

REVIEW

Has stem cell transplantation come of age in the treatment of sickle cell disease?

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Currently, hematopoietic SCT (HCT) is the only intervention that can restore normal hematopoiesis to provide a 'cure' in sickle cell disease. Yet, this treatment modality is used sparsely—a total of less than 400 transplants are reported in the Center for International Blood and Marrow Transplant Research database despite 70 000 afflicted in the United States; 88% of transplants are from HLA-matched sibling donors and 84% are <16 years of age at transplant. Overall survival at 3 years is over 90% after HCT in the young but 62% in adult HCT recipients due to increased disease and transplant-related morbidity. The decision and timing of HCT is a dilemma for physicians and families due to the need to consider HCT before severe organ damage in a disease that is generally not fatal in children with adequate supportive care. From the transplant physician's perspective, however, advances in the ability to identify well-matched donors, supportive care and promising conditioning regimens with low toxicity and transplant complications support the development of new HCT trials for sickle cell disease as the risk/benefit ratio can be balanced better. With the recognition of new predictors of early mortality, the anticipation of extensive and expensive life-long medical support, and the poor quality of life despite medical care, the scales tip in favor of HCT. This is prime time for the development of careful unrelated donor HCT trials for sickle cell disease. Research efforts targeting HCT will need to be directed at seeking safe and effective transplant methods applicable to all patients who might derive benefit.

Bone Marrow Transplantation (2007) **40**, 813–821; doi:10.1038/sj.bmt.1705779; published online 20 August 2007

Keywords: sickle cell disease; hematopoietic cell transplant; preparative regimen

Introduction

Hematopoietic SCT (HCT) successfully establishes donor hematopoiesis and restores cellular, immune or enzymatic function to provide a cure for many non-malignant disorders. Successful HCT for transfusion-dependent thalassemia as well as a report of HCT for acute myeloid leukemia in 1984 that cured sickle cell disease led to transplant studies for sickle cell disease.¹ The risks and benefits of HCT and disease-specific issues influencing transplant trials for sickle cell disease have provided valuable data for the development of further trials for this disorder. As scientific advances are made in the field of both HCT and sickle cell disease, these insights are poised to advance HCT and make it applicable for more patients afflicted by the disorder.

Scope of the problem

Over 70 000 people live with sickle cell disease in the United States. Over 1000 afflicted babies are born in this country each year. In African countries such as Nigeria, 45 000–90 000 babies are born with the disease each year. Although disease manifestations vary in severity, no organ is spared the ill effects of vaso-occlusion and endothelial damage. Vital organs that bear the brunt of damage include the brain, lungs, heart, joints and kidney.² Eleven percent of patients develop a stroke by 18 years of age.³ The development of a stroke is an accepted indication for chronic transfusions and must be continued indefinitely despite the cost and risks of infection, alloimmunization and iron accumulation. Twenty percent of patients with previous strokes develop a recurrent stroke despite transfusion therapy and 5% die in the second decade.⁴ Other manifestations such as acute chest syndrome, visceral infarcts, painful priapism, osteonecrosis and chronic unremitting pain can be debilitating. This translates into an inability to attain educational, social and psychosocial age appropriate goals in childhood and negatively impacts productivity in adulthood. Pulmonary hypertension and increased serum lactate dehydrogenase levels were recently recognized to correlate best with sudden mortality.^{5,6} Clinical manifestations are benefited by supportive care measures such as red cell transfusions, parental or oral

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Received 8 June 2007; accepted 8 June 2007; published online 20 August 2007

chelating agents, fetal hemoglobin upregulators such as hydroxyurea and decitabine, pulmonary vasodilators, asthma therapy and infection control.^{7–10} The long-term benefits of these interventions are unknown. Attempts have been made to identify patients predisposed to serious complications using indicators such as dactylitis in infancy, Hb level, leukocytosis and acute chest syndrome in the young.^{11–13} The applicability of these predictors to define mortality is controversial but evidence suggests that these are indeed the patients who are chronically symptomatic.¹⁴ Median survival described in two separate studies range between 42–48 years and 32–38 years for severely affected patients.^{15,16} Cumulative overall, sickle cell disease-related and stroke-free survival are 85.6, 93.6 and 88.5%, respectively, by 18 years of age; overall rates of death and stroke are 0.59 and 0.85/100 patient-years.¹⁷ These numbers that describe mortality do not account for another large group of patients with sickle cell disease who have poor quality of life (QOL) secondary to non-stroke-related complications.¹⁸

