The ethics of a proposed study of hematopoietic stem cell transplant for children with "less severe" sickle cell disease

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Hematopoietic stem cell transplant (HSCT) is the only cure for sickle cell disease (SCD). HSCT using an HLA-identical sibling donor is currently an acceptable treatment option for children with severe SCD, with expected HSCT survival >95% and event-free survival >85%. HSCT for children with less severe SCD (children who have not yet suffered overt disease complications or only had mild problems) is controversial. It is important to consider the ethical issues of a proposed study comparing HLA-identical sibling HSCT to best supportive care for children with less severe SCD. In evaluating the principles of nonmaleficence, respect for individual autonomy, and justice, we conclude that a study of HLA-identical sibling HSCT for all children with SCD, particularly hemoglobin SS and Sβ^0-thalassemia disease, is ethically sound. Future work should explore the implementation of a large trial to help determine whether HSCT is a beneficial treatment of children with less severe SCD. (*Blood*. 2014;124(6):861-866)

Introduction

Transplant to cure sickle cell disease

Sickle cell disease (SCD) is an inherited disorder of the hemoglobin protein in red blood cells that causes serious acute and chronic complications affecting multiple organs. In the early 1980s, a child with SCD who also developed acute myeloid leukemia at age 8 became the first person cured of SCD when she underwent allogeneic hematopoietic stem cell transplant (HSCT) to treat her leukemia.[1] Although this initial case demonstrated the curative potential of HSCT for SCD, at that time, transplant was not considered a treatment option for SCD given the significant morbidity and mortality associated with HSCT. However, as transplant care improved, a few years later, a small group of patients in Belgium was successfully transplanted explicitly for SCD.[2] This work helped lead in the 1990s to an international trial of HLA-identical sibling HSCT for SCD.[3] This study was limited to patients with severe SCD who had suffered certain complications like a stroke (Table 1). The results of the study were encouraging, with >93% of patients surviving the transplant and 85% successfully cured of SCD.[4] Similar results involving other centers,[5-7] as well as long-term follow-up studies of transplanted patients, have demonstrated that HSCT definitively cures SCD, preventing further, and in some cases even reversing, SCD-mediated organ damage.[8-10] More recent studies of HLA-identical sibling HSCT for SCD have reported even better results, with overall survival approaching 100% and SCD cure rates of ~90%.[11-18]

Because HSCT is associated with serious toxicities, its initial use was limited to treating patients with severe SCD in research settings. These patients with severe SCD had a high risk of further SCD-related complications and death at a young age. The risk/benefit ratio of a curative treatment—even one associated with its own risk of death—was reasonable for them. Now, given the existing research on HSCT for SCD, many experts currently agree that HSCT is a good treatment option for these SCD patients with severe disease who have HLA-identical siblings.[14,19,20] The concept of promoting HSCT for children with less severe SCD, however, is controversial, given that their disease is not as predictably life shortening to the degree of severe SCD, and it is less clear that the benefits of transplant outweigh the risks. Is it ethical to conduct a trial of HLA-identical sibling HSCT vs supportive care for children with less severe SCD?

What is less severe sickle cell disease?

It is first necessary to define our concept of less severe SCD. We do not use this term to refer to patients who have had serious SCD complications that fall just short of restrictive established transplant eligibility criteria (Table 1). We also do not use this term to refer to patients started on chronic transfusion therapy for primary stroke prevention due to an elevated transcranial Doppler velocity, as these patients are at high risk of serious clinical events even if they have not yet had any problems.[21] Although still not viewed as first-line therapy by some hematologists,[22] an HLA-identical sibling transplant is less controversial for these types of patients. We instead define less severe SCD to refer to children who have had only minor or no overt SCD complications. Some have used the term mild SCD or asymptomatic SCD to refer to this group of patients. We believe this language is misleading because a child with initially mild SCD may suffer life-threatening SCD complications as a young adult. The term asymptomatic SCD is especially problematic as it wrongly implies that some children with SCD are not affected by the condition, when, in reality, most will typically suffer at least some pain, and their hemoglobinopathy will cause progressive multiorgan damage. Even at the very young age of 12 months, the overwhelming majority of infants with hemoglobin SS and Sβ^0-thalassemia disease have evidence of splenic dysfunction,[23] and most show signs of renal dysfunction.[24] Especially concerning is the finding that >25% of young (age < 6 years) neurologically asymptomatic children with hemoglobin SS disease have evidence of ischemia on screening brain magnetic resonance images,[25] and

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Table 1. Eligibility criteria used to define severe SCD by the Collaborative Group Study of Marrow Transplantation for Sickle Cell Anemia

