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Stem cell transplant for sickle cell disease

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BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

STEM CELL TRANSPLANT FOR SICKLE CELL DISEASE

by

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B.A., College of the Holy Cross, 2008

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ABSTRACT

Background

Sickle cell disease (SCD) is the most common inherited blood disorder in the United States. As SCD can cause significant morbidity and decrease in life expectancy, further research on curative options is of great interest. Hematopoietic stem cell transplant (HSCT) is the only treatment option offering a chance of cure, but the risks of treatment are not negligible. Because the outcomes of HSCT are best when the procedure is performed at a younger age, understanding what parents know about transplant, their opinion on this option and the risks they are willing to take to achieve a cure is of great value. As sickle cell disease has changed in the United States from a life-threatening condition of childhood to a chronic condition with most of the burden of morbidity and mortality shifted towards adulthood, it is necessary for parents to be fully aware of long term risks and educated on all therapeutic options, so the optimal decision can be made.

Objectives

(i) To learn about parents' recollection and pursuit of further information after undergoing an educational session on risks and benefits of HSCT. (ii) To learn about their worries about transplant and the highest mortality and infertility risks they are willing to accept in order to achieve a cure for their child. (iii) To learn about parents' readiness to proceed to transplant based on a hypothetical scenario.

Methods

This project was performed as part of an ongoing prospective, observational study in which parents were approached for an educational session and a series of surveys, during their child's routine visits to the Pediatric Hematology Clinic at Boston Medical Center. Subjects were parents or guardians of children with SCD under the age of twenty-one. All subjects answered an anonymous baseline questionnaire and underwent a standardized educational session on the role, benefits and risks of stem cell transplant. Those who provided informed consent completed a post-encounter questionnaire on their perceptions about transplant and a follow-up questionnaire. The aims of this study were met by design and administration of the follow-up questionnaire; which consisted of 11 open and close-ended questions administered over the phone, 14 to 30 months after completion of the educational session.

Results

Thirty-five parents had been previously enrolled in the study and 26 of these (74%) responded to the follow-up questionnaire. Two subjects actively declined participation and 7 passively declined participation by repeated claim of unavailability. The risk of death that parents were willing to accept ranged from 0 to 50%. Thirteen were not willing to accept any risk, seven were able to accept a 5% risk, three a 10% risk, one a 20% risk and two a 50% risk. The risk of infertility that parents were willing to accept ranged from 0 to 100%. Three were not willing to accept any risk of infertility, five were able to accept a 5% risk, seven a 10% risk, one a 15% risk, two each for 20%, 25% and 50% and four 100%. Nine parents worried most about death, while another nine worried most about the transplant not working. Two stated infertility, one said graft-versus-host disease and five were most concerned about the recovery process. For the option of proceeding to transplant (based on a hypothetical scenario), nineteen parents (73%) were willing to accept the risk now; five would decline the offer and two were undecided and unable to answer.

Conclusions: Stem cell transplant is often performed on children for treating sickle cell disease, which creates importance for educating parents and understanding their concerns. Parents were willing to accept higher risks of death and infertility as a child's severity of disease increased. Families of children from all disease severities chose to accept transplant in a hypothetical scenario. Physicians may introduce transplant to all SCD families as opposed to viewing this option as a last resort.

TABLE OF CONTENTS

Title	i
Reader's Approval Page	ii
Acknowledgements	iii
Abstract	iv
Table of Contents	vii
List of Tables	x
List of Figures	xi
List of Abbreviations	xii
Introduction	1
Pathophysiology:	2
Inheritance:	4
Prevalence:	5
Treatment:	6
Pain-Relieving Medications	6
Hemoglobin-F Increasing Medications	6
Blood Transfusions	8
Nitric Oxide	9
Antibiotics	10

Hematopoietic Stem Cell Transplant	12
Specific Aims	18
Methods	19
Study Design	19
Target Population	19
Survey Design	20
Conducting the Survey	21
Ethical Considerations	21
Data Analysis	22
Results	23
Searched For More Information About Stem Cell Transplant	24
Recollection of Information	26
Risk of Death Associated With Transplant	27
Risk of Infertility Associated With Transplant	29
Most Common Concern Associated With Transplant	31
Hypothetical Scenario	33
Discussion	35

Appendix 1	40
Appendix 2	44
References	48
Curriculum Vitae	50

LIST OF TABLES

Table	Title	Page
1	Age and Sickle Cell Disease Type for 26 Children Answering Follow-Up Questionnaire	24
2	Parents Searched For More Information About Stem Cell Transplant	25
3	Recollection of Information About Stem Cell Transplant	26
4	Highest risk of death parents willing to accept from stem cell transplant	28
4	Highest risk of infertility parents willing to accept from stem cell transplant	30
6	Most common parental concern for stem cell transplant procedure	32
7	Hypothetical scenario in which parents could choose transplant if child's sibling was a perfect match	33

LIST OF FIGURES

Figure	Title	Page
1	Amino Acid Chains For Normal and Sickle Cell Disease Hemoglobin	3
2	Oxygen Bonding of Fetal Hemoglobin versus Adult Hemoglobin	8
3	Published criteria for proceeding to HSCT in patients with SCT	14
4	Searched For More Information About Stem Cell Transplant	25
5	Recollection of Information	27
6	Highest risk of death parents willing to accept from stem cell transplant	29
7	Risk of Infertility Associated With Transplant	31
8	Most Common Concern Associated With Transplant	32
9	Hypothetical Scenario	34

ABBREVIATIONS

BPG	bisphosphoglycerate
GVHD	Graft-versus-host disease
Hb-F	fetal hemoglobin
Hb-S	sickle cell hemoglobin
Hb-SS	sickle cell anemia
Hb-SC	sickle hemoglobin C disease
Hb-SB+	sickle beta plus thalassaemia
HSCT	hematopoietic stem cell transplant
pO ₂	oxygen partial pressure
SCD	sickle cell disease

INTRODUCTION

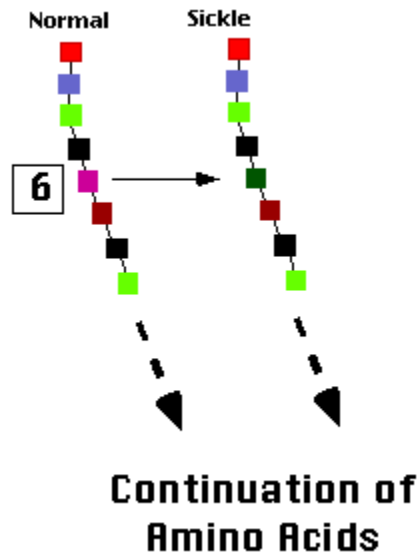
Sickle cell disease (SCD) is the most common inherited blood disorder in the United States. It occurs most frequently in African-Americans, but has prevalence as high as 30% in some countries (Ender, 2011). As SCD can cause morbidity and decrease in life expectancy, further research on curative options is of great interest. Hematologic stem cell transplant (HSCT) is the only treatment option offering a chance of cure, but the risks of treatment are not negligible (Bernaudin, 2009). Because the outcomes of HSCT are best when the procedure is performed at a younger age, understanding what parents know about transplant, how they feel about this option and the risks they are willing to take to achieve a cure is of great value. It is also necessary to understand what type of information parents retain and whether education changes their short or long-term perceptions.

To analyze what factors influence parents' perceptions, this introduction will review the pathophysiology, inheritance, prevalence, complications and treatment options for SCD. It will also provide a framework and justification for the study, which will contribute to improved understanding of parental awareness of HSCT's risks and benefits, parental willingness to take risk to achieve a cure and their readiness to proceed to transplant.

Pathophysiology:

Sickle cell disease is marked by defective hemoglobin. Hemoglobin is the iron-containing oxygen-transport metalloprotein found in red cells of vertebrates and other animals. In mammals, the protein is approximately ninety-seven percent of the cell's dry content and about thirty-five percent of the total content. Hemoglobin transports oxygen from the lungs to the rest of the body, where it is released. The protein molecule has a tetrameric structure, which consists of two alpha and two beta subunits that are held together by non-covalent interactions (Williams, 2010). In sickle cell anemia, however, there is a point mutation in the beta-globin chain (Figure 1). The amino acid glutamic acid is replaced by the less polar amino acid valine at the sixth position of the beta chain. This mutation favors a hydrophobic interaction between each strand and its neighbor. Thus, the abnormal hemoglobin becomes less soluble and polymerizes into crystals that distort the red blood cells into a sickle shape (O'Brien, 2010).