The medical cost (apart from the psychosocial cost) of supporting a patient with chronic disease manifestations is not trivial; it spans the lifetime of each patient in many countries.¹⁹ The disease is not just confined to people of African origin but affects many other ethnic groups in Italy, Greece, Turkey, Saudi Arabia, India, Pakistan, Bangladesh, China and Cyprus. Patients with sickle cell disease incur large numbers of hospital admissions, emergency department visits and outpatient visits at substantial costs. Obtaining adequate health insurance is a problem for many patients. A small proportion of patients with severe disease tend to account for a majority of the total health-care costs.

HCT for sickle cell disease—objectives and obstacles

HCT can abrogate sickle cell disease manifestations and is the best option for cure today. Molecular interventions such as gene therapy are also designed to meet curative goals by replacement of Hb S with normal Hb A. But gene therapy is currently an experimental approach and is not yet a viable therapeutic option.^{20,21} HCT goals include establishment of stable donor engraftment and long-term donor-derived red cell hematopoiesis. This can be achieved

even with mixed donor/recipient chimerism. A recent trial of sibling donor transplants for sickle cell disease described Hb S levels as low as 7% with donor cell chimerism of 11%.²² Transplants were also successful when donors had Hb S trait. Hb S levels were as low as 36% even when post-transplant donor chimerism was 25%. However, despite this success, transplant-related toxicities remain obstacles to HCT for fear of mortality, GVHD or preparative regimen-related acquired complications. Thus, although HCT comes with the likelihood of a cure, and many afflicted patients have a bleak prognosis for survival or QOL otherwise, HCT remains largely unacceptable to medical caregivers especially in the unrelated donor setting. The small numbers of HCT performed relative to the size of the affected population, and the absence of formal unrelated donor transplant trials for sickle cell disease attest to this. In the ideal setting, the definition of a successful transplant for sickle cell disease would need to include the following (Table 1).

Many of the goals listed in Table 1 are predicted by outcomes of HCT for other non-malignant disorders when developing transplant trials. Perhaps the best applicable to sickle cell disease are thalassemia transplant outcomes; they are best in young patients without extensive organ damage.²³ Comparable outcomes in related and unrelated donor transplants are recently described following myeloablative conditioning in thalassemia but only in the young with extended haplotype matching of donor recipient pairs at class I and -II HLA loci (A, B, C, and extended DRB and DQB loci).²⁴ Related donor transplants in young thalassemia recipients (<17 years) have 93% overall survival (OS) and 92% disease-free survival (DFS) with a myeloablative/immunoablative conditioning approach.²⁵ Unrelated donor transplants for children with thalassemia without a large iron load (class I and -II) have OS and DFS rates of 96.7 and 80%, respectively.²⁶ Unrelated donor cord blood transplants can successfully engraft in young thalassemia recipients, proving acceptability of unrelated donor cord blood as a stem cell source.²⁷

Although they share some similarities with thalassemia patients, sickle cell disease patients are unique in other respects such as the relative unpredictability in childhood of the severity of disease, and the anticipated morbidity of organ damage. Further, endothelial damage in the central nervous system (CNS), lungs and kidneys may be