One or more of the following[3]:
Stroke or central nervous system event lasting longer than 24 hours
Acute chest syndrome with recurrent hospitalizations or previous exchange transfusions
Recurrent vaso-occlusive pain (≥2 episodes per year for several years) or recurrent priapism
Impaired neuropsychological function and abnormal cerebral MRI scan
Stage I or II sickle lung disease
Sickle nephropathy (moderate or severe proteinuria or a glomerular filtration rate 30% to 50% of the predicted normal value)
Bilateral proliferative retinopathy and major visual impairment in at least one eye
Osteonecrosis of multiple joints
Red cell alloimmunization (≥2 antibodies) during long-term transfusion therapy

these "silent strokes" are associated with poor school performance[26] and a global loss of intellectual function.[27]

In our defined group of children with less severe SCD, if we could predict which patients would later develop serious SCD-related problems and which patients would instead continue to enjoy mostly good health as adults, then it may be prudent to only consider HSCT in those children who would later develop significant problems. Unfortunately, despite research in this area,[28-30] clinical markers have failed to reliably predict later SCD severity,[31] and, given advances in our care, historic predictive models have limited applicability to patients with SCD today.[32] Although some laboratory tests in early childhood may prove to be helpful in forecasting later SCD severity,[33] a hallmark of SCD is its unpredictable clinical course, so accurately predicting the extent of an individual child's future SCD complications is likely impossible.

We use the general term SCD to refer to all SCD genotypes (hemoglobin SS, $S\beta^0$-thalassemia, $S\beta^+$-thalassemia, SC disease); however, we recognize that the prognosis of patients with $S\beta^+$-thalassemia and SC disease is typically much better than patients with hemoglobin SS and $S\beta^0$-thalassemia disease. The risk of SCD-related death and stroke in children with hemoglobin $S\beta^+$-thalassemia and SC disease is extremely low,[34] and overall life expectancy of individuals with these genotypes is significantly greater than individuals with hemoglobin SS and $S\beta^0$-thalassemia disease.[35,36] Thus, when considering transplant for children with SCD who have not yet suffered any overt disease-related complications (asymptomatic patients), it seems prudent to initially consider transplant only for individuals with hemoglobin SS and $S\beta^0$-thalassemia disease. However, we feel that there is a role for HSCT for some children with hemoglobin $S\beta^+$-thalassemia and SC disease, as some individuals with these genotypes experience major SCD complications,[37] suffer with pain,[38] and report reduced quality of life,[39] similar to patients with hemoglobin SS and $S\beta^0$-thalassemia disease.

Is there clinical equipoise?

A basic ethical requirement of any proposed clinical study involving different interventions is that there must be "clinical equipoise" regarding the interventions. In other words, experts must be uncertain if intervention A or intervention B is superior. In this case, the research question is as follows: is an HLA-identical sibling HSCT or current supportive care the best treatment approach for less severe SCD? We believe that there is definite clinical equipoise in this setting, as recent reviews have opposing conclusions. Kassim and DeBaun,[32] especially noting further improvement in SCD supportive care with hydroxyurea therapy, are "hesitant" to recommend HSCT for asymptomatic children. In contrast, Sheth et al[14] assert that HSCT "should be considered a first-line therapy for all children with a matched sibling."

What is our obligation to "first, do no harm"?

The principle *primum non nocere* (first, do no harm) is revered as fundamental to medical ethics. Some have cited this concept of nonmaleficence as a reason to potentially not perform HSCT in children with less severe SCD.[40] First, although the risk of transplant-related mortality is low for HLA-identical sibling HSCT (<5%, possibly lower for children with less severe SCD[5]), it is almost certainly higher than the short-term mortality risk of less severe SCD, as we now expect virtually all children with SCD in developed countries to survive childhood with current supportive care practices.[41,42] This small but important risk of death is, however, not the only potential harm of transplant. Importantly, HSCT is also associated with a risk (10-20%)[43] of graft-versus-host disease (GVHD). Although most GVHD can be managed well (and even eliminated), transplant may rarely cause extensive GVHD that may be comparable to or even worse than SCD in its impact on health and quality of life. Another important potential harm of HSCT involves long-term side effects including gonadal dysfunction and infertility,[8,44] although this risk will likely decrease in the future with the increased use of less gonadotoxic conditioning regimens. Additional long-term follow-up is also needed on patients transplanted for SCD to determine if they are at an increased risk of malignancy years after HSCT. Finally, transplant would likely harm the short-term psychosocial well-being of the apparently asymptomatic child and family by requiring them to miss school and work, to endure a long hospitalization possibly far from home, and to follow a strict regimen of medicines, restrictions, and medical appointments for months.