Figure 1: Amino Acid Chains For Normal and Sickle Cell Disease Hemoglobin



The chain of colored boxes represent the first eight amino acids in the beta chain of hemoglobin. The sixth position in the normal beta chain has glutamic acid, while sickle beta chain has valine. This is the sole difference between the two. Available from: http://sickle.bwh.harvard.edu/scd_background.html. Accessed on March 14, 2012.

Normal red blood cells are elastic, allowing them to flow through blood vessels. Unlike normal red blood cells, red blood cells with sickle hemoglobin (sickle cells) assume the shape of a sickle or crescent when oxygen levels are low. This finding is due to precipitation of the polymerized hemoglobin molecule within the cell (Hsieh, 2009).

Once sickle cells assume the crescent shape they become less elastic and can either break (in capillaries or the spleen) and release their contents or block small veins and capillaries and prevent adequate oxygen delivery to tissues (Gazaiev, 2011).

Obstruction of small capillaries causes decreased oxygen delivery to the organ, inflammation, and pain. Over time, tissues are increasingly damaged, which can lead to organ dysfunction in any organ, but typically in the lungs, spleen, kidneys, bone, retina, and brain. If sickle cells become lodged and break down, they release their heme products into the bloodstream and cause jaundice, a classic finding in SCD (Gupta, 2010).

Due to their fragility, sickle cells have a shortened life span lasting from ten to twenty days. In contrast, normal red blood cells survive for approximately one hundred and twenty days. Sickle cells' decreased life span causes an insufficient supply of red blood cells, resulting in anemia. Acute anemia can cause fatigue or shortness of breath upon exertion (Buchanan, 2010). Chronic anemia of sickle cell disease, however, can cause multi-organ dysfunction.

Inheritance:

Sickle cell disease follows an autosomic recessive inheritance, meaning a person must inherit two copies of the sickle cell gene, one from each parent. The HBB gene codes for hemoglobin and is located at position 15.5 on chromosome 11. Mutations in this gene produce various hemoglobin variants. Some of these variants maintain normal function; however, the majority of them produce disease states. When a person is heterozygous for the mutation (inheritance of one sickle cell gene), their condition is called sickle cell trait. People with sickle trait generally have no symptoms, lead normal lives and are thought to be more tolerant of the malaria infection (Hsieh, 2009). This form of the disease, however, is hereditary. Other forms include sickle hemoglobin C disease (HbSC) and

sickle beta plus thalassaemia (HbSB+). These forms are heterozygous states in which one mutated allele creates abnormal hemoglobin S and the other allele creates another form of abnormal hemoglobin. Each of these other genotypes has a slightly varied clinical phenotype (Vermylen, 1997).

Prevalence:

Sickle cell disease is present mainly in the African-American population and is found with less frequency in the eastern Mediterranean and Middle East populations. The sickle cell gene is present in eight percent of black Americans with more than seventy thousand people in the United States having SCD. However, sickle cell trait has prevalence as high as thirty percent in several African countries. Although hematologic changes are evident in the first few weeks of life and the disease can be diagnosed by newborn screen, clinical manifestations are often not seen until the second half of the first year of life (Ender, 2011). By this time, in the absence of normal adult hemoglobin, the fetal hemoglobin (Hb-F) has sufficiently decreased for Hb-S to express itself. Children with SCD experience a variable clinical course, ranging from asymptomatic, to mild infrequent pain crises, to chronic, severe and debilitating pain, restrictive lung disease, growth restriction and stroke. Other complications, more often seen in adolescents and adults include leg ulcers, osteonecrosis, gallstones, renal failure, and retinal damage. Life expectancy is decreased compared to the general population, with an average life span into the mid to late forties (Fry, 2010).

Treatment:

Most treatments and interventions (medications, transfusions, surgeries), can only assist with lessening of acute and chronic symptoms or with reducing the risk of some complications. Hematopoietic stem cell transplant (HSCT) is currently the only curative treatment for SCD (Gaizev, 2005). HSCT, however, is not a risk-free intervention and the decision to proceed to transplant must incorporate the parent's preferences and willingness to accept risks for a chance of cure.

Pain-Relieving Medications

Pain medications, such as non-steroidal anti-inflammatory agents and narcotics, along with adequate hydration and avoiding extremes in temperature play a major role in preventive and symptomatic relief of pain (Gaizev, 2005). Patients with SCD usually have a home pain management plan, but patients can require intermittent hospitalizations for acute pain.

Hemoglobin-F Increasing Medications

Hydroxyurea is the only medication available for SCD reduction of symptoms. It is most frequently prescribed to patients with moderate-to-severe disease as characterized by frequency and intensity of pain crises and history of acute chest syndrome.

Hydroxyurea works by increasing the amount of fetal hemoglobin. Fetal hemoglobin is

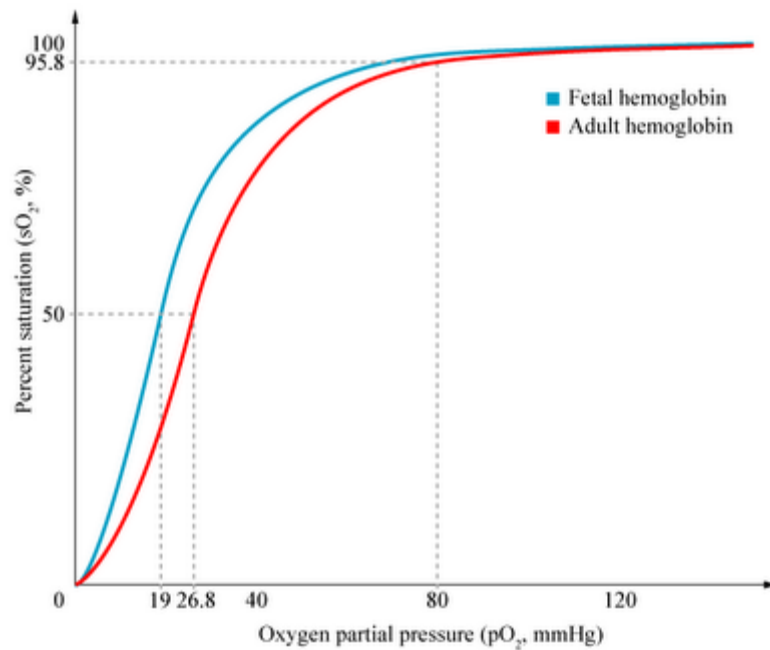
the main hemoglobin present in fetuses and infants and generally disappears by six months of age (Kaye, 1996). The presence of fetal hemoglobin in a red cell containing sickle hemoglobin prevents sickling of the red blood cell by interfering with the hydrophobic interactions that tend to occur between sickle hemoglobins and therefore, by reducing polymerization of sickle hemoglobin inside the cell (Wynn, 2009).

Hemoglobin F has higher affinity for oxygen than hemoglobin B or S (Figure 2). This phenomenon occurs, because fetal hemoglobin must be oxygenated in the placenta, where the oxygen partial pressure (pO₂) is lower than in the lungs. The higher affinity of fetal hemoglobin is due to its lower affinity for bisphosphoglycerate (BPG). Once fetal hemoglobin undergoes its normal decline by 6 months of age, the proportion of sickle hemoglobin increases and symptoms arise (Van Besien, 2010). Children and adults with elevated levels of fetal hemoglobin, either from treatment with hydroxyurea or due to persistent activation of the hemoglobin F gene, tend to have milder symptoms than their peers.

Although hydroxyurea is generally considered to be safe and can be taken indefinitely, not every patient achieves the full benefit. Some patients do not respond to hydroxyurea, while others have side effects consisting of nausea, constipation and drowsiness, neutropenia or thrombocytopenia (low neutrophil count and low platelet count, respectively) (Walters, 2010).

