POINT-COUNTERPOINT

blood advances

POINT The case for HLA-identical sibling hematopoietic stem cell transplantation in children with symptomatic sickle cell anemia

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This article has a companion Counterpoint by DeBaun and Clayton.

Sickle cell disease (SCD) is a hereditary red blood cell disorder that is characterized by early mortality and severe morbidity, including debilitating painful crises, chronic kidney injury that can progress to renal failure and dialysis,[1,2] avascular necrosis frequently culminating in joint replacement at an early age,[3] stroke,[4] poor neuropsychologic performance,[5,6] and cardiopulmonary complications.[7] Furthermore, adults can experience a chronic pain syndrome that is typically managed with long-term opioid administration. Sickle cell–associated complications, particularly painful episodes, are associated with high health care utilization[8-11] and extraordinary financial burden. One study reported that total health care costs increase with age from $892 per month in the 0 to 9 age group to $2853 per month in the 30 to 39 age group.[12] For these reasons, it is not unreasonable or controversial to assume that a successful outcome after a curative therapy for SCD early in life would have a significant beneficial effect on lifespan and the quality of life and reduce life-long health care expenditures.

Hydroxyurea (HU) was the initial US Food and Drug Administration–approved drug for SCD and is widely available, although approved only in adults. Although HU has been shown to significantly improve acute complications such as vaso-occlusive crises and acute chest syndrome in children of all ages,[13-16] there are challenges with HU adherence over the long term,[17] and HU has not been shown to prevent the organ damage that is associated with early mortality in adults.[18,19] The full benefit of HU is achieved only after a decade or longer of uninterrupted adherence; thus not all individuals experience its optimized effect. The vagaries of assuring continuous health insurance coverage in this and other chronic illnesses with access to informed, high-quality providers also impact the long-term outlook. Another supportive care option is regular red blood cell (RBC) transfusions to alleviate symptoms, but which can be complicated by alloimmunization, transfusion reactions, and iron overload. Although the vast majority of children survive to adulthood,[20] adults continue to die prematurely,[21,22] many clustered near the age of transition to adulthood,[20] and there are no reliable risk factors in children that predict severe disease and early mortality in adults. Last, some patients, not unlike the example chosen for this point-counterpoint discussion, continue to have significant sickle cell–specific complications despite receiving the maximum tolerated dose of HU. Recurrent vaso-occlusive complications have a negative impact on the quality of life.[23-27]

In contrast to life-long supportive care measures, hematopoietic stem cell transplantation (HSCT) offers a curative option for selected patients with SCD. Children who have a HLA-matched sibling donor traditionally have been treated with myeloablative conditioning chemotherapy and bone marrow grafts to replace the recipients' bone marrow with that of their donors. The most common indications for transplant are stroke, recurrent vaso-occlusive crises, and acute chest syndrome.[28] A recent study described the results of 1000 children who underwent HLA-identical transplant after predominantly myeloablative conditioning with a 5-year overall survival (OS) of 95% and 93% disease-free survival (DFS) in those <16 years of age.[29] Interestingly, Dedeken et al reported an 8-year OS and DFS of 97.4% after HLA-identical sibling bone marrow transplant (BMT) after the administration of HU for at least 3 months pretransplant.[30] Similarly, an Italian group reported a 7-year OS of 100% with 96% DFS among 24 patients.[31] After successful transplant, an improved quality of life in children with SCD has been observed.[32] Table 1 summarizes the recent experience of BMT for SCD with overall and DFS rates in patients who received myeloablative HLA-matched sibling transplantation. Although the success rate is improving, the treatment can be limited by severe chronic graft-versus-host disease (cGVHD), which is also associated with a decreased quality of life.[33-35] However, as seen in Table 1, the incidence of severe cGVHD is expected to be ~5% or less when an HLA-identical sibling donor is used.

Table 1. Survival and extensive cGVHD incidence among children undergoing myeloablative HLA-matched sibling hematopoietic stem cell transplantation

Reference	Survival	N	2 y (%)	4 to 5 y (%)	6 to 8 y (%)	cGVHD (%)
31		24				4
	OS		100	100	100	
	DFS		96	96	96	
30		38				0
	OS		97.4	97.4	97.4	
	DFS		97.4	97.4	97.4	
54		40				5
	OS		91	91	NR	
	DFS		91	91	NR	
36		130				5*
	OS		NR	NR	95*	
	DFS		NR	NR	92	
55		25				0
	OS		96	96	NR	
	DFS		96	96	NR	
49		57				8
	OS		93	93	93	
	DFS		85	85	85	
56		10				10
	OS		90	90	NR	
	DFS		90	90	NR	
57		67				5
	OS		97	97	NR	
	DFS		85	85	NR	
51		44				2.4
	OS		NR	100	NR	
	DFS		NR	95.6	NR	
58		50				6
	OS		98	96	NR	
	DFS		88	86.1	NR	
Total		485				5
	OS†		95	96	95	
	DFS†		89	90	91	

*Incidence not differentiated between patients with sickle cell anemia and thalassemia.
†Percentages are calculated based on the total number of patients reported at that time period because some manuscripts did not report survival at every interval listed in the table.
NR, not reported.

The results after related donor umbilical cord transplantation in children have also been encouraging. The largest study to date included 96 patients (30 with SCD and 66 with thalassemia major) who underwent HLA-identical sibling umbilical cord blood (UCB) transplant.[36] With a median follow-up of 5.8 years, OS was 97% with a DFS of 90%, and there was no chronic extensive graft-versus-host disease (GVHD). Other smaller studies have reported similar results.[37-39] Although ~40% of patients received HLA-identical sibling UCB supplemented with bone marrow from the same donor, this was accompanied by a very low incidence of GVHD.