Table 1 Goals of an 'ideal' transplant for sickle cell disease

<i>Transplant outcomes</i>	<i>Essential</i>	<i>Desirable</i>	<i>Undesirable</i>	<i>Unnecessary</i>
HCT applicable to all patients (eligibility)		X		
'Ideal' donor identification (related/unrelated)	X			
Stable donor chimerism (full or partial >25%)	X			
Donor-derived RBC hematopoiesis (complete or partial)	X			
Donor-derived myelo/thrombopoiesis				X
Donor-derived immune functions				X
Rapid immune reconstitution		X		
Immediate or delayed transplant-related toxicities (mortality/morbidity)			X	
GVHD (acute and chronic)			X	
Reversal of established disease related organ damage		X		
Absence of disease progression after HCT	X			

Abbreviation: HCT = hematopoietic SCT.

exacerbated during HCT depending on the approach used, and is worse in older transplant recipients.²⁸ The reversal of pre-existent organ damage such as cerebral infarction after SCT requires long-term vigilant follow-up. Preliminary reports support stabilization and/or improvement in neurologic manifestations in the short term.²⁹ Magnetic resonance imaging changes and long-term benefits are harder to determine at early follow-up.^{30,31} Ovarian function is impaired in the majority of female recipients after myeloablative transplants.³² Growth is relatively unimpaired especially if transplants are performed in the young, before the adolescent growth spurt.³³ Busulfan, the backbone of myeloablative transplants, has associated pulmonary, liver and neurotoxicity.^{34–36} These outcome measures of disease and transplant complications, and potential drug-induced toxicities are crucial in determining when and how to transplant to ensure the maximum chance of success.

For ease and safety, HCT for sickle cell disease has been mainly limited to HLA-matched related donor transplants in children, as outcomes are better. Although this severely limited the number of patients who benefited by transplant, they were instrumental in supporting the proof of principle that transplant ‘works’ and disease symptoms are abrogated. Patients successfully discontinued chronic transfusion therapy and had no progression of neurologic symptoms or clinical manifestations such as acute chest syndrome or pain.

Of 373 transplants reported to the Center for International Blood and Marrow Transplant Research registry, only 8% were unrelated donor transplants, presumably due to poorer outcomes with unrelated donor transplantation and the absence of formal trials. Overall, the total number of transplants performed and reported internationally is very small compared with the large numbers of affected patients who live with the disease.

Preparative regimen

The ideal preparative regimen should be tolerated by patients of all ages with minimal early organ toxicity and late effects, and support donor cell engraftment with acceptable rates of mortality and GVHD. Table 2a is a summary of transplants and outcomes for sickle cell disease, based on preparative regimen. The majority of recipients were transplanted for stroke; manifestations such as acute chest syndrome and chronic pain were less frequent indications.

A multicenter study from Oakland is in progress with myeloablative busulfan, cytoxan and rabbit antithymocyte globulin as conditioning in related umbilical cord blood (UCB) transplants for hemoglobinopathies, and outcomes are comparable to BMT with 89% OS, 84% DFS and low graft rejection rates of 4%.⁴² These outcomes show that sickle cell disease patients tolerate SCT and have successful outcomes. Although children have a lower incidence of acute toxicities, adult patients do not fare as well, and have unacceptable CNS toxicity and high mortality with standard conditioning regimen.⁴³ Long-term toxicities such as sterility are a concern.²⁸ GVHD and graft rejection rates