Figure 2. Oxygen Bonding of Fetal Hemoglobin versus Adult Hemoglobin

Fetal hemoglobin differs from adult hemoglobin in that it is able to bind oxygen with greater affinity than the adult form. This gives the developing fetus better access to oxygen from the mother's bloodstream. Available from: http://faculty.ucc.edu/biology-potter/mechanics_of_breathing.htm. Accessed on March 18, 2012.



Blood Transfusions

Blood transfusions play a central role in the management of sickle cell disease. Episodic transfusions are critical for treatment of acute complications such as acute chest syndrome, hypersplenism, and stroke. Chronic (monthly) transfusions are used for prevention of stroke. Monthly transfusions aid in improving height and weight for children with sickle cell disease. Transfusions, however, have short term and long term risks, such as hyperviscosity, immune reaction, and iron overload (Davies, 1997).

Nitric Oxide

Acute management and prevention of vaso-occlusive crises (pain crises) is of great interest. Research has focused on nitric oxide, a natural chemical produced in the body that relaxes smooth muscles and expands blood vessels. Patients with sickle cell disease are deficient in nitric oxide. This lack of nitric oxide constricts blood vessels and it thought to causes pain in sickle cell disease (Griffths, 2005). Several studies suggest that inhalation of nitric oxide decreases the severity and frequency of sickle cell crises.

In a study by Fry et al. 2010, the investigators wanted to determine how children with sickle cell disease responded to nitric oxide and whether this treatment lessened symptoms. The researchers found that nitric oxide was effective by decreasing the severity and frequency of pain episodes.

Another study by Griffths et al. 2005, studied whether inhalation of nitric oxide reduced crisis pain in adult patients and the safety of inhaled nitric oxide. This study demonstrated that inhaled nitric oxide significantly reduced pain scores compared to placebo. Morphine use for pain was also lower in the inhaled nitric oxide group.

A third study by Jordan et al. 2011, examined nitric oxide's effect on acute respiratory distress syndrome. They found that nitric oxide lessened the duration for pressure controlled mechanical ventilation and hospitalization stay.

There is interest in arginine supplements as possible treatment for sickle cell disease. Arginine contributes to the production of nitric oxide and the prevention of pulmonary hypertension. There is also much interest in preventing red blood cell dehydration (Bernaudin, 2005). Sickle cells' crescent shape cause them to lose volume and develop localized increases of intracellular calcium. This calcium activates the membrane protein Gardos channel, which helps to maintain erythrocyte potassium levels. Once activated, the Gardos channel leaks potassium into the plasma. Water then leaves the cell, resulting in erythrocyte dehydration. This dehydration increases the hemoglobin S concentration, leading to further sickling of red blood cells. Several mineral supplements, such as magnesium pidolate and zinc sulfate, may prevent potassium loss and red blood cell dehydration (Gupta, 2010).

Antibiotics

Antibiotics prevent infections in infants with sickle cell disease. Children with sickle cell anemia are highly susceptible to infections due to splenic autoinfarction. Functional asplenia makes patients vulnerable to infections with encapsulated organisms, such as *Streptococcus pneumoniae* and *Haemophilus influenzae* (Gaizev, 2005). Additionally, some studies suggest that neutrophils do not function properly in patients with sickle cell disease.

Neutrophils are the most abundant type of white blood cell in mammals and are part of the innate immune system. In a study by Rehman et al. 1996, investigators evaluated whether impaired neutrophils may play a role in the pathogenesis of vasocclusive crises.

Results showed that impaired neutrophils from sickle cell patients showed dysregulated L-selectin shedding and increased H₂O₂ production. These impairments were able to immobilize neutrophils on the endothelium, thereby reducing blood flow and allowing microvascular occlusion and vascular damage. In a study by Wynn et al. 2009, researchers found a significant difference in neutrophil activation between sickle cell patients and healthy controls as indicated by decreased L-selectin expression, enhanced expression of CD64 and increased levels of soluble markers like elastase. The conclusion was that impaired neutrophils played a large role in the initiation and propagation of vaso-occlusive crises.

In reaction to these findings, established guidelines recommend that children with sickle cell disease begin taking prophylactic antibiotics at two months of age and continue until five years (Bernaudin, 2005). Penicillins are the antibiotic of choice for this prophylaxis, and implementation of these guidelines, along with immunizations, has significantly decreased mortality of children with sickle cell disease in the first five years of life.

Surgical Interventions

There is no surgical cure for sickle cell disease; however, surgery is used to treat certain sickle cell disease complications. Splenectomy, the removal of the spleen, is used to treat splenic sequestration, which can cause hemodynamic instability and death from trapping of red blood cells in the spleen. Cholecystectomy, the removal of the gallbladder, is used to prevent or treat problems caused by gallstones. Urologic

procedures are performed to resolve priapism, a persistent, painful erection of the penis unrelated to sexual desire. If left untreated, priapism can lead to permanent erectile dysfunction and penile necrosis. Hip replacement is performed in response to osteonecrosis, the break down and death of bone tissue due to insufficient blood supply (Davies, 1997).

Hematopoietic Stem Cell Transplant

Hematologic stem cell transplant (HSCT) is the only potential curative treatment option; however, the risks of treatment are not negligible. The first transplant for SCD was reported in 1984 when a subject with leukemia and SCD was cured of both diseases after undergoing HSCT for treatment of leukemia (Hsieh, 2009).

The Procedure: The bone marrow is the substance in the center of the bones, which hosts the hematologic stem cells and produces red blood cells, white blood cells and platelets, among other blood and immune cells. By undergoing a bone marrow transplant, the person is treated with high dose chemotherapy to destroy his/her bone marrow stem cells. The person then receives donated bone marrow stem cells from a closely matched donor through injection into a vein. Over time the donor's stem cells grow in the recipient's bone marrow, thus allowing for the production of normal hemoglobin (Bernaudin, 2009).

The Donors: Full siblings are the preferred donors, but the chance of being a match is only about twenty-five percent for each sibling. If there is no sibling or sibling that is a

genetic match, the person can receive stem cells from a matched donor found in the National Marrow Donor Program.

The Criteria: The criteria to proceed with HSCT in SCD are currently a moving target. In the United States, HSCT is mostly considered for children younger than sixteen, who have an available donor, no significant damage to major organs and have experienced or are determined to be at risk for severe SCD complications. Some of the complications of interest include risk of stroke, recurrent acute chest syndrome and high frequency of pain crises. The most widely accepted criteria were published by Walters, et al in 1996, and are displayed in Figure 3. In the absence of these complications physicians often seek other treatment alternatives as transplant has its own serious risks. However, in Europe, consideration is underway to recommend HSCT for all children with SCD who have a sibling who is a match (Walters, 1996).

Figure 3. Published criteria for proceeding to HSCT in patients with SCT. Table taken from Walters, et al in 1996.

TABLE 1. CRITERIA FOR ELIGIBILITY FOR TRANSPLANTATION IN CHILDREN WITH SICKLE CELL DISEASE.
<p>Criteria for inclusion</p> <p>Sickle cell disease (sickle cell anemia, sickle cell-hemoglobin C disease, or sickle cell-β-thalassemia)</p> <p>Age less than 16 years</p> <p>HLA-identical related donor</p> <p>One or more of the following:</p> <ul style="list-style-type: none"> 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 <p>Criteria for exclusion</p> <p>Age greater than 15 years</p> <p>Lack of availability of HLA-identical donor*</p> <p>One or more of the following:</p> <ul style="list-style-type: none"> Karnofsky or Lansky functional performance score < 70† Acute hepatitis or evidence of moderate or severe portal fibrosis or cirrhosis on biopsy Severe renal impairment (glomerular filtration rate, $< 30\%$ of the predicted normal value) Severe residual functional neurologic impairment (other than hemiplegia alone) Stage III or IV sickle lung disease Demonstrated lack of compliance with medical care Seropositivity for the human immunodeficiency virus
<p>*Patients with HLA-matched related donors with the sickle-cell trait were not excluded.</p> <p>†The Lansky performance score is a measure of functional status in children.</p>

The Risks: The risks of HSCT are broad but include graft failure, death, sepsis, infertility, graft-versus-host-disease and mixed chimerism. Graft failure occurs when the transplanted stem cells fail to grow in the recipient's bone marrow. Death can occur from toxicity of the high dose chemotherapy but also from infections and other events. The

risk of death from sibling-matched HSCT is likely 5-15%. However, European case-series in which children with mild to no symptoms went through HSCT, showed 100% survival (Brown, 2011). Sepsis and death from infection can occur after destruction of the patient's bone marrow, because he/she has insufficient white blood cells and therefore compromised immunity.