Less intensive conditioning has been evaluated as a means of decreasing toxicity while maintaining efficacy in children and adults with SCD who have a HLA-matched sibling donor, but less often in children. With a median follow-up ranging from 3 to 4 years, 3 studies, each of which enrolled 7 to 15 patients, reported OS of 100% and DFS 86% in 1 study, and 100% OS and DFS in the other 2 studies. None of the patients experienced severe cGVHD.[40-42] A larger study was reported more recently that included 43 patients with SCD and 9 with transfusion-dependent thalassemia.[43] The OS was 94.2% and DFS 92.3% in patients with SCD. Although 7 patients (13%) experienced chronic extensive GVHD, all patients with cGVHD were >14 years of age. Thus, there might to be an opportunity to modify the transplant intensity and thereby further reduce transplant-related toxicity while ensuring a successful outcome.

Because full donor chimerism is not necessary for a successful outcome in SCD and because mixed chimerism may lower the risk of GVHD,[44,45] investigators have pursued a nonmyeloablative regimen with the goal of tolerance induction and stable mixed chimerism. The approach has been successful in adults, with OS of 97% and DFS of 87% in 1 study involving 30 patients.[46] Importantly, none of the patients experienced GVHD despite using mobilized peripheral blood stem cells in lieu of marrow. Eight children were recently reported to have received identical conditioning.[47] With follow-up ranging from 1 to 52 months, OS and DFS are both 100%, with no GVHD.

Together, these studies show excellent results after HLA-ID sibling HSCT, regardless of the conditioning regimen used and the source of hematopoietic cells selected for transplant. However, there is a persistent risk of mortality that ranges from 3% to 7% across the patient series reported, and which almost certainly is higher than the mortality risk experienced by children with SCD through the first 2 decades of life. Thus, the position argued here is that the short-term risks of HLA-identical sibling HSCT are favorably balanced by the long-term certainties of early mortality, extensive morbidity, and poor quality of life, with limited and inadequate supportive care options for adults with SCD.

We also refer to long-term follow-up studies after HSCT that have shown that sickle-related organ damage in most cases is stabilized, and in rare cases, improved. For example, although the benefit of RBC transfusions to prevent stroke in children with silent cerebral infarction was an important finding of the SIT trial, it was also observed that regular RBC transfusions did not universally prevent the progression of silent cerebral infarcts (6 of 99 children had progressive neurologic disease that included stroke in 1 and new or enlarged silent cerebral infarction in 5).[48] In 2 transplant observational series, central nervous system lesions were stable to improved after HSCT in patients with a history of stroke and/or silent cerebral infarct.[46,49] Elevated tricuspid regurgitant velocities, which are associated with early mortality in adults,[18] decreased to the normal range,[46] and 1 adult had resolution of pulmonary hypertension after transplant.[50] Osteonecrosis[51] and abnormal transcranial Doppler velocities[52] have also been shown to improve after successful transplant. However, this is balanced by long-term complications related to myeloablative busulfan that include infertility, primary or secondary gonadal failure, and cardiopulmonary complications. Although the risk of a malignancy related to HSCT is low in this population, systematic follow-up to characterize the incidence has not been universal and is indicated.

The gold standard when comparing 2 therapies, such as HLA-identical sibling HSCT and supportive care for SCD, is a randomized design. Unfortunately, it is not feasible to conduct a randomized transplant trial because there are very few patients who have an HLA-identical sibling donor and because the treatments are quite disparate in their intensity, risk of toxicity, potential for cure, and cost. Together, these considerations make it very unlikely that a comparative trial could be completed in an acceptable period of time, or that equipoise could be sustained in a trial in which 1 intervention generates a cure in most study participants, whereas the other treatment offers none. The decision to undergo HSCT is a complex process, and once physicians and patients accept the idea of curative therapy despite its risks, they are often unwilling to accept noncurative treatment when a suitable donor is available. In addition, the case presented here involves a treatment decision that is limited by the young age of the child. In 2010, Iltis examined whether guidelines made by the United Nations Convention on the Rights of the Child were based on a suitable framework for pediatric bioethics.[53] The Convention stated that for children who are not able to articulate views about decision making, decisions should be made per the patient's best interest. The American Academy of Pediatrics confirmed that health care decisions should be made according to what is best for them, and what is best should be based on parental consent and obtained in collaboration with the child's health care providers, who can offer critical information and guidance.[53] The notion of not pursuing a therapy with curative potential, based upon an assessment only of survival through the first 20 years of life after HSCT and supportive care, and in the absence of a randomized study, seems restrictive with a potential to limit family-centered decision making.

In conclusion, the results of HLA-identical sibling HSCT for SCD, although very good, show that the short-term mortality of the procedure is fixed at 5% to 10% and significantly exceeds the mortality rate experienced by children through the first 2 decades of life who receive optimal medical therapy. The data also strongly show that children after successful transplantation no longer experience vaso-occlusive episodes nor progressive sickle-related organ damage and do not appear to be at risk for early mortality beyond 1 year posttransplant. The ethical question we raise here is the following: should early mortality risk alone be used to restrict treatment choices in a child with SCD? Should this decision making exclude HSCT as a therapeutic option considered only as an experimental treatment of children with SCD, as has been suggested by the counterargument? We disagree strongly about restricting the option of transplantation in children with symptomatic SCD. This is based in part on our reasoning that, all things considered, given the option of living with the disease vs not having the disease, that a reasonable person, parent, child, and physician might choose not to have the disease and that the same decision-making group might also be able to carefully consider the risks and benefits of the therapy.

Authorship

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