indication for children with SCD, especially given recent data showing that red cell exchange transfusions are not as effective as previously thought in preventing secondary

vascular events (14). Recurrent acute chest syndrome or frequent vaso-occlusive crisis despite hydroxyurea with good compliance are also considered to be good indications for BMT in children. Others feel that all symptomatic children with SCD be transplanted as soon as possible if they have a fully matched HLA-sibling donor. In adult patients common indications have included cerebrovascular disease, recurrent vaso-occlusive crisis despite hydroxyurea, osteonecrosis, red cell alloimmunization, and recurrent acute chest syndrome (9;13). While pulmonary hypertension is a known cause for morbidity and mortality in these patients, there is no agreement on whether should be used as indication to proceed to transplant and at least in one study these patients were excluded (13). The indications for BMT in children and adults with SCD will continue to evolve as the availability of alternative donors, engraftment rates, and safety of BMT increases. Some degree of renal dysfunction should not be seen as a reason to avoid transplant (given the use of nephrotoxic drugs such as calcineurin inhibitors or fludarabine), however, data on patients transplanted for this indication on renal replacement therapy is very limited (15).

Patient and family perspectives

Regardless, all patients and families of patients with symptomatic SCD should be educated about the potential risks and benefits BMT at an early age since BMT is the only proven cure for SCD. At the same time, physicians may not be aware of the perceptions that SCD patient have of BMT. Chakrabarti and Bareford surveyed thirty adult patients with SCD about their feelings towards receiving a reduced intensity BMT for the management of their disease (16). Sixty-two percent were willing to accept a ten-percent transplant related mortality and a third of patients even a thirty-percent transplant related mortality. Most patients, 62%, were willing to accept a 10% risk of graft failure, fifty-percent were willing to accept infertility, but only 20% considered chronic graft-versus-host disease acceptable. In fact, 60% of those surveyed would consider joining a clinical trial of reduced intensity BMT. These authors conclude that SCD patients are willing to consider the option of BMT despite the morbidity and mortality associated with the procedure.

High dose chemotherapy in sickle cell disease: early experiences

Historically, myeloablative conditioning regimens have been used to condition SCD patients for BMT (see Tables 2 and 3). In 1993, Bernaudin et al. published their results on 15 children with severe SCD transplanted with bone marrow from HLA identical siblings (6). At BMT, mean age was 8 years and 7 months. Donors were hemoglobin AS (n = 11) or AA (n = 4). Conditioning regimens employed busulfan and cyclophosphamide with or without anti-thymocyte globulin (ATG) or total lymphocyte irradiation. Graft-versus-host disease prophylaxis included cyclosporine and metothrexate. Median follow-up was 28 months. Ten patients engrafted with stable complete donor chimerism; 4 patients had mixed chimerism.

In 1996, Walters et al. published a series of 22 children with SCD conditioned with ATG (or alemtuzumab), cyclophosphamide and busulfan and transplanted bone marrow grafts from HLA-identical donors (7). All patients were younger than sixteen and had “advanced” disease (history of stroke, recurrent acute chest syndrome, abnormal brain imaging, retinopathy, bone disease, etc). With a median follow-up of two year 90% of the patients

survived and 72% had stable chimerism. The graft-rejection rate was low (13%). Neurologic events were relatively common and included seizures and stroke as well as 2 deaths due to stroke.

Vermylen et al. reported on fifty pediatric patients with SCD transplanted (48 bone marrow and 2 cord blood) in Europe (17). Overall survival was over 90% at eleven years. Acute graft-versus-host disease was present in twenty patients and one patient developed acute myeloid leukemia. Of these 50 patients, 36 had severe disease that met consensus criteria for BMT; 14 had less severe disease and were transplanted because they decided to return to their country of origin. In the 36 patients with more severe SCD overall survival, event-free survival and disease-free survival at 11 years was 88, 76 and 80%, respectively. Outcomes were slightly better for the less symptomatic and less transfused cohort of 14 patients. Gonadal dysfunction was present in all patients transplanted close to or after puberty.

In 2000, Walters et al. published on another group of fifty patients with symptomatic SCD transplanted between 1991 and 1999(11). Again all were young (less than fourteen years of age). Overall survival was 94% and there was an improvement in pulmonary and neurological parameters in many patients. Of 26 patients that had at least 2 years of follow up, 22 had stable engraftment.