Graft-versus-host disease (GVHD) is an inflammatory disease in which there is attack of the new bone marrow's immune cells against the recipient tissues. This disease can occur despite the donor and recipient being HLA-identical, because the immune cells recognize other differences in the tissues. Acute GVHD usually occurs within the first three months after transplant. Chronic GVHD occurs after the first three months of transplant and can last a lifetime. Rates of GVHD vary between thirty to forty percent for related donors and sixty to eighty percent for unrelated donors (Buchanan, 2010). Mixed chimerism is the coexistence of donor and recipient hematopoietic cells, resulting in the variable presence of normal hemoglobin and hemoglobin S in the recipient's blood (Boncimino, 2010).

Parents' Opinions: Few studies have addressed parental attitudes regarding the use of HSCT as a treatment option for SCD. In a study by Kodish et al. 1991, researchers assessed parental attitudes on bone marrow transplant mortality risk. After briefly describing bone marrow transplant and graft-versus-host disease to parents, the study investigators presented a series of hypothetical situations. The result was that 36 of 67 (47%) parents were willing to accept some risk of short-term mortality. A total of 25 of

67 (37%) parents were willing to accept the current 15% mortality risk, and 8 of 67 (12%) were willing to accept a mortality risk of 50% or more. Only 9 of 67 (13%) stated that they would accept a 15% or more mortality risk and an additional 15% risk of GVHD. The parents' decisions were not related to the clinical severity of their child's illness (Kodish, 1991). Although this study examined familial attitudes about mortality risk, it is unclear if these attitudes have changed since the study's occurrence in 1991. The study also did not examine parental knowledge of bone marrow transplant at the start of the study and whether attitudes changed afterwards.

A study by Walters et al. 2010 indicated that parental refusal accounts for 9.5% of reasons for not proceeding to transplant. For patients less than 16 years of age who met study protocol criteria, only 41% agreed to have HLA typing. Of those who agreed to be HLA typed, 57% underwent transplant. These results indicate parents' initial apprehensiveness about transplant but their increased comfort level as they learn more about the procedure.

Many parents understand little science about stem cell transplant. Therefore, investigation is needed to see what parents currently think about the procedure, what risks they are willing to accept and what they would like to know more about. Parental concerns must be efficiently addressed since child's age plays an important role in determining who fits inclusion criteria. Thus, the goal of the overlying project being conducted at Boston Medical Center was to educate parents on transplant's curative potential, assess what parents understand about curative treatment and obtain information

on their most common concerns and worries. The purpose of the follow-up questionnaire was to learn if knowledge motivated parents to learn more about transplant, what continued to worry them about transplant, the risk they were willing to take for cure and their readiness for transplant, based on a hypothetical scenario. .

SPECIFIC AIMS

Sickle cell disease (SCD) can have a variable and unpredictable clinical course. Although mortality in childhood has decreased, the morbidity and early mortality for adults with SCD remains noteworthy (Bernaudin, 2005). The use of hematopoietic bone marrow transplant (HSCT) as a therapeutic approach shows great promise but also presents many ethical and clinical dilemmas. Studies suggest that outcomes after HSCT are best when the procedure is done at a younger age, particularly in childhood, thus the burden of the decision-making falls on the parent(s) of children. Literature on parental understanding and attitudes towards HSCT is limited. A study to address this knowledge gap has been underway at the Pediatric Hematology Clinic at Boston Medical Center since 2009. The current study entailed a follow-up survey and had the following aims:

- (i) To learn about parents' recollection and pursuit of further information after undergoing an educational session on risks and benefits of HSCT
- (ii) To learn about their worries concerning transplant and the highest mortality and infertility risks parents are willing to accept in order to achieve a cure for their child
- (iii) To learn about parent's readiness to proceed to transplant based on a hypothetical scenario

METHODS

This project was performed as part of an ongoing prospective, observational study in which parents were approached for an educational session and a series of surveys, during their child's routine visits to the Pediatric Hematology Clinic at Boston Medical Center. Subjects were parents or guardians of children with SCD under the age of twenty-one. All subjects answered an anonymous baseline questionnaire and underwent a standardized educational session on the role, benefits, and risks of stem cell transplant. Those who provided informed consent completed a post-encounter questionnaire on their perceptions about transplant and a follow-up questionnaire. The aims of this study were met by design and administration of a follow-up questionnaire.

Study Design

Because little is known about parental attitudes toward HSCT, an exploratory and qualitative research strategy was considered to be most appropriate and used.

Target Population

Subjects were parents of children with SCD who had previously consented to the educational study being conducted at Pediatric Hematology Clinic at Boston Medical Center on parental awareness and interest in HSCT for their children with SCD. Inclusion criteria for this study had been child's age <21 years, diagnosis of SCD of the HbSS, HbSC or HbSB+ and arrival to clinic for a routine or "well child" visit. Verification of child's sickle cell disease type and clinical course was performed through

a medical record review. This review recorded baseline medical data, including white blood cell count, hemoglobin, reticulocyte count, bilirubin, LDH and creatinine and whether the child was prescribed any narcotics or hydroxyurea for home use. Study investigators obtained information on history of stroke, acute chest syndrome, pain crises, abnormal MRI and past hospital admits.

Survey Design

Every effort was made to design a clear and easily understood phone follow-up questionnaire (Appendix 2). This questionnaire used sixth-grade language and gave the option of access to an interpreter in order to ensure families' complete understanding. The survey avoids any jargon and double negatives. Questions were designed to be short, used simple language and follow a similar format to the rest of the questions. The goal of this format was to improve predictability and for parents to become more comfortable with answering questions as they moved through the questionnaire. Seven of the ten questions were "yes/no", but always included the option "I don't know". These numbers were coded, using 0 = "no" or "I don't know" and 1 = "yes". Each yes/no question included examples in order to avoid any recall bias. These close-ended questions allowed the subject to focus on certain choices, ensure that he/she considered each possibility and allowed for more direct route to quantitative statistical results. Numerical answer choices did not contain overlapping numbers, in order to reduce misclassification (the possibility of being put in the wrong study category).

Conducting the Survey

The follow-up questionnaire was administered over the phone to subjects enrolled in the parent study 14 to 30 months after the date of enrollment. Parents were phoned three times during business hours with alternate times if needed. If parent did not answer phone or did not complete questionnaire after three attempts, their response was assumed to be passive refusal. All questions and statements guiding the subject through the questionnaire were fully written out. This layout provided the caller with a standard format to complete each interview. Each question was asked one at a time and referred to parents' knowledge or attitudes since their last appointment. For the three open-ended questions, parents were able to give a range of answers but were encouraged to narrow them down to one. These questions allowed parents more opportunity to share their personal experiences and to state what the research team did not consider. For all ten questions, potentially ambiguous terms were discussed and clear explanations were available and standardized.

Ethical Considerations

The principal investigator and study staff were sensitive to patient confidentiality and aware of patient rights. The project for baseline and parents' perspective questionnaires was approved by the Boston Medical Center Institutional Review Board (BMC IRB) in the summer of 2009. The follow-up questionnaire was submitted to the BMC IRB in summer 2011 and approved on August 19, 2011. All data was de-identified, and only the investigator and study staff had access to this material. All data was

password protected and saved in the principal investigator's computer under restricted access. Information will be saved until completion of data analysis and publication.

