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Blood and marrow transplantation for sickle cell disease: Overcoming barriers to success

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Abstract

Purpose of the review—Sickle cell disease (SCD) is a common health problem in the United States yet the only curative therapy (a bone marrow transplant) is seldom applied. The objective of this report is to review the most recent clinical trials involving blood and bone marrow transplantation (BMT) for SCD and to discuss novel approaches to overcome the many barriers to successful use of BMT for SCD.

Recent findings—In selected patients, disease-free and overall survival is greater than 80% following matched sibling BMT for SCD. Unfortunately, most patients with SCD do not have a suitable HLA-matched sibling donor. In an attempt to expand the donor pool several groups are beginning to explore the use of alternative sources of stem cells such as haploidentical donors and umbilical cord cell blood.

Summary—The curative potential of bone marrow transplantation in sickle cell disease is irrefutable, outstanding results in children following a myeloablative conditioning regimen and a matched sibling donor transplant. Safe and effective application of alternative sources of stem cells for BMT in SCD could greatly increase the cure rate for this devastating disease.

Keywords

sickle cell disease; bone marrow transplantation; umbilical cord transplantation; haploidentical bone marrow transplant

Introduction

Hemoglobinopathies such as sickle cell disease (SCD) and β -Thalassemia major cause substantial morbidity and mortality. SCD affects nearly 100,000 people in the United States. BMT from a non-affected donor, usually a human lymphocyte antigen (HLA) matched sibling, is the only known curative therapy(1–4). The indications for BMT in patients with SCD are not well established but selection criteria have been proposed. Ideally, patients

should be < 16 years old, have an HLA-identical related donor and have at least one of the following signs or symptoms: stroke or central nervous system event lasting more than 24 hours, acute chest syndrome, recurrent severe pain episodes, impaired neuropsychological function with an abnormal magnetic resonance imaging scan, stage I or II sickle lung disease, sickle nephropathy, bilateral proliferative retinopathy, osteonecrosis of multiple joints, or red cell alloimmunization during long-term transfusion therapy(1). The majority of the series published so far report on patients with advanced disease that meet the above criteria(1;2;4). However, sickle cell patients, their family and their physicians are often reluctant to pursue BMT due to the inherent risk of morbidity and mortality from BMT. Even a relatively low mortality rate following BMT may be difficult to accept in a child with SCD given that the average life span for SCD is now over 40 years of age. Chakrabarti and Bareford surveyed thirty adult patients with SCD about their feelings towards receiving a reduced intensity BMT for the management of their disease(5). Interestingly, sixty-two percent were willing to accept a ten-percent transplant related mortality and a third of patients were willing to accept a thirty-percent transplant related mortality. A similar number, sixty-two percent accepted a ten-percent risk of graft failure. Fifty-percent were willing to accept infertility, but only twenty-percent considered chronic graft-versus-host disease as an acceptable alternative. Overall, sixty percent of those surveyed would consider joining a clinical trial of reduced intensity BMT. These results suggest that many SCD patients are willing to accept relatively high toxicities for a potentially curative therapy.

High dose chemotherapy in sickle cell disease the old and the new

In 1988, the first successful BMTs specifically for SCD were reported(6) and in 1996, Walters et al published the first “large” series of BMT for SCD(1). Twenty-two children with SCD received an HLA-identical sibling BMT after receiving busulfan, cyclophosphamide and anti-thymocyte globulin or alemtuzumab based regimens. All patients were less than sixteen-years-old and had “advanced” disease (history of stroke, recurrent acute chest syndrome, abnormal brain imaging, retinopathy or bone disease, etc). Ninety percent of the patients were alive after 2 years of follow up and 72% had stable chimerism. Graft-rejection was low (18%); however, neurologic events including seizures and cerebral hemorrhage occurred in 7 patients.

In Belgium, Vermynen et al., reported on fifty patients with SCD who received an HLA-matched sibling BMT using bone marrow (48 patients) or cord blood (2 patients) after conditioning with busulfan and cyclophosphamide based regimens (some patients also received total lymphocyte irradiation or anti-thymocyte globulin)(3). In these fifty patients there two groups: Group I included 36 patients with symptomatic SCD fulfilling the criteria that were discussed earlier, and Group II included fourteen patients with asymptomatic disease (less than 3 transfusions of red cells). Median age at time of BMT was 7.5 (range 0.9 to 23) years, and the probability of survival was 93%. Acute graft-versus-host disease occurred in twenty patients and one patient developed acute leukemia. Group II had better outcome than Group I (overall survival of 100 vs. 88% and event-free survival of 93 vs. 76%).