Panepinto et al. reported outcomes after myeloablative BMT from HLA-matched sibling donors in 67 patients with SCD transplanted between 1989 and 2002 as reported to the Center for International Blood and Marrow Transplant Research (18). The most common indications for transplantation were neurological events and recurrent vaso-occlusive crisis in 38% and 37% of patients respectively. The median age at transplantation was 10 years and 67% of patients were heavily transfused before transplant. Busulfan and cyclophosphamide based regimens were used in over 90% of patients and bone marrow was the most common source of stem cells. Sixty-four of 67 patients are alive with 5-year probabilities of disease-free and overall survival of 85% and 97% respectively. Nine patients had graft failure with recovery of sickle erythropoiesis and eight patients had recurrent sickle-related events.

Locatelli et al. analyzed outcomes of 485 patients with thalassemia major (n=326) or SCD (n=159) receiving HLA-identical sibling cord blood transplantation (n=96) or BMT (n=389) (19). All patients received busulfan-based regimens and a majority received ATG. With a median follow up of 70 months, disease-free survival in the SCD patients with bone marrow and cord blood was 92% and 90%, respectively. Disease-free survival at 6 years was 92 +/ −2% in patient with SCD. These studies demonstrate that BMT or cord blood from HLA-matched sibling donors following a myeloablative conditioning regimen in children with SCD is highly successful. Overall survival is expected to be over 90% with cure rates over 80%(12).

High dose chemotherapy in sickle cell disease: current standard of care

Bernaudin et al. reported a large group of patients transplanted for SCD using HLA-matched sibling donors (12) and demonstrated that the addition of ATG to the conditioning regimen improved engraftment. All patients had severe SCD with neurological complications as the

main indication for BMT (bone marrow in 74 cases and cord blood in 10). The conditioning regimen consisted on cyclophosphamide, busulfan. ATG was added to the conditioning regimen because of a high incidence of graft failure in the first 12 patients. Overall, the rejection rate was 7% (22.6% before and 3% after ATG). Overall survival was 93% (median follow up 6 years). This group developed a strict protocol for prevention of neurological complications post BMT involving the use of clonazepam starting with busulfan and continuing for as long as the patient was taking cyclosporine, control of arterial hypertension, maintaining hemoglobin levels over 9mg/L and platelets over 50×10^9/L.

Given these results, HLA-identical sibling BMT after myeloablative conditioning should be considered the standard of care for children and young adults with severe SCD.

Non-myeloablative BMT

Non-myeloabative conditioning regimens have several theoretical advantages over myeloablative regimens in patients with SCD. First, patients with SCD, especially adults, often have significant end-organ damage (renal, pulmonary, liver etc). Nonmyeloablative regimens are less toxic; thus, children and adults with mild to moderate end organ toxicity would still be eligible for BMT. Second, most nonmyeloablative regimens do not lead to gonadal failure. Lastly, acute toxicity with nonmyelablative conditioning regimens tends to be less. A potential drawback off non-myeloablative conditioning is a higher rate of graft failure and mixed chimerism.

Jacobsohn et al. studied 13 pediatric patients with non-malignant disorders who underwent a reduced intensity BMT from an HLA-matched sibling (20). Three out of 4 patients with hemoglobinopathies rejected the graft. These findings have been duplicated in other small studies. Horwitz et al. reported the outcome of two adult patients (age 21 and 27 years, respectively) with SCD (one with end-stage renal disease) that received a fludarabine-based non-myeloablative BMT from HLA-matched sibling donors (15). Both patients achieved full donor erythroid chimerism with normal blood counts and were able to discontinue immunosuppression.

In 2009, Hsieh et al. has published the first highly successful series of nonmyeloablative BMT from matched sibling donors in adults with SCD (9). Conditioning included alemtuzumab, a single total body irradiation dose of 300cGy, and oral sirolimus. Twenty-three patients have been reported, with ages ranging from 17 to 64 years (median 28). All are alive at 2 months to 7 years post BMT. The graft consisted of unmanipulated G-CSF mobilized peripheral blood progenitors obtained from 8/8 HLA-matched siblings. Three patients engrafted temporarily but lost their grafts between the 2nd and 3rd months post-transplant and had recurrent SCD. Twenty patients engrafted with mean myeloid chimerism of 97.5% (median 89%) and CD3 chimerism of 42% (median 49%). In 17 patients at 1 year or more post-transplant, 5 had CD3 chimerism >50% which allowed complete withdrawal of immunosuppression and they have maintained stable mixed chimerism. No engrafted patient to date has developed any evidence of acute or chronic GVHD. These data suggest that non-myeloablative conditioning followed by HLA-matched sibling donor BMT can lead to high level engraftment and alleviate signs and symptoms of SCD. A drawback of this approach is