Table 2a Outcomes following myeloablative HCT

Author	Number of recipients/ median age in years (range)	Donor source/median follow-up (years)	Conditioning	Deaths N (%)	OS N (%)	DFS N (%)	aGVHD N (%)	cGVHD N (%)	Graft rejection N (%)	Comments
Walters ²²	59/10 (3–15)	Sib BM/3.5	Bu/Cy/ATG or alemtuzumab	4 (6.7)	55 (93)	50 (84.7)	11 (19)	11 (19)	9 (15)	Patients with severe CNS, renal, pulmonary and hepatic disease excluded
Vermyley ³⁷	50/7.5 (0.9–23)	Sib BM/11	Bu/Cy± TLI or ATG	2 (4)	46 (93)	42 (85)	20 (40)	10 (20)	5 (10)	Asymptomatic patients had better OS and DFS than patients with disease manifestations
Bernaudin ³⁸	34/8 (2–14)	Sib BM/1	Bu/Cy± TLI or ATG	3 (9)	31 (91)	30 (85)	9 (26)	2 (6)	1 (3)	HCT benefited silent stroke patients; all deaths were GVHD induced
Locatelli ³⁹	11/5 (1–20)	Sib UCB/2	Bu/Cy± ATG/ALG Bu/Flu/TT	0	11 (100)	10 (90.9)	1 (9)	(6)	1 (9)	7 patients had disease manifestations other than stroke; low rates of GVHD
Panepinto (CIBMTR) ⁴⁰	67/10 (2–27)	BM, PB, UCB/5	Bu/Cy 63 (94%) Other 4 (6%)	3 (4.4)	64 (97)	55 (85)	10 (4–19) probability (95% CI)	22 (13–34) probability (95% CI)	9 (13)	GVHD remained a problem
Adamkiewicz ⁴¹	3/6 (3–12)	4/6 URD UCB/4	Bu/Cy/ATG	0	3	2	3	1	1 (33)	URD HCT less successful than matched sibling transplants

Abbreviations: ATG = antithymocyte globulin; BM = bone marrow; Bu = busulfan; Cy = cytoxan; CI = confidence interval; CNS = central nervous system; DFS = disease-free survival; Flu = fludarabine; GVHD = graft-versus-host disease; HCT = hematopoietic SCT; HU = hydroxyurea; N = number; OS = overall survival; PBSC = peripheral blood stem cell; Sib BM = sibling bone marrow; TBI = total body irradiation; TLI = total lymphoid irradiation; TRM = treatment-related mortality; TT = thiotepa; UCB = umbilical cord blood; URD = unrelated donor.

Table 2b Outcomes following reduced intensity HCT

Author	Number of recipients/ median age in years (range)	Donor source/ follow-up (years)	Conditioning	Deaths N	OS/DFS N	aGVHD N	cGVHD N	Graft rejection N	Comments
Van Besien ⁴⁴	2/40, 56	Sib BM	Flu/Mel/ATG	2	0	2	—	—	High mortality in older patients
Schleuning ⁴⁵	1/22	Sib BM/1	Flu/Cy	—	1/1	0	Yes	—	Reduced intensity conditioning well tolerated
Iannone ⁴⁶	6/8 (3–20)	Sib BM/ PBSC	Flu/TBI ± ATG	0	6/0	0	—	6	All children eventually rejected grafts
Horan ⁴⁷	4/25 (9–30)	Sib BM/1	Flu/ATG/200 cGy TBI	1	3/1	0	—	2	Increased graft rejection in alloimmunized patients
Jacobsohn ⁴⁸	3/14 (4–22)	Sib (2) and URD PBSC	Bu/Flu/ATG	1	2/0	1	—	2	Increased graft rejection in sickle cell disease recipients
Mazur ⁴⁹	1/8	4/6 URD UCB/2	HU/rituximab/alemtuzumab/ thiotepa/TBI 6Gy	—	1/1	0	—	0	Second transplant successful after increased immunosuppression with preparative regimen
Krishnamurti ⁵⁰	1/8	Sib BM/1	Bu/Flu/ATG/TLI 500 cGy	—	1/1	0	—	0	Patient with stroke—tolerated conditioning well
Shenoy (unpublished)	6/11 (2–17)	3 sib BM 3 URD/0.8	Alemtuzumab/Flu/Mel 140	—	6/6	0	1	0	Tolerated preparative regimen; patients with stroke; stable mixed chimerism; low rates of GVHD

Abbreviations: ATG = antithymocyte globulin; BM = bone marrow; Cy = cytoxin; DFS = disease-free survival; Flu = fludarabine; GVHD = graft-versus-host disease; HCT = hematopoietic SCT; HU = hydroxyurea; N = number; OS = overall survival; PBSC = peripheral blood stem cell; Sib BM = sibling bone marrow; TBI = total body irradiation; TLI = total lymphoid irradiation; TRM = treatment-related mortality; TT = thiotepa; UCB = umbilical cord blood; URD = unrelated donor.

remain a concern despite the ideal donor source, a matched sibling. This severely limits the applicability of this intervention in the absence of related donors for fear of high rates of morbidity and death.