Walters and colleagues published an additional fifty patients with symptomatic SCD transplanted between 1991 and 1999(2). These patients received matched sibling bone marrow grafts after conditioning with busulfan and cyclophosphamide and either anti-thymocyte globulin or alemtuzumab. The median age in this trial was 9.9 (range, 3.3 to 15.9) years. Overall survival was 94%, event-free survival was 84% and an improvement in pulmonary and neurological parameters was observed. One patient died from an intracranial bleed and 2 died from complications of chronic graft-versus-host disease. There were five cases of graft rejection.

More recently, Bernaudin et al., reported results of 87 patients transplanted for SCD(4). Neurological complications were the main indication for BMT. Stem cells were harvested from bone marrow in 74 cases and from cord blood in 10 patients, bone marrow and cord blood in 2 cases, and peripheral blood stem cells in 1 case. The conditioning regimen consisted of cyclophosphamide and busulfan; however, anti-thymocyte globulin was added to the conditioning regimen after the first 12 cases due to a high rate of graft failure (4 out of 12 cases). After the addition of ATG, the rate of graft failure was just 3%. Overall survival was 93% at 6 years. This group developed a strict protocol for prevention of neurological complications after BMT involving the administration of clonazepam starting on day - 8 and continuing for as long as the patient remained on cyclosporine. The investigators kept tight control of arterial hypertension, transfused red cells to maintain a hemoglobin levels over 90 g/L, and transfused platelets to maintain a platelet count greater than $50 \times 10^9/L$. Based on the results of this relatively large study, the authors concluded that HLA-identical sibling BMT after myeloablative conditioning should be considered the standard of care for children with SCD.

The Center for International Blood and Marrow Transplant Research reported outcomes after myeloablative BMT from HLA-matched sibling donors in 67 patients with SCD transplanted between 1989 and 2002(7). The most common indications for BMT 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 BMT. Twenty-seven percent of patients had a poor performance status at transplantation. Ninety-four percent received busulfan and cyclophosphamide based regimens and bone marrow was the most common source of hematopoietic 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.

In summary, results of HLA-matched sibling BMT following a myeloablative conditioning regimen for children with SCD are encouraging. The risk of graft failure is 5–10%, the risk of acute GVHD is 15–20%, the risk of chronic GVHD is 10–20% and overall and event-free survival are roughly 90% and 80%, respectively. A brief summary of the outcomes can be seen in the Table.

Reduced intensity preparative regimens

Due to end-organ damage from SCD (e.g, pulmonary, renal, hepatic etc.) there is great interest in performing reduced intensity BMT for SCD. Successful application of this approach would make more SCD patients eligible for BMT, since end-organ toxicity often excludes patients from myeloablative conditioning regimens such as busulfan/cyclophosphamide. Unfortunately, the risk of graft failure following reduced intensity BMT for SCD is very high. Jacobsohn et al studied 13 pediatric patients with non-malignant disorders who underwent a reduced intensity BMT(8). A uniform preparative regimen consisting of fludarabine, busulfan, and anti-thymocyte globulin was used. The 1-year overall survival was 84%, but 3 of the 4 patients transplanted for a hemoglobinopathy rejected their graft. These findings have been duplicated in other small studies(9;10). Nevertheless, Horwitz et al., reported the outcome of two adult patients with SCD who received a fludarabine, total body irradiation, alemtuzumab and cyclophosphamide conditioning regimen followed by transplant of peripheral blood stem cells(11). The transplants were successful in both cases and at 20 months no graft-versus-host disease was diagnosed in either patient.

Long-term side effects

Late side-effects are another concern for patients undergoing BMT for SCD. Since these transplants are usually done in children, the effects on growth and development are relevant. Eggleston et al., reported on the effect on growth of BMT in fifty-three children with SCD(12). In these patients, growth was not affected unless the transplant was carried out near the growth spurt of adolescence. Another cohort of children reported by Brachet et al., was followed after for growth and gonadal function after BMT for SCD (13). There were no problems with growth; however, gonadal function was severely compromised. Only three out of ten females were able to sustain ovarian function (menses and pubertal development); one successful pregnancy was reported. All males had normal pubertal development, but all had small testis and most had increased follicle-stimulating and luteinizing hormone levels, as well as low to normal testosterone levels. Two males had a spermogram; one had oligospermia and one had azoospermia. The study by Bernaudin et al., also failed to show any growth abnormalities after BMT for SCD, but did show a significant number of females having ovarian failure, and only five out of seventeen girls had spontaneous puberty(14). They also reported no secondary malignancies.