Data Analysis

Data organized through Excel spreadsheets. Frequencies and proportions were calculated and organized in tabular form to present the full cohort and compare parents' responses with their perceived child's severity of disease. For open-ended questions, the study team maintained a record of all responses. The follow-up questionnaire was analyzed against the parents' perspective questionnaire to find any change in the percentage of responses. The parent's perspective questionnaire is one of the tools used in the overall study and is available in the attachments for reference. Due to the small sample size and qualitative nature of this research study, testing for statistical significance was not pursued.

RESULTS

Of the 35 subjects enrolled in the overall study twenty-six (74%) responded to the follow-up questionnaire. All subjects are referred to as parents. Their children included 14 girls and 12 boys with SCD. As seen in Table 2, the children ranged from 9 months to 18 years. Two parents declined to complete the follow-up questionnaire, and seven passively refused through continued unavailability after three phone attempts. Of the children, whose parents responded to the survey twenty-one had Hb-SS sickle cell disease, four had Hb-SC disease and one child had HB-SB+ disease. Furthermore, based on parents' responses to the baseline questionnaire, none of the children had any symptoms, 12 had mild symptoms, 12 had moderate symptoms and 1 had severe symptoms. One parent did not record severity of symptoms. The respondents included twenty mothers, four fathers and two aunts.

Table 1. Age and Sickle Cell Disease Type for 26 Children Answering Follow-Up Questionnaire

	Enrolled (n=26)
Age in years (range)	Mean: 11 years (9 months to 18 years)
Sickle Cell Disease Type	
HBSS	21 (84%)
HB-SC	4 (16%)
HB-SB+	1 (4%)
Sickle Cell Disease Severity	
No symptoms	0 (0%)
Mild symptoms	12 (46%)
Moderate symptoms	12 (46%)
Severe symptoms	1 (4%)
Not reported	1 (4%)

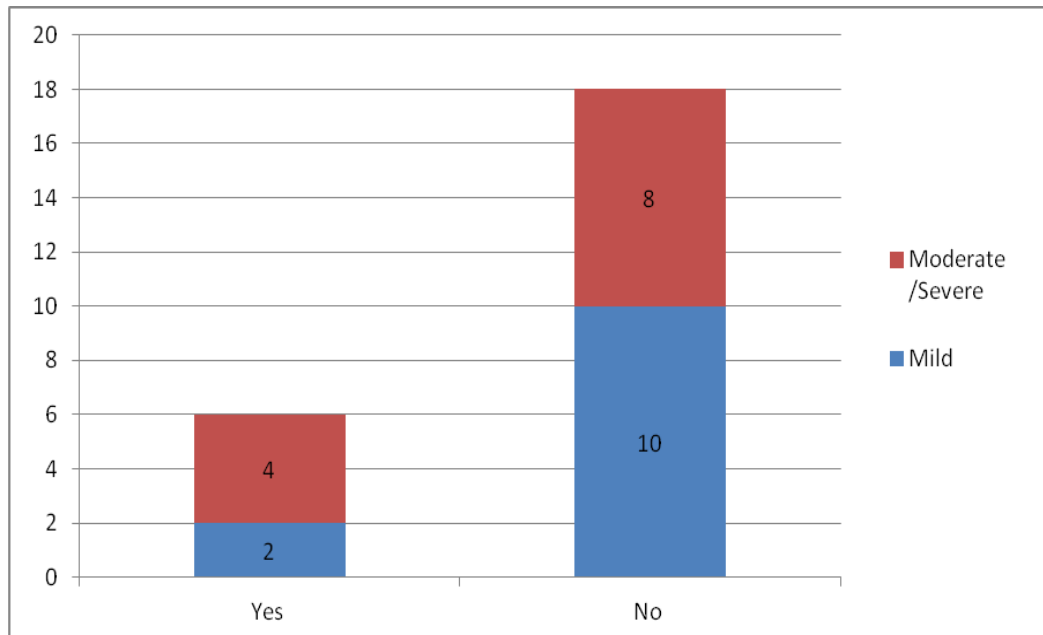
Searched For More Information About Stem Cell Transplant

Parents were asked if they had searched for more information (ex. Google, medical journal etc.) about stem cell transplant since their enrollment visit at Boston Medical Center. Of the twenty-six parents, six (23%) had searched for more information and twenty did not. Of the parents who had searched for more information, four had spoken to another person about stem cell transplant. Two considered their children to have mild disease and four considered their children to have moderate disease.

Table 2. Parents Searched For More Information About Stem Cell Transplant

Parent's Answer	Enrolled (n=26)	Child's Severity of Disease Considered By Parent
Yes	6 (23%)	Mild=2 Moderate=4
No	20 (77%)	Mild=10 Moderate=8 Severe=1 Missing=1

Figure 4. Searched For More Information About Stem Cell Transplant



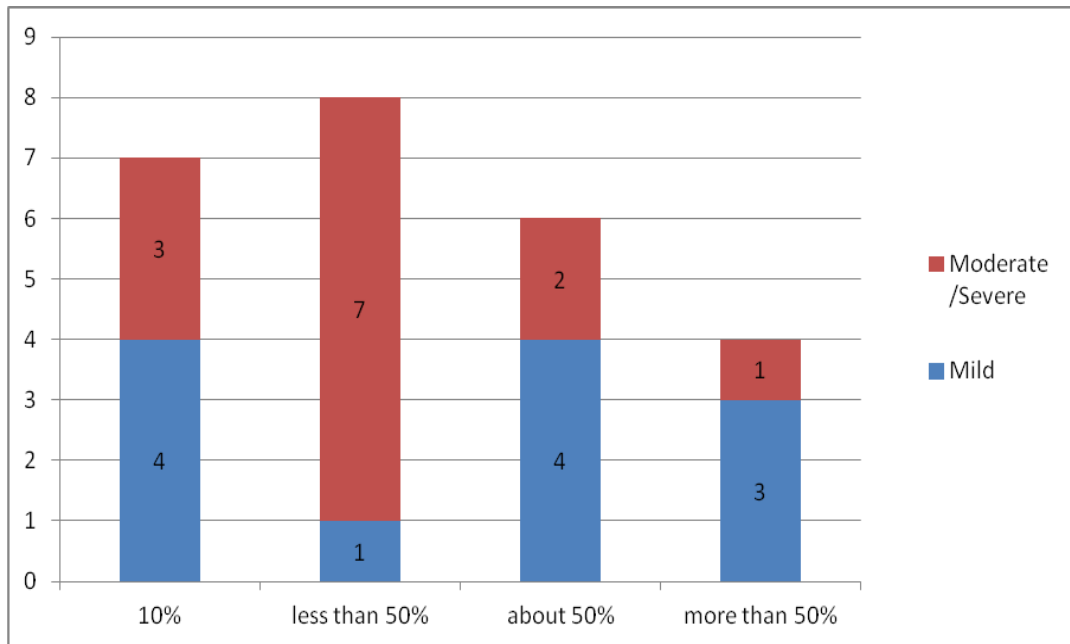
Recollection of Information

Parents were asked if they remembered how often a full sibling is a genetic match. Of the twenty-six parents nine responded with the correct answer of less than half the time or 25% percent, seven responded 10%, six responded half the time and four responded more than half the time. Of the nine who answered correctly, one considered their child's disease mild and seven considered their child's disease moderate. Of the seven who responded 10%, four considered their child's disease mild, two moderate and one severe. Of the six who responded 50%, four considered their child's disease mild and two considered their child's disease moderate. Of the four who answered severe, three considered their child's disease mild and one moderate.