that only 5 of the 20 engrafted patients (25%) have been able to discontinue immunosuppressive therapy. Another drawback is that fewer than 10% of patients screened were able to proceed to BMT due to lack of a suitable HLA-matched sibling donor. A recent update from this group shows continued success (21). The authors screened 287 patients with SCD for matched sibling donors and were able to transplant 30 (10.5%) patients. A total of 26 patients (87%) engrafted donor leukocytes and had no acute or chronic graft-vs-host disease. Fifteen of these disease-free patients are no longer receiving immunosuppression medication. The mean donor T-cell chimerism level was 48% (95% CI, 34%–62%) and myeloid chimerism level was 86% (95% CI, 70%–100%). Four patients had temporary engraftment and then developed recurrent sickle cell disease; 1 of these 4 with a history of stroke and moyamoya disease died following an intracranial hemorrhage. The 43% of patients with elevated tricuspid regurgitant velocity experienced a mean decrease from2.84m/s (95%CI, 2.71–2.99) to 2.33 m/s (95% CI, 2.14–2.51) at 3 years, suggesting that BMT can abate pulmonary damage from SCD. The importance of this confirmatory trial is that it demonstrates that adult patients with severe sickle cell disease should be considered for BMT.

Alternative donors

While bone marrow transplantation is an effective therapy to cure SCD, the large majority of patients will lack an HLA identical sibling donor. In fact, Hsieh et al. reported that out of 112 patients referred to their study, they were able to find HLA matched potential donors for only 24, and of these 4 were excluded for ABO incompatibility (9). Therefore it is clear that donors other than HLA matched siblings are needed if BMT is to be more widely used to treat SCD. Unrelated BMT are seldom performed for SCD (22). This is because the majority of patients with SCD in the US are African-American and less than 20% of African-Americans can find MUDs in the registry. As of now, the published data using unrelated donors is very limited. Kharbanda et al. for example recently published on 2 children with SCD undergoing an unrelated BMT, both died (22). However, the Blood and Marrow Transplant Clinical Trials Network has a study open (BMT CTN 0601) addressing this issue (clinicaltrials.gov NCT00745420). This study is exploring the use of unrelated donors on patients receiving a non-myeloablative conditioning. This study is of great importance given the lack of data on BMT for SCD using unrelated donors.

Mismatched Cord blood transplantation

The use of cord blood as a stem cell source has potential to expand the donor pool; however, to date, results of cord blood BMT in SCD has been disappointing.

Adamkiewicz et al. reported on seven children with SCD and stroke (HLA match 4/6 n=5; 5/6 n=2)(23). Four patients received myeloablative conditioning regimens. One had primary graft failure, 3 engrafted, two with grade III–IV GvHD (one died, one developed chronic GVHD), and one with stable mixed chimerism. Three patients treated with reduced-intensity regimens failed to engraft. In fact, graft failure continues to be such an important issue on patients receiving cord transplants that the BMT CTN 0601 study closed its cord blood arm due to excessive graft failures (63%)(24).

Ruggeri et al. published the results from registry data of 16 children receiving cord blood transplants for SCD (25). Overall survival and disease-free survival were 94% and 50%. Primary graft failure was the main cause of treatment failure occurring 7 children. They found that the cell dose correlated with outcome and that only cord units with a cell dose of >5 × 10(7)/kg should be considered for transplantation for patients with SCD.