Attempts to avert the toxicities of myeloablative regimen have resulted in transplant trials with reduced intensity conditioning regimens. They are summarized in Table 2b.

Because reduced intensity transplants are more recent, the numbers are small. Owing to recipient immunocompetence, graft rejection rates have often been high after reduced intensity conditioning. Graft rejection risks are compounded by blood group incompatibility between donors and recipients, recipient exposure to multiple blood products and alloimmunization, and use of a ‘weaker’ stem cell source such as UCB with higher baseline rejection rates.⁵¹ Nevertheless, the advent of newer combinations of immunosuppressive preparative regimens remains promising for patients who are at high risk for toxicities with myeloablative conditioning. The ‘intensity’ of conditioning is variable between regimens, and immunoablative agents such as alemtuzumab have improved engraftment, and can be beneficial against GVHD.⁵² The time is right for unrelated donor transplant trials using newer agents as reduced intensity conditioning regimen that may be better tolerated by patients with advanced disease. Transplant methods safe for adult patients with sickle cell disease would be a welcome area of advancement.

A combination of alemtuzumab, fludarabine and melphalan that was previously successful in non-malignant disorder transplants has had initial success in a small number of hemoglobinopathy patients.⁵³ Graft rejection (5%) and GVHD rates (15% acute; 11% chronic) were low in 62 non-malignant disorder transplants. Initial experience with 11 hemoglobinopathy transplants showed that the regimen was well tolerated and supported engraftment of related and unrelated donor cells when the melphalan dose was 140 mg/m² but not 70 mg/m². This early experience where the conditioning regimen was administered without major toxicity has prompted the development of an unrelated donor transplant trial supported by the National Marrow Donor Program and the Bone Marrow Transplant Clinical Trials Network (BMT CTN). The study will evaluate the ability of this conditioning regimen to achieve sustained donor cell engraftment using well-matched unrelated donor bone marrow or UCB as the stem cell source, and monitor the safety of using such a regimen.

Graft source

Graft rejection remains an obstacle to HCT especially with the use of a reduced intensity regimen in non-malignant disorders (Table 2b). Bone marrow and peripheral blood cells (PBSCs) may have benefit over UCB for engraftment. However, PBSC transplants are associated with higher rates of chronic GVHD in retrospective studies and a prospective trial is in progress (BMT CTN 0201) in malignant disorders to evaluate the risks and benefits of PBSC or BM as stem cell source.⁵⁴ Until these are better defined, PBSC transplants are not preferred especially for non-malignant disorders where GVHD is unnecessary and

a significant risk in unrelated donor transplants. Manipulation of stem cell grafts to enrich for stem cells or deplete T cells to reduce this risk may hold future promise.^{55,56} UCB grafts are dependent on cell dose to ensure adequate engraftment. Graft rejection rates are higher than with bone marrow cells.⁵⁷ UCB transplant outcomes are also dictated by the level of HLA-matching and speed of immune reconstitution.^{58,59} HLA-matching at the molecular level at 8 loci (A, B, C and DRB1) for marrow grafts and 5–6/6 loci (A and B at the antigen level; DRB1 at the allele level) for UCB grafts have similar outcome and are currently considered the optimum grafts. Studies to determine if double cord transplants increase availability of cord transplantation to older recipients and improve outcomes are in progress.