Table 3. Recollection of Information About Stem Cell Transplant

Parent's Answer	Enrolled (n=26)	Child's Severity of Disease Considered By Parent
10%	7 (27%)	Mild=4 Moderate=2 Severe=1
Less than half the time	9 (35%)	Mild=1 Moderate=7 Missing=1
Half the time	6 (23%)	Mild=4 Moderate=2
More than half the time	4 (15%)	Mild=3 Moderate=1

Figure 5. Recollection of Information



Risk of Death Associated With Transplant

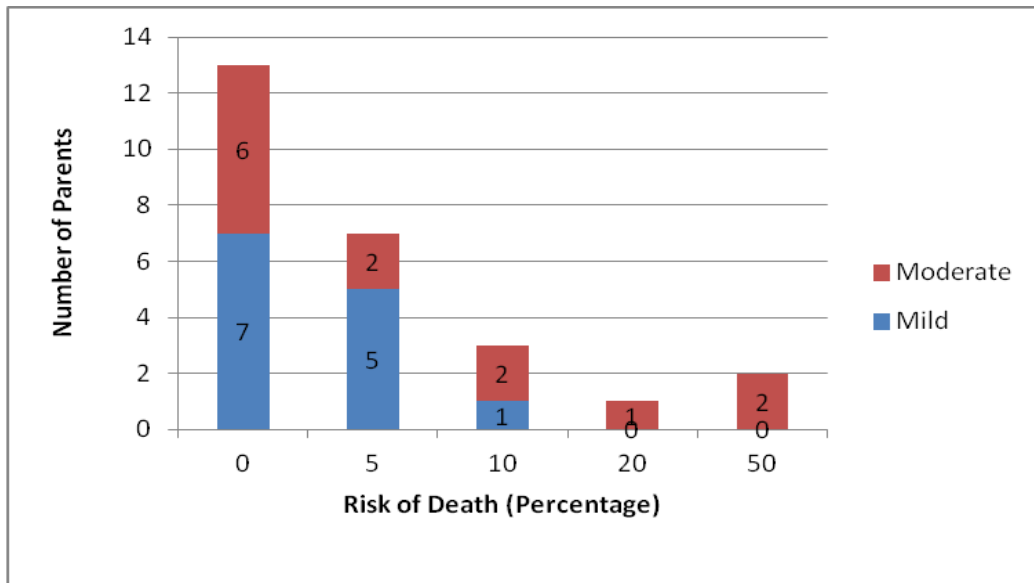
The risk of death that parents were willing to accept during the follow-up questionnaire ranged from 0 to 50% (Table 3). Of the twenty-six children thirteen were not willing to accept any risk, seven were able to accept 5% risk and three were able to accept a 10% risk. One was able to accept a 20% risk, and 2 were able to accept a 50% risk. Two of the three individuals willing to accept a 20% or 50% risk of death considered their children to have moderate sickle cell disease, had not spoken to anyone else for more information about stem cell transplant and were willing to accept the

procedure now. Six of the thirteen parents who weren't able to consider any risk of death considered their child to have mild sickle cell disease, while six of the seven remaining parents considered their child to have moderate disease.

Table 4. Highest risk of death parents willing to accept from stem cell transplant

Parent's Answer	Enrolled (n=26)	Child's Severity of Disease Considered By Parent
0%	13 (50%)	Mild=6 Moderate=6 Missing=1
5%	7 (26.9%)	Mild=4 Moderate=2 Severe=1
10%	3 (11.5%)	Mild=1 Moderate=2
20%	1 (3.8%)	Moderate=1
50%	2 (7.6%)	Mild=1 Moderate=1

Figure 6. Highest risk of death parents willing to accept from stem cell transplant



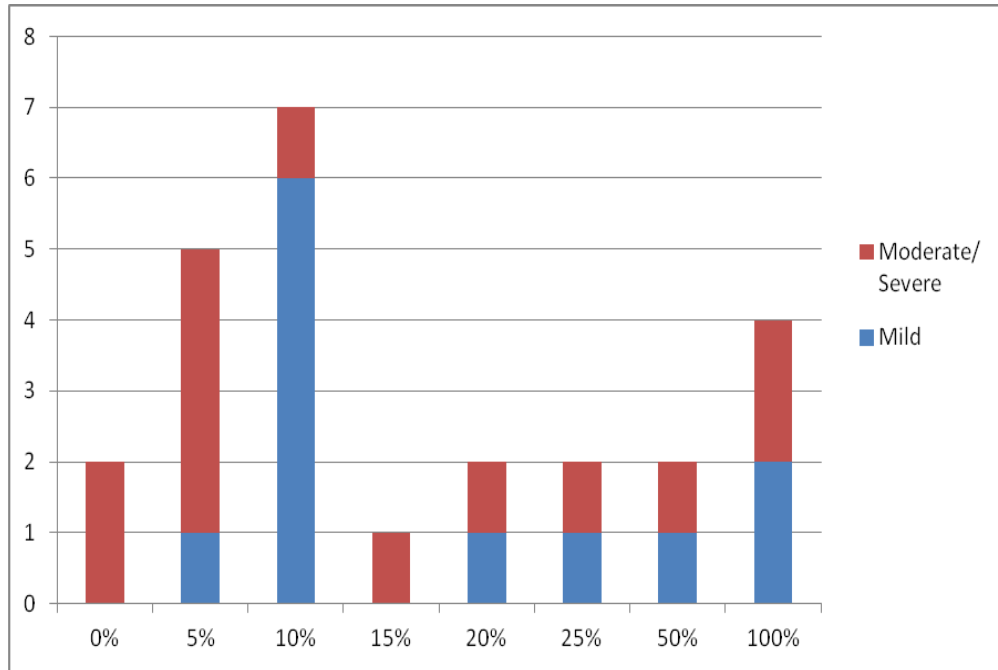
Risk of Infertility Associated With Transplant

The risk of infertility that parents were willing to accept ranged from 0 to 100% (Table 4). Of the twenty-six parents, three were not able to accept any risk of infertility, five accepted 5% risk and seven accepted 10% risk. One accepted 15% risk, two 20% risk and another two 25% risk. Two parents accepted 25% risk, another two 50% risk and four 100% risk. Two of the four parents willing to accept a 100% infertility risk considered their child to have mild disease, while the other two believed their children to have moderate disease. Two of the three parents unable to accept any infertility risk considered their child's disease to be moderate.

Table 5. Highest risk of infertility parents willing to accept from stem cell transplant

Parent's Answer	Enrolled (n=26)	Child's Severity of Disease Considered By Parent
0%	3 (11.5%)	Moderate=2 Missing=1
5%	5 (19.2%)	Mild=1 Moderate=3 Severe=1
10%	7 (26.9%)	Mild=6 Moderate=1
15%	1 (3.8%)	Moderate=1
20%	2 (7.6%)	Mild=1 Moderate=1
25%	2 (7.6%)	Mild=1 Moderate=1
50%	2 (7.6%)	Mild=1 Moderate=1
100%	4 (15.3%)	Mild=2 Moderate=2

Figure 7. Risk of Infertility Associated With Transplant



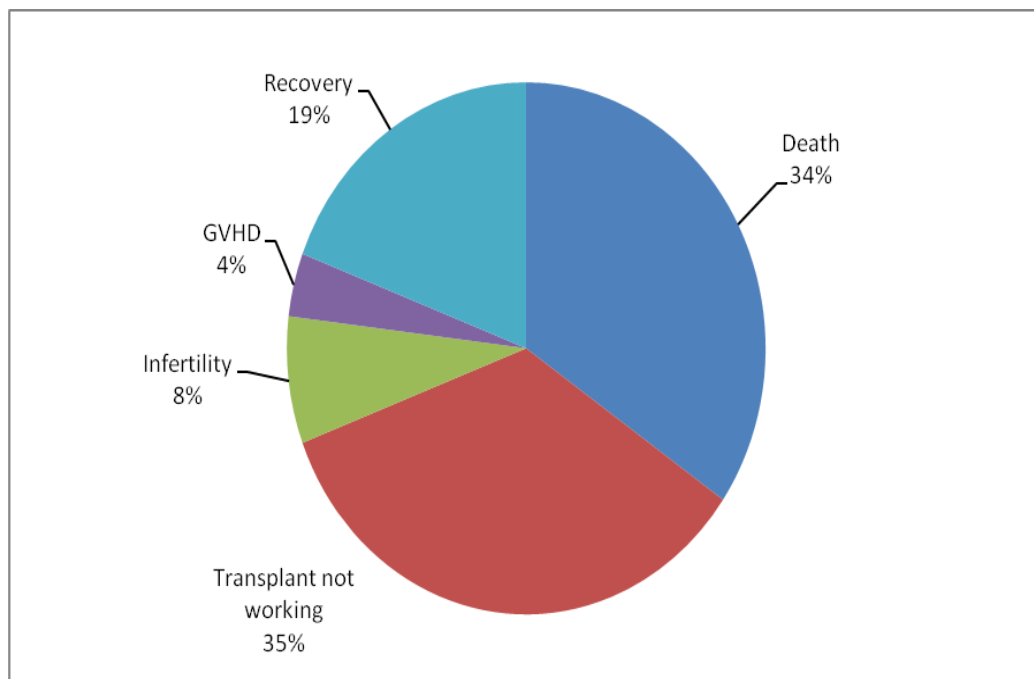
Most Common Concern Associated With Transplant

The second to last question in the follow-up questionnaire assessed what worried parents the most about the transplant procedure (Table 5). Of the twenty-six parents, nine worried most about death, while another nine worried most about the transplant not working. Two stated infertility, and one said graft-versus-host disease (GVHD). The remaining five parents were most worried about the recovery process after transplant. Three, however, spoke and searched for more information about transplant. These three parents were all willing to accept the offer of transplant and wanted to know more about its success rate.