Although the potential harms of HSCT are significant, especially for a child with less severe SCD, it is important to consider these potential harms relative to the risks of having SCD (Table 2). Although childhood mortality in SCD has been dramatically reduced and some individuals even with hemoglobin SS disease are living past age 60,[45] many people with SCD die before age 40.[46-49] In addition to this >20-year reduction in life expectancy, many adults with SCD experience pain most days,[38] have high rates of disability,[50] and report poor overall quality of life.[39,51] Although the long-term prognosis of children with initially less severe SCD may be better (especially in the future with continued improvements in supportive care), an individual patient's disease course is likely to involve significant problems. The specific risk of infertility secondary to HSCT also has to be balanced with the risk of reproductive problems related to SCD complications (impotence from priapism for men,[52-54] increased pregnancy complications for women[55-57]) and also weighed against hydroxyurea therapy toxicity.[44,58,59] Thus, given the serious problems caused by SCD, some have questioned: Is the medical community actually harming patients with SCD by not offering them a curative therapy (HSCT) early and forcing these patients to live with a disease that causes high morbidity and premature mortality?[60]

We believe that currently we do not have sufficient evidence to answer the above question when considering HLA-identical sibling HSCT for SCD. While the potential harms of HSCT are significant, so are the potential harms of SCD (even SCD that is viewed initially as less severe). Given this uncertainty, a trial studying HLA-identical

Table 2. Summary of key potential harms of HLA-identical sibling HSCT and SCD

Harm	HSCT	SCD
Death	Low risk of dying from transplant complication	Very low risk of dying as a child with current supportive care, high risk of dying prematurely as an adult
Infection	Severely immunocompromised for weeks post-transplant	Defective or absent splenic function
Acute complication	Mucositis, hair loss, veno-occlusive disease, cerebral hemorrhage, posterior reversible encephalopathy syndrome	Vaso-occlusive crisis, acute chest syndrome, cholecystitis, priapism, splenic sequestration, aplastic crisis, stroke
Chronic complication	Graft-versus-host disease	Chronic pain, avascular necrosis, progressive multi-organ damage (retinopathy, kidney dysfunction, pulmonary hypertension)
Reproductive problems	Possible secondary to gonadotoxic conditioning	Possible secondary to organ damage (men: erectile dysfunction; women: pregnancy complications) or hydroxyurea therapy
Social	Intense short-term burden due to transplant hospitalization and care post-transplant	Life-long burden of chronic disease

sibling HSCT in less severe SCD does not violate the principle of nonmaleficence. However, it is important to clarify that the transplants being discussed herein are all from HLA-identical sibling donors. At present, we believe it is appropriate to restrict HSCT using alternative donor sources (unrelated cord blood units, unrelated bone marrow donors, haplo-identical family members) to patients with more severe SCD. Currently alternative donor HSCTs for SCD are much more likely to cause harm (higher risk of death, GVHD, graft rejection)[61-64] than are HSCTs from matched sibling donors. Thus, until the potential harms of alternative donor HSCTs can be decreased, they cannot ethically be used to treat children with "less severe" SCD.

Who should decide?

Our society has rejected the notion that a doctor should unilaterally dictate the treatment of a specific patient as medical paternalism. Instead we now embrace the principle of respect for autonomy—an individual patient is honored as the person who makes the final medical decisions regarding his or her treatment. In the research setting, respect for autonomy requires that we obtain the informed consent of the research participant. However, here we are considering a study on young children who cannot consent to participate. Can parents of a child with less severe SCD ethically permit a study of HSCT on their child?

Some may argue that HSCT for young children with less severe SCD violates that child's autonomy. An informed adult with SCD may view HSCT as too dangerous and be unwilling to accept the risks of such an intervention—so why should a young child with less severe SCD be subjected to such a risky intervention (with potential long-term side effects) even if his or her parents give full, informed consent? It would be ethically preferable to wait until the child becomes an adult (or at least an adolescent) who can make his or her own autonomous choice regarding this very difficult decision.