Recently the results of the umbilical cord arm of BMT CTN 0601 were reported (24). Eight children with severe SCD underwent unrelated donor cord blood transplantation (CBT) following alemtuzumab, fludarabine, and melphalan. Cyclosporine or tacrolimus and mycophenolate mofetil were administered for GvHD prophylaxis. Donor/recipient HLA match status was 6 of 6 (n = 1) or 5 of 6 (n = 7), based on low/intermediate-resolution molecular typing at HLA -A, -B, and high-resolution typing at -DRB1. Median recipient age was 13.7 years. The median pre-cryopreservation total nucleated cell dose was 6.4×10^7/kg, and the median postthaw infused CD34 cell dose was 1.5×10^5/kg. All patients achieved neutrophil recovery. Three patients who engrafted had 100% donor cells by day 100, which was sustained, and 5 patients had autologous hematopoietic recovery. Two patients developed grade II acute GvHD. Of these, 1 developed extensive chronic GvHD and died of respiratory failure. With a median follow-up of 1.8 years, 7 patients are alive, and 3 of 8 are alive without graft failure or disease recurrence. Based upon the high incidence of graft rejection after unrelated donor cord transplant enrolment on this arm was closed and continues on the unrelated donor arm.

Cord blood transplants for patients with SCD is only recommended in the setting of clinical trials and should not be considered standard for these patients.

Haploidentical donors

The use of HLA-haploidentical donors has enormous potential to expand the donor pool since parents and children are guaranteed to share at least 1 haplotype. Moreover 50% of full-siblings and 50% of half-siblings will share one haplotype. Historically, results of HLA-haploidentical BMT in patients with hematologic malignancies was associated with transplant related mortality in excess of 50%(26;27). However, the use of post-transplantation, high-dose cyclophosphamide for GvHD prophylaxis, has markedly improve the safety of HLA-haploidentical BMT (13;28;29). In fact, this approach has been used in both malignant and benign conditions with similarly encouraging results.

Researchers at Johns Hopkins published their initial results using haploidentical donors (13). The regimen consisted of antithymocyte globulin, fludarabine, cyclophosphamide, and total body irradiation, with GvHD prophylaxis with post-transplant cyclophosphamide, mycophenolate mofetil, and tacrolimus or sirolimus. They transplanted 17 out of 19 referred for BMT, demonstrating that the use of HLA-haploidentical donors markedly improves the donor pool for patients with SCD and makes BMT more widely available. Of the 17 SCD patients, 14 received transplants from HLA-haploidentical donors and 3 from HLA-matched related donors. Median age was 30, with a range of 15 to 46. Eleven patients engrafted including 6 patients that achieved full donor chimaerism (all haploidentical) with the rest being mixed chimeras. At the time of the report, the median follow-up was 711 days

(minimal follow up 224 days), 10 patients were asymptomatic, and 6 patients were off immunosupression. There was no mortality and no GvHD requiring treatment. The main problem was that 43% of the haploidentical transplant patients experienced graft failure. In an attempt to improve engraftment without increasing toxicity, the investigators modified the protocol for the last 3 patients to use growth factor primed bone marrow grafts. Of the three patients receiving the growth factor primed donor grafts (all haplo donors) two engrafted achieved full donor chimerism. Several groups world-wide have adopted this approach but their results have not been published at this time.

HLA-haploidentical BMT is becoming widely used for other indications due to proven efficacy and low toxicity. In sickle cell disease the approach clearly expands the number of potential donors. Enrollment in clinical trials exploring this option is encouraged.

Long term follow up

Walters et al. published recently long-term follow up on their group of patients transplanted for sickle cell disease (30). Gonadal dysfunction is a common complication of these patients. On their study, Walters et al. reported that 77% of males had low testosterone, and 30% had abnormal LH and FSH. In females, 57% developed ovarian failure, but 2 patients were able to give birth. Brachet et al. reported on gonadal function for 30 children with SCD who underwent BMT (31). They all received busulfan and cyclophosphamide. Seven out of 10 girls had ovarian failure and required estrogen replacement. Three out of 10 girls recovered some ovarian function with spontaneous pubertal development, menses, and 1 successful normal pregnancy. FSH serum levels were very high during spontaneous puberty and slowly normalized thereafter in these 3 patients. All boys showed spontaneous pubertal development. However, most of them had small testis and elevated serum FSH levels and in the 2 males tested, one had oligospermia and 1 azoospermia. While similar reports are not available for patients undergoing non-myeloablative transplants for sickle cell disease, patients receiving transplants with conditioning similar to the one reported by Bolaños-Meade et al. have preserved fertility when transplanted for hematologic malignancies (32). In this regard it appears that non-myeloablative regimens may have a benefit over myeloablative conditioning regimens. Other patients have been able to have children post BMT after ovarian autografting, allografting, and hormonal manipulation (33–35). Therefore, while fertility preservation seems an achievable goal in patients receiving non-myeloablative transplants this issue requires detailed discussions with the patient (and parents if still underage) to be sure that the potential outcomes are reviewed and there is an understanding about the possible loss of fertility of the patient. As far as pulmonary function, most patients had stable pulmonary function post-BMT. Those who had normal pulmonary function testing pre-transplant were likely to remain normal. After BMT, patients with stroke who had stable engraftment experienced no subsequent stroke events after BMT, and brain magnetic resonance imaging exams demonstrated stable or improved appearance. Therefore it appears that successful BMT abates end-organ damage of SCD as both neurologic and pulmonary function was preserved.