Family perceptions of HCT

Patient and family opinions regarding the acceptability of a curative intervention such as transplant for sickle cell disease patients was previously explored in 67 parents by Kodish *et al.*⁶⁰ with a questionnaire regarding transplant acceptability. Twenty-four percent were unwilling to accept BMT even with 100% chance of cure and 0% short-term mortality; 22% were accepting of 5% mortality, 37% were accepting of 15% mortality and 12% were willing to accept even 50% mortality in exchange for a cure. Acceptance of transplant increased with education, employment, higher socioeconomic status and an afflicted child. In the national trial of sibling donor transplant for sickle cell disease, the primary reasons for not pursuing HLA typing for transplant was the lack of a sibling (24%). Lack of financial or psychosocial support and parental refusal rates were lower at 10.5 and 9.5%, respectively.⁶¹ When adult patients with sickle cell disease were polled regarding their acceptance of SCT, 62 and 30% accepted a treatment-related mortality (TRM) of over 10 and 30%, respectively. Sixty-four and forty-one percent accepted graft rejection rates of over 10 and 30%. Only 50% accepted infertility and 80% rightly thought chronic GVHD was unacceptable. Sixty percent were willing to participate in a RIT study suggesting that ‘acceptable’ outcomes would need to be set at different target levels for pediatric and adult sickle cell disease HCT trials.⁶² With improving methods of providing supportive care, the use of innovative transplant approaches, better education and understanding of the process, it is time to discuss the pros and cons of transplant with affected families in conjunction with the hematology teams that direct medical care for patients with sickle cell disease.⁶³

Donor availability

Almost all HCT experience for sickle cell disease has involved matched sibling donors to ensure better outcomes. A major obstacle to related donor HCT is the presence of suitable sibling donors in <18% of sickle cell disease patients.⁶⁴ The paucity of matched sibling donors prompted many transplant physicians to investigate availability of

Table 3 Probability of finding a matched unrelated donors for African-American HCT recipients

Author	Population HLA typed	Probability of matching (%)			
		8/8 BM	6/6 BM	6/6 UCB	5/6 UCB
Krishnamurti ⁶⁵	Sickle cell disease		33.77		19.48
Adamkiewicz ⁶⁶	Sickle cell disease				50
Stevens ⁶⁷	African Americans			1.7	44
NMDP ^a	African Americans	36.1		24.5	

Abbreviation: HCT = hematopoietic SCT.

^aPersonal communication D. Confer NMDP: National Marrow Donor Program.

matched unrelated donors in African-American recipients. They are summarized in Table 3.

The tremendous expansion of both bone marrow and cord blood registries nationally and internationally, the focus on minority donations and increased awareness of voluntary donation are promising for unrelated donor transplant trials involving minority patients.

The ideal time to transplant/predicting the ‘bad’ actors

There is wide variation in the natural history of even patients afflicted with the more severe forms of sickle cell disease such as Hb SS and Hb S β^0 thalassemia. An inability to accurately predict in children the severity and course of the disease, and target organs to be eventually affected, make it difficult to accept a non-trivial intervention such as HCT early. Ironically, ‘early’ transplants are likely to provide the best outcomes if mortality and GVHD rates are acceptable.

Several investigators have tried to define a population based on symptoms that is likely to have ‘bad’ sickle cell disease with time, but it remains a moving target without an accurate method of prediction until complications set in. The current consensus for HCT indications include stroke, severe acute chest syndrome and chronic unremitting pain associated with vaso-occlusion despite supportive care or the inability to provide adequate supportive care such as chronic transfusion therapy. The best-defined group for HCT is patients with stroke as second strokes occur in as many as 20% of patients despite transfusion therapy and mortality rates remain as high as 5%. The natural history of other complications is less clear for mortality but is more relevant for predicting poor QOL, productivity, self-support and the need for extended medical care. Emerging predictors of the risk of sudden death such as pulmonary hypertension are likely to advance the field in this respect in the future.