If there was no potential downside in waiting until a child with SCD could consent and make his or her own decision regarding HSCT as an adult, then it would be unethical to transplant children with less severe SCD. However, from a medical perspective, it is likely better to transplant an individual with SCD as a child rather than as an adult. Initially patients with SCD over the age of 16 years were not even considered eligible for transplant because of legitimate concerns that older patients who had already suffered SCD-related organ damage would not tolerate myeloablative conditioning.[3] Even when solely considering pediatric patients, evidence exists that younger children with other conditions have better HSCT outcomes[65] and in particular less GVHD[66-68] possibly due to better pretransplant thymic function compared with older patients.[69]

Regarding SCD specifically, Vermylen et al[5] reported that a group of young (median age, 2.0 years) children transplanted for less severe SCD had an impressive 100% overall survival and 93% event-free survival with no severe GVHD, outcomes significantly better than their older group of patients (median age, 8.6 years) transplanted because of SCD severity. Additional research is needed to confirm this finding that children with SCD transplanted at a younger age and for less severe disease have better HSCT outcomes. In addition to having less organ damage before HSCT that would likely decrease transplant toxicity, younger and less severe patients also have received fewer blood transfusions. Blood transfusions cause alloantibody formation in many SCD patients, and transfusion-related alloimmunization may complicate future HSCT.[70-73] Finally, although a recent study using reduced intensity conditioning was successful in curing adults with SCD with acceptable toxicity (suggesting it is possible to wait until children with SCD become adults to pursue HSCT), these patients required long-term immunosuppression to prevent graft rejection.[12] Even if HSCT as an adult is feasible, it seems desirable to transplant individuals with SCD before they suffer permanent organ damage and other complications of SCD, which, as detailed above, unfortunately begin in infancy.

It is also prudent to consider the idea that restricting a child with less severe SCD from undergoing HSCT violates that child's theoretical future autonomous choice to have wanted to pursue HSCT as a child instead of as an adult. As part of this consideration, it should be noted that adult SCD patients' desire to pursue HSCT and to accept the risk of transplant-related mortality does not appear to be associated with their disease severity or health care providers' assessment of risk.[74] Patients with SCD thus appear to have different perceptions about the acceptability of HSCT risk than physicians and are often willing to accept more risk to achieve cure. Rather than maintaining a paternalistic system in which physicians only consider patients with severe SCD eligible for HSCT, to promote the principle of autonomy, informed patients should be allowed to make their own decision regarding HSCT. Because children are not capable of making such a decision, we believe that, like in other difficult medical decisions and research involving children, parents should decide what is best for their child and thus can ethically consent for the proposed study. Although some may worry that this decision may burden parents or that parents are not capable of properly weighing the risks and benefits of participation for their child (Tables 2 and 3), parents are likely the best agents to represent their child. Of note, parents' willingness to accept hypothetical varying risks of transplant-related mortality for SCD is very similar to the risks that adult patients with SCD would accept,[74,75] supporting the concept that parents make reasonable decisions on behalf of their children.

Table 3. Potential reasons for early transplant vs reasons to wait for transplant in children with less severe SCD

Transplant early to:	Wait to consider transplant because:
Prevent early organ damage secondary to SCD	Advances in HSCT technology may further improve HSCT outcomes in the future
Avoid SCD complications in childhood	Other curative therapy (gene therapy) may be developed in future with less risks than HSCT
Achieve better HSCT outcomes secondary to less pre-HSCT organ damage and alloimmunization	Further improvement in SCD supportive care (new medications other than hydroxyurea) may make curative therapy less important

Justice concerns

It is worth noting that SCD disproportionately affects minority groups traditionally viewed as vulnerable research populations. Although people of many different races have SCD worldwide, in the United States, SCD primarily affects African Americans, a group that historically has suffered serious injustice in medical research as demonstrated by the infamous Tuskegee syphilis study. Given this background, the proposed study of an intervention with serious potential risks on seemingly asymptomatic children for a genetic condition that primarily affects a historically disadvantaged racial group could raise concerns that this group is unfairly being subject to experimentation. However, because the proposed research is seeking to benefit the vulnerable group (and no other group), we argue the opposite idea: justice, with its goal to distribute the benefits of research to all groups, demands that we pursue research like the proposed study on children with SCD to ensure this group receives the best treatment. It unfortunately appears that SCD has not received a fair distribution of research funding compared with conditions like cystic fibrosis that do not primarily affect minorities.[76]

Conclusion

We conclude that a study of HLA-identical sibling HSCT for children with less severe SCD is ethically sound. Such a study must be conducted with strict safeguards in place to monitor safety and to ensure informed parental permission, and patients with certain justified contraindications to HSCT should be excluded. Whereas actual design and feasibility are critical issues for the proposed study comparing HSCT to supportive care, these challenges should not prevent the medical community from conducting this important research. We believe such a trial would be pivotal in advancing the pursuit of optimal treatment options for children with SCD.

Authorship

Contribution: R.S.N. wrote the paper; and J.E.H. and A.E.H. critically reviewed and edited the manuscript.

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