Table 6. Most common parental concern for stem cell transplant procedure

Parent's Answer	Enrolled (n=26)
Death	9 (34.6%)
Transplant Not Working	9 (34.6%)
Infertility	2 (7.6%)
Graft-Versus-Host-Disease (GVHD)	1 (3.8%)
Recovery Process After Transplant	5 (19.2%)

Figure 8. Most Common Concern Associated With Transplant



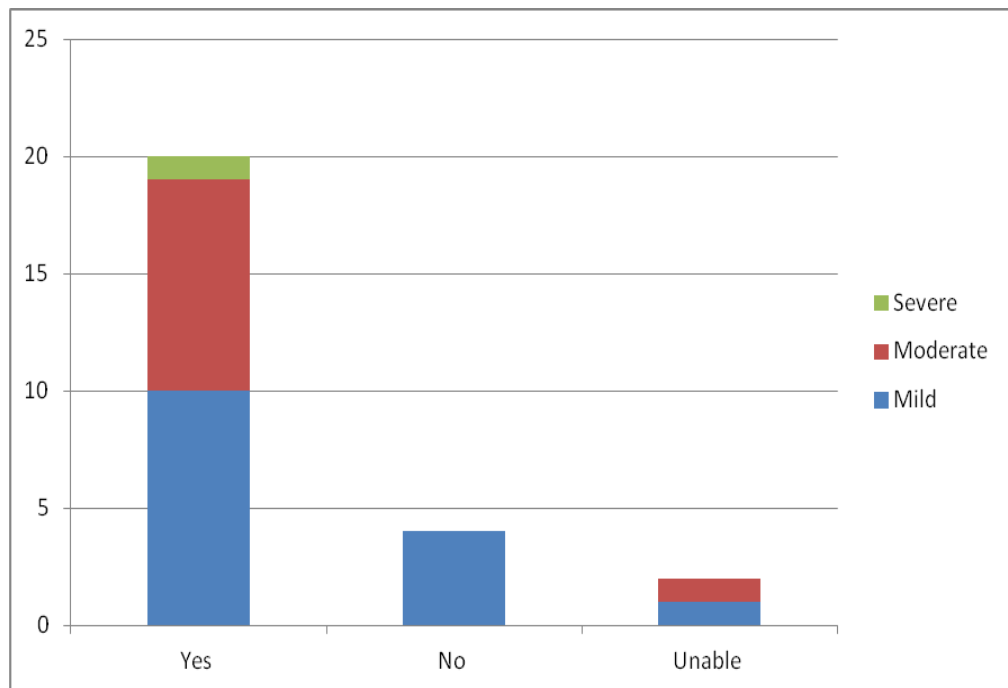
Hypothetical Scenario

The last question on the follow-up questionnaire posed a hypothetical scenario in which a parent could choose transplant if the child's sibling was a perfect match (Table 6). Of the twenty-six parents, nineteen parents (73%) reported willingness to proceed to transplant and five (19%) reported they were not willing to accept the risk. The parents not willing to proceed to transplant had not spoken or searched for more information about stem cell transplant and considered their child's sickle cell disease to be mild. Of the nineteen parents willing to proceed to transplant, ten believed their child's disease to be mild, seven considered their child's disease moderate and one believed her child's disease to be severe.

Table 7. Hypothetical scenario in which parents could choose transplant if child's sibling was a perfect match

Parent's Answer	Enrolled (n=26)	Child's Severity of Disease Considered By Parent
Yes	19 (73%)	Mild=10 Moderate=7 Severe=1 Missing=1
No	5 (19%)	Mild=1 Moderate=4
Unable To Answer	2 (8%)	Mild=1 Moderate=1

Figure 9. Hypothetical Scenario



DISCUSSION

This study, started in 2009, is the first to investigate what parents know about stem cell transplant, their opinions about the procedure, what they would like to know more about and the risks they are willing to accept for their child. It examines whether briefly educating parents influences their short or long-term perspectives about the procedure. This information is essential to physicians who may have patients with more severe sickle cell disease as well as social workers, hematologists or pediatricians who may serve as advocates for parents with children having sickle cell disease.

Of the risks described to parents for transplant, infertility, isolation and death generated the most concern. Parents were willing to accept between 0 and 50% risk of death. Eleven of the twelve parents who considered their child's disease to be mild stated mortality risks of 0, 5 or 10%. Two of the three parents who were willing to accept a 20 or 50 percent risk considered their child's disease moderate. These findings correlate with previous studies. For parents with SCD, one study found that only thirty-seven percent were unwilling to accept any risk of death, forty-six percent were able to accept a 15% mortality, and fifteen percent were willing to accept more than a 35% risk. Another study by Van Besien et al. 2010 indicated that sixty-two percent of adults with SCD were willing to accept more than a 10% risk and thirty percent of parents more than a thirty percent risk. These results demonstrate how as a child's sickle cell disease progresses in severity, the parents' willingness to accept death risk increases. Those living with sickle

cell disease are willing to accept more mortality risk. This finding may be present, because those with sickle cell disease have experience with potential complications.

Parents were willing to accept between a 0 to 100% risk of infertility. Seven of the thirteen parents who considered their child's disease mild were willing to accept a 10% or less risk of infertility. Four of the twelve parents who considered their child's disease moderate were willing to accept a 25, 50 or 100% risk. These results indicate that as a child's severity of disease increases, parents on average become more willing to accept a higher risk of infertility. Of the parents who considered their child's disease mild, one was willing to accept a 25% risk and two a 100% risk. Therefore, the correlation between infertility risk and child's severity of disease although present does not appear to be as strong as that between risk of death and disease severity.

Although sickle cell disease has multiple risks, HSCT has been challenged as a treatment option due to limited donors. It is estimated that approximately eighteen percent of children will have a matched sibling donor (Wynn, 2009). Cord blood can be used as a source of stem cells for HSCT. Parents, however, have reported limited consideration of saving cord blood from past or future pregnancies (Boncimino, 2010). It is necessary for parents of children with severe sickle cell disease to consider transplant as it is the only treatment option. The study begun in 2009 and demonstrated that most parents (71%) considered it important to know if siblings were a match and 59% would consider having another child to find a donor. This positive attitude toward matched donors is reflected in the recollection of information in the follow-up questionnaire. The

most selected answer to the question of how often a full sibling is a match was the correct response of less than half the time. The two answers closest to less than half the time: 10% and half the time each had seven and six parental responses, respectively. This result indicates how parents value matching donor information and thus are able to make a correct or close approximation. They reflect the importance of discussing HSCT and HLA typing as part of routine SCD care and teaching about transplant's role as a potential curative option.

Sickle cell anemia's varied clinical course and phenotype make HSCT's recommendation difficult. HSCT, however, has had much success in children of good health including no organ impairment and no chronic conditions (Bernaudin, 2005). Treatment has not had this success in the adult population (Abboud, 2009). Therefore, much focus has been on the interest and concerns of the parent population. To learn parents' interest in HSCT and whether education prompted the search for more information, we asked parents in the follow-up questionnaire if they had looked for more information since their enrollment visit. Six of the parents stated that they had looked for more information while the remaining twenty stated that they did not. Although the majority of parents had not searched for more information, this finding may be due to parents' lack of resources. This possibility would agree with what we found in the study begun in 2009. Forty percent of parents had not heard of HSCT, and fifty-eight percent did not believe there was any curative therapy for SCD. After receiving a brief education about HSCT, sixty-seven percent agreed to consider transplant, and seventy-one percent

believed it was important to know if siblings were a match. These results indicate the importance of educating parents about HSCT, informing them that there is a potential cure for SCD and testing siblings to see if they are a match. It may be helpful to distribute information to patients to aid their long-term recollection.