Using the indicators described above, the morbidity of the disease is often fully recognized only in late adolescence or adulthood at the time medical care is transitioned from pediatrics into adult medicine. Transplant risks and mortality are higher in this age group although recognition of the need for HCT is often only apparent at this age. This group of older patients is likely to be more accepting of transplant having experienced the ravages of disease first hand. Expectations of transplant outcomes and definitions

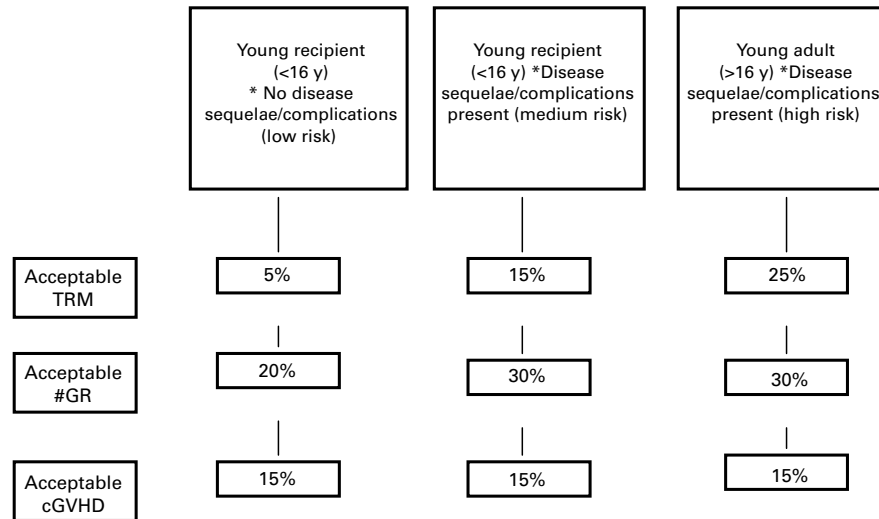


Figure 1 Acceptable outcomes for sickle cell disease HCT based on recipient status. *Disease sequelae/complications: stroke, recurrent acute chest syndrome, avascular necrosis, red cell alloimmunization. #GR graft rejection.

Table 4 Indications and contraindications for HCT in sickle cell disease

Recipient characteristics/disease manifestations	Absolute Indication	Relative indication	Relative contraindication	Absolute contraindication
Asymptomatic child (<16 years)		X		
Symptomatic child (<16 years)	X			
Symptomatic adolescent (16–19 years)		X		
Symptomatic young adult (20–30 years)			X	
Older adult (>30 years)				X
Overt stroke	X			
Silent stroke		X		
Recurrent ACS/severe VOC/AVN		X		
Poor QOL due to disease		X		
Pulmonary hypertension			X	
Renal failure				X
Hepatic cirrhosis				X

Abbreviations: ACS = acute chest syndrome; AVN = avascular necrosis; HCT = hematopoietic SCT; QOL = quality of life; VOC = vaso-occlusive crisis.

of success are likely to vary between parents of young children with sickle cell disease and older patients considering this intervention. Figure 1 is a recipient-based algorithm for HCT outcomes based on age and disease sequelae.

With current regimens, older patients with established pulmonary hypertension, hepatic fibrosis or renal compromise are likely to have very high mortality rates with transplant and are unacceptable candidates, based on experience with small numbers of sickle cell disease but larger numbers of patients with thalassemia.^{2,3} Disease manifestations that guide considerations for transplant are listed in Table 4.

More than one relative contraindication would make HCT an expensive endeavor with poor outcomes. Ultimately, for all patients, the benefits of transplant need to outweigh the risks associated with the procedure. At the current time, the balance between medical management of severe sickle cell disease versus consideration of HCT as a curative option early (in childhood before disease manifestations) weighs in favor of the former due to the fear of transplant-related complications such as mortality, sterility

and chronic GVHD. Improving transplant outcomes by carefully choosing donors, conditioning regimen and supportive care strategies are the only way to prove that transplant benefits outweigh the risks. If good outcomes are assured, many relative indications listed in Table 4 will become absolute indications for HCT with fewer contraindications. Separate trials will need to be designed in step-wise manner keeping in mind the variables in transplant recipients such as age, weight, disease manifestations and organ damage criteria.