Conclusion

BMT is the only potential cure available for SCD. The cure rate in children using an HLA-matched sibling donor following a myeloablative conditioning regimen is over 85%. Unfortunately, most sickle cell patients in need of a BMT are not eligible due to an inability to tolerate myeloablative conditioning or and lack of a matched sibling donor. Moreover, gonadal failure is a major drawback of myeloablative regimens. This explains why fewer than 1300 transplants for SCD have been recorded in BMT registries around the world. Thus, in order to make BMT more widely available to patients with SCD, it is essential to develop safe, non-myeloablative conditioning regimens and to make use of alternative donors while limiting transplant related morbidity and mortality from GVHD. The recent reported success of non-myeloablative, HLA-haploidentical BMT with post-transplant cyclophosphamide is encouraging and promises to greatly improve the potential donor pool for patients with severe SCD; however, improvement in the engraftment rate to over 75% before this approach is more widely applied.

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Practice points

- Patients with severe SCD (particularly those with neurologic complications) should be offered BMT.
- Patients should be enrolled in clinical trials when possible.
- The best results are obtained in children offered busulfan, cyclophosphamide, and ATG and fully matched sibling donors, but this approach is not available to most patients with SCD. However, non-myeloablative regimens (experimental) may be less toxic while effective.

Research agenda

- Current transplant strategies are exploring the use of non-myeloablative conditioning regimens, given that these are less toxic.
- Exploring the use of alternative donors, such as haploidentical, unrelated, and cord blood is of paramount relevance for the treatment of SCD (clinicaltrials.gov NCT00745420, NCT02013375, NCT00152113, NCT01461837, NCT00977691, and of course NCT00489281).
- Non-myeloablative HLA-haploidentical BMT is now feasible for SCD; it markedly expands the donor pool, but improved rates of engraftment will be necessary for more widespread use of this approach.

Table 1

Common indications to proceed with BMT.

Indications for BMT	
Commonly accepted	Stroke/cerebral ischemia
Frequently accepted	Recurrent acute chest syndrome
	Frequent vaso-occussive/pain crises
	Red cell alloimmunization
	Osteonecrosis

Table 2

Results of selected BMT reports using different strategies for allogeneic transplantation in patients with sickle cell disease: myeloablation and non-myeloablation.

	Myeloablative matched				Non-myeloablative matched
	Walters (11)	**Vermylen (17)**	**Bernaudin (12)**	**Panepinto (18)**	**Hsieh et al. (9)**
Number of patients	26	50	87	67	30
OS	94%	96%	96%	96%	96%
EFS	84%	82%	91%	85%	87%
TRM	6%	7%	7%*	0	0
Graft failure	10%	10%	7%	13%	13%**
Ages	3–15	1–23	2–22	2–27	17–65
Acute GvHD	3	20	17	8	0
Chronic GvHD	2	10	11	13	0

*Estimated at 5 years.

**3 patients required a second BMT, 2 engrafted after the second.

OS: overall survival; EFS: event-free survival; TRM: transplant related mortality; GvHD: graft-versus-host disease.

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Table 3

Results of selected BMT reports using different strategies for allogeneic transplantation in patients with sickle cell disease: myeloablation and non-myeloablation.

	Alternative donors		
	Cord	**Cord**	**Haploidentical non-myeloablative**
	Ruggeri (25)	**Kamani (24)**	**Bolaños Meade (13)**
Number of patients	16	8	17
OS	94%	87%	100%
EFS	50%	25%	57%
TRM	6%	13%	0
Graft failure	43%	63%	43%
Ages	Median 6	Median 13	15–46
Acute GvHD	11*	2	1
Chronic GvHD	10*	1	0
Comments	Retrospective registry study	High rejection rate	Small prospective study

* The report does not specify if the patients who developed GvHD had thalassemia or sickle cell disease or a mix.