Other benefits derived from transplantation

Mixed chimerism is considered an undesirable outcome of BMT in patients with hematologic malignancies, and is common in SCD. For patients with SCD who are “mixed chimeras” there are still important health benefits. Wu et al., reported on nine patients who were mixed chimeras after BMT for SCD. These authors documented improvement in markers of intravascular hemolysis (e.g., lactate dehydrogenase and free hemoglobin) as well as markers of vascular function (e.g., plasma nitric oxide consumption and sVCAM-1 levels) after BMT(15).

Alternative donors for sickle cell disease patients

The greatest barrier to more widespread use of BMT to cure SCD is the lack of a suitable HLA-identical donor. Walters et al., reported that among the 4848 sickle cell patients less than 16 years-of-age that were followed in 22 centers, only 315 (6.5%) fulfilled protocol entry criteria for BMT. Among these 315 eligible patients, 128 (2.6% of the original group) had HLA typing performed, and of these, 44 had an HLA-identical sibling: just 0.9% of the original 4848 patients. Thus, less than 1% of patients with SCD will have a suitable HLA identical sibling donor. These data underscore the point that if BMT is to become more widely available to treat SCD, novel strategies that address expanding the donor pool will be necessary. Three major sources of alternative donor stem cells for BMT are currently being studied with hopes of making BMT for SCD more widely available: umbilical cord blood and unrelated or haploidentical bone marrow.

Some of the large studies mentioned earlier used cord blood cells as the source of stem cells. Also, small groups of patients receiving umbilical cord cells have been reported independently with similar overall survival and event-free survival to those reports obtained with bone marrow(16). Adamkiewicz et al., reported on seven children on chronic transfusions with a history of SCD and stroke who received an unrelated cord blood BMT(17). Five patients received a HLA 4/6 and two an HLA 5/6 unrelated cord blood transplant. Four patients received myeloablative conditioning. Of these, one had primary graft failure and three had sustained engraftment, two with grade III-IV acute graft-versus-host disease (one of whom died), and one achieved stable mixed chimerism. Three patients treated with reduced-intensity regimens failed to engraft.

In another attempt to expand the donor pool for patients needing a BMT, researchers from Johns Hopkins reported the successful use of reduced intensity haploidentical BMT. Related haploidentical BMT is an alternative method for expanding the potential pool of bone marrow donors; any patient shares exactly one HLA haplotype with each biologic parent or child, and siblings or half-siblings have a 50% chance of being haploidentical. The disadvantage of this approach has been the high incidence of graft rejection and severe graft-versus-host disease. Recently, this group has shown that haploidentical BMT using non-myeloablative conditioning and high-dose, post transplantation cyclophosphamide is associated with low rates of fatal graft failure, infection, and severe acute graft-versus-host disease in patients with hematologic malignancies(18). The Hopkins group reported 68 patients, most of whom had advanced hematologic malignancies, and found that the cumulative incidences of grades II-IV and grades III-IV acute by day 200 were 34% and 6%, respectively, with non-relapse mortality of 15%(18). They have also used this approach to treat 3 patients with paroxysmal nocturnal hemoglobinuria, one of whom also had severe SCD. Rapid engraftment without graft versus host disease occurred in 2 of the patients, including the patient with sickle cell disease. Both patients are disease free with full donor chimerism and require no immunosuppressive therapy, with follow-up of 1 and 4 years respectively(19).

Conclusion

Bone marrow transplantation is a curative option for patients with SCD and other hemoglobinopathies. However, it is clear that the number of transplants performed for this indication is low and very few studies have been published to guide clinicians. Given the large number of patients at risk (African-Americans, Arabs and other groups from Mediterranean ancestry) it is clear that this procedure should become more prevalent and more studies should be ongoing. The major obstacle to more widespread use of BMT for SCD is the paucity of suitable donors. The use of “alternative” donors would increase the potential pool of donors available to these patients, but important obstacles of toxicity from the conditioning regimen, graft failure, and graft-versus-host disease must be overcome.

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Table

	Walters et al.(1)	Vermeylen et al.(3)	Walters et al.(2)	Bernaudin et al.(4)	Panepinto et al.(7)
Patients	22	50	50	87	67
Median Age (range)	10.4 (3.3–13.9)	7.5 (1.7–23)	9.9 (3.3–15.9)	9.5 (2–22)	10 (2–27)
Neurologic complications *	7	18	9	16	11
Graft failure	18%	10%	10%	7%	13%
Overall survival	91% at 4 years	93% at 5 years	94% at 6 years	93% at 6 years	97% at 5 years
Event free survival	73% at 4 years	82% at 5 years	84% at 6 years	86% at 6 years	85% at 5 years

* Seizures or intracranial bleeding.