Parents of children with severe sickle cell disease were more aware of HSCT than those with asymptomatic or mild disease. Parents of children taking hydroxyurea were the least likely to know there was a curative option while those with children with moderate to severe disease were the most likely to know. These differences indicate physicians' practice of discussing HSCT with only those who have more severe disease. It may be beneficial for health care providers to discuss transplant with parents in SCD's early stages. This practice would allow parents to make fully informed decisions and consider transplant when it has the highest rate of success.

The follow-up questionnaire assessed whether parents would consider transplant if given the knowledge and opportunity. Parents were asked if they would accept transplant for their child upon learning that the child's sibling was a match. Nineteen agreed to accept transplant, five refused the option and two were unable to answer. Of the parents who agreed, ten considered their child to have mild disease, seven moderate and one severe. Of the parents who refused transplant, four considered their child's disease moderate and one mild. These results highlight how parents of children with mild disease will consider transplant and are interested in understanding all their options. Physicians look at transplant as a "last resort" once the child has taken hydroxyurea and develops

complications. To target patients during their opportunity window, physicians may want to view transplant as a first-line treatment strategy to be discussed with all patients. The finding that one of the four parents who refused transplant considered their child's disease mild and the other three moderate suggests that as SCD progresses, parents are more willing to consider alternative options. Physicians may introduce HSCT to all patients but emphasize this option more to those with severe disease.

Hydroxyurea in addition to antibiotics and blood typing have prolonged the lives of those with SCD from fifty years ago. The life expectancy in America for those with SCD has risen from fourteen years in 1974 to fifty-three years in 2007 (Ender, 2011). Despite these treatments patients still live approximately thirty years less than the general African population. Fifty percent die by age fifty from stroke, organ failure, opioid-seeking behavior and pregnancy complications (Marengo, 2007). It is unclear if parents are aware of this difference for their children. In the study begun in 2009, sixty-five percent of parents reported having another family member with SCD, and sixty-six percent reported fear for their child's future. This fear may result from parents seeing relatives suffer due to pain crises, organ damage, gallstones or blindness. By understanding the potential future of their children with sickle cell disease, parents who consider their child's disease mild may want to learn more about curative options and high-risk treatments. The majority of parents willing to accept transplant in each disease severity category indicates families' openness to treatment options as opposed to a risk-averse response.

APPENDIX 1

Baseline Questionnaire

Please answer the following questions to the best of your knowledge.

1. What is the age of your child? _____ Years _____ Months

2. Does he have any siblings? _____ Yes _____ No

_____ Number of siblings (same mother and father)

_____ Number of half-siblings (share one parent)

3. What kind of sickle cell disease does your child have? (Please mark with an X)

- a) SS c) SC e) Not sure
b) S-B⁰ thal d) Other (please write in) _____

4. What is the severity of your child's sickle cell disease?

- a) No symptoms (ever)
b) Mild (infrequent symptoms that do not interfere with quality of life)
c) Moderate (frequent symptoms, but able participate in age appropriate activities)
d) Severe (frequent symptoms interfering with quality of life)

5. Has your child ever experienced any of the following conditions? (Check all that apply with an X):

	No	Yes	Do not know	Times/year (past year)	Total (approximately)
Pain episodes leading to visit to the emergency room or hospital					
Acute Chest Syndrome (Bad lung disease)					
Transient Ischaemic Event (TIA: short lasting change in consciousness or activity)					
Stroke (long lasting change in consciousness or activity)					
Abnormal neurologic study (transcranial Doppler or MRI/MRA)					
Osteonecrosis (thinning of the bone of the hip or shoulder)					
Priapism (spontaneous erection)					

of the penis)					
Antibodies against red cells for a blood transfusion.					

6. Has your child been treated with any of the following? (Check all that apply with an X)

	No	Yes	Do not know
a) Hydroxyurea: a medicine for sickle cell disease			
b) Single blood transfusion			
c) Many blood transfusions (but not on a regular basis)			
d) Monthly blood transfusions			
e) Medicine to remove excess iron			

7. Is there a cure for sickle cell disease? (Please mark with an X)

1. No _____

2. Yes _____

8. Do you know any adults with sickle cell disease? (Please mark with an X)

1. No _____

2. Yes _____

9. Have you ever heard about stem cell or bone marrow transplantation as a treatment option for sickle cell disease? (Please mark with an X)

1. No _____

2. Yes _____

10. Have you ever discussed or considered stem cell or bone marrow transplantation for your child? (Please mark with an X)

1. No _____

2. Yes _____

11. Would you be interested in learning about the role of stem cell transplant as treatment option in sickle cell disease? (Please mark with an X)

1. No _____

2. Yes _____

If you are not interested in learning more and would like to tell us why not, please write your reasons below (you do not have to write anything if you do not want to).

Informed Consent obtained _____ Study Number _____ Date _____

APPENDIX 2

Parent's Perceptions Questionnaire

Rate each the following questions from 1-5 with rising level of agreement with the statement.

	1 Dis- agree	2 somewhat disagree	3 neutral	4 agree	5 strongly agree
1. The information provided to me today about stem cell transplant was valuable.	1	2	3	4	5
2. I wish I had heard this information before.	1	2	3	4	5
3. I would consider stem cell transplant as a treatment option for my child any time.	1	2	3	4	5
4. I would consider stem cell transplant as a treatment option for my child only if his sickle cell disease worsens.	1	2	3	4	5
5. Knowing if my child has a "matched-sibling" that can serve as donor is important to me.	1	2	3	4	5
6. If my child does not have a "matched sibling" that can serve as donor, I would consider having another child to try again to find a donor.	1	2	3	4	5
7. If my child does not have a "matched sibling" that can serve as donor, I would consider using a donor from a bank.	1	2	3	4	5
8. I have saved the umbilical cord blood of my children in a	1	2	3	4	5

bank (for use by my family).					
9. I have donated the umbilical cord of my children to a bank (for use by anyone who needs it).	1	2	3	4	5
10. I have considered saving the umbilical cord blood of my next child.	1	2	3	4	5
11. Seeing family members or friends with severe sickle cell disease makes me worry about my child's health when he grows up.	1	2	3	4	5
12. Hearing the information about transplant has changed my mind in a positive way (now I feel interested in considering transplant).	1	2	3	4	5
13. Hearing the information about transplant has changed my mind in a negative way (now no longer would consider transplant).	1	2	3	4	5
14. The risks of transplant outweigh the benefit of a cure.	1	2	3	4	5

15. If your child had a sibling that could serve as donor, how strongly would you consider transplant?

1. Not at all
2. Somewhat strongly
3. Very strongly

16. How much do the following situations make you consider transplant?

	1	2	3
	Not at all	Somewhat	A lot
Frequency of pain episodes	1	2	3
Need for pain killers (narcotics)	1	2	3
Need for blood transfusions	1	2	3
Worry about lung problems (acute chest syndrome)	1	2	3
Worry about increased risk for stroke	1	2	3
Worry about increased risk for osteonecrosis (bone thinning)	1	2	3
Worry about increased risk for kidney problems	1	2	3

17. Among the risks of transplant explained to be today, I am most concerned about:

(Rate in order of 1-7 with 1 being most important to you and 7 least important to you)

_____ Only achieving partial response (chimerism)

_____ Graft versus host disease (donor cells attack the child's skin, gut and/or liver)

_____ Need for isolation and restrictions (need to decrease contact with other for almost a year)

_____ Graft failure (transplant not working)

_____ Risk of death (risk of dying from transplant related reasons)

_____ Infertility (inability to have children after transplant)

_____ Other: _____

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CURRICULUM VITAE

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