Access to transplant or long-term supportive care

Patient access to medical care is dependent on the economics and health-care system of the country. Although patients in affluent countries such as the United States and Western Europe have the benefit of access to modern therapeutic interventions for extended periods and even a lifetime, developing countries are unable to support the same. In many health-care systems, a life-saving curative intervention such as transplant (as in the case of matched

sibling donor transplants for CML) was found more cost-effective than continued expensive medication and supportive care. In other countries, it was harder to support the upfront high costs of transplant although there was promise for cure.^{68,69} However, the need for chronic supportive care such as chronic transfusion therapy as in the case of sickle cell disease will eventually incur costs in excess of the transplant costs especially if transplant outcomes (such as absence of chronic GVHD) are successful in withdrawal of all medications after recovery. This needs to become a consideration given the financial burden of chronic disease on the health-care system.

Pros and cons to consider

Until the maturation and safe applicability of gene therapy or a similar curative alternative, SCT is the only approach that holds promise for cure in sickle cell disease. In trying to successfully apply this treatment modality, consensus between families, hematologists and transplant physicians needs to be obtained in several 'gray zone' areas of varied opinions between specialists.

1. Age at transplant

The lowest incidence of TRM, and morbidity associated with transplant is in the young child before the development of disease-related permanent organ damage or complications of prolonged analgesia. Complications will be higher with organ damage and older recipients and transplant outcomes will need to be adjusted for the same. Consensus will need to be developed to describe the patient unacceptable for transplant—such as the presence of liver cirrhosis, severe pulmonary hypertension or interstitial lung disease, renal failure or severe neurologic manifestations of stroke.

2. Choice of donor

The choice of ideal donor is currently a matched related or unrelated well-matched bone marrow or cord blood donor with adequate numbers of nucleated cells as described previously. Future cellular options may include double cords, CD34-selected cells, mesenchymal stem cells against GVHD, and so on.

3. The timing of transplant

Early recognition of disease complications should prompt transplant referrals to allow for good transplant outcomes. For example, patients with overt stroke would benefit from consideration of transplant early, as outcomes with supportive care are less than optimal.

4. Monitoring transplant outcomes

Transplant-related outcomes in most cases are limited to donor engraftment, TRM, organ toxicities and GVHD. In the case of sickle cell disease, additional considerations for amelioration of symptoms, reversal of pre-existing damage, QOL and performance scores need to be carefully monitored to assess risk/benefit ratios of the HCT intervention.

5. Ethics of transplant for a non-malignant disorder

Family/recipient understanding of the goals of transplant, the associated risk/benefit ratio and the indications for HCT in the affected individual is crucial to ensure compliance with transplant-related supportive care.

Conclusion

Transplant as a cure for sickle cell disease is poised to benefit increasing numbers of patients who would previously have succumbed to the disease. However, consideration of the associated risks, mortality and transplant-related complications especially with a borderline recipient or suboptimal donor will continue to restrict application of this intervention for all ages, especially older recipients. Although prospective transplant trials are a reality, the ideal setting of randomized trials of HCT versus supportive care are not feasible due to the variability in disease manifestations, choice of patients and availability of donors. In patients with symptomatic sickle cell disease, HCT can now achieve OS ranging from 89 to 100% and DFS from 84 to 88% in children with matched sibling donor BM or UCB transplants. Unrelated donor transplant trials are closer to becoming a reality due to advances in transplant strategies and supportive care. The low numbers of transplants performed world-wide for sickle cell disease reflect many obstacles, many yet to be overcome—advanced disease precluding transplant, conditioning-related early and late toxicities of preparative regimen, lack of related donors, morbidity associated with unrelated or mismatched transplants, high graft rejection rates due to immunocompetence and/or alloimmunization and an inability to predict the course and extent of disease at a young age. Carefully designed HCT trials can affect the risk benefit ratio of HCT positively. This can be advantageous not just to patients suffering from a chronic debilitating disease but also to rising health-care costs for the management of a chronic disorder. Medical personnel such as the transplant and hematology teams, supportive care personnel and support staff are poised to work in conjunction to make transplant a viable and safer option for increasing numbers of affected patients. Such progress will be yet another victory in a battle against a chronic and devastating disorder.

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