Hematopoietic stem cell transplant : is this the definite cure for sickle cell anemia?

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2016

Dedication

My scholarly project is dedicated to God for his infinite wisdom in my life. Also, to my husband for his constant love and support. Also to my children, Anyanna and Nyenna, thank you for your patience and love. You all make my life beautiful.

Acknowledgments

I would like to thank my scholarly project advisor, Dr. Carolina Wishner, MD, MPH, for her guidance, support, and assistance throughout the development of my project. I appreciate her knowledge and advice in creating a well-structured and thorough clinical paper.

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CHAPTER 1

INTRODUCTION

Sickle cell disease (SCD) affects millions of people around the world and is associated with significant morbidity and premature mortality. It is caused by a genetic abnormality commonly seen in people with ancestors from sub-Saharan Africa, South America, the Caribbean, Central America, Saudi Arabia, India, Turkey, Greece, and Italy (Lipton, 2015).

Sickle cell disease (SCD) is a devastating disease that affects virtually every tissue in the body, causing significant morbidity and resulting in a reduced life expectancy. Recent studies have shown that the median life expectancy for SCD individuals in the US is less than half of the general population, patients with SCD are expected to die before their 40th birthday (Bhatia & Sheth, 2015). In 1973, the average lifespan of a person with SCD in the United States was only 14 years. Advances in the diagnosis and care of SCD have made this improvement possible.

Currently, we have limited options in the treatment of SCD, including transfusion therapy, hydroxyurea (HU), and the only definitive curative modality–hematopoietic stem cell transplantation (HSCT). HSCT is a complex and expensive treatment, with some mortality and short- and long-term morbidity, but recent advances have greatly improved outcomes (Oringanje, Nemecek, & Oniyangi, 2013).

There is no widely available cure for sickle cell disease. Some children with the disease have been successfully treated with blood stem cell, or bone marrow transplants. This treatment modality was thought to be toxic for use in adults; therefore it is used more in children and adolescents (Bhatia & Sheth, 2015). High doses of chemotherapy are used to destroy all of a child's bone marrow, which is then replaced with marrow from a donor. Stem cell recipients

typically need to take immunosuppressants for months to a few years. These medications can cause serious side effects.

At the present time, hematopoietic stem cell transplantation (HSCT) is the only cure for SCD. Unfortunately, most people with SCD are either too old for a transplant, and the limited amount of donors acts as a disadvantage to the use of HSCT (Omondi et al., 2013). A well-matched donor is needed to have the best chance for a successful transplant. A typical donor for this procedure is usually a sibling without sickle cell disease, which is limiting in the first instance.

There are other effective treatments that can reduce symptoms and prolong life. Such as regular health checkups, immunizations, the use of pain relieving medicines and adequate oral or intravenous fluids for patients during pain crises, and blood transfusions and hydroxyurea for patients who develop more serious complications (Vermylen, 2013). Early diagnosis and regular medical care to prevent complications also contribute to improved well being. These treatments improve the outcome of patients with sickle cell disease. These treatments are not definite cure for the disease and do not effectively reduce several issues associated with the disease. Early diagnosis and regular medical care to prevent complications also contribute to improved well-being.

Problem Statement

Sickle cell disease is not a common disease in the United States; it affects mostly people of African descent in the United States. It is largely seen in other parts of the world such as sub-Saharan parts of Africa and the Mediterranean countries. With recent increase in immigrants into the United States, patients with sickle cell disease is expected to increase. But with increasing

awareness and knowledge of the disease and preventative measures, such as matching blood types prior to procreation, SCD is expected to be on the decline and effectively managed from the onset of life. Since the disease is gotten only through inheritance from both parents, the only means to avoid rapid increase of the disease is to educate carriers of the genes from procreation with other carriers. This is difficult to achieve, therefore it is important to provide an accessible definite cure of the disease.

Purpose

The purpose of this literature review was to determine current treatment, complications, inheritance pattern, recent research of HSCT, risk factors, limitation, future use and to determine if HSCT is a standard definite cure of the disease.

Scope

This review focused on risk factors, prevalence, ethnicity, and clinical manifestations of SCD. This review also investigated the efficacy of HSCT and other treatment options available for SCD.

Methods

A clinical review was conducted using multiple search engines, federal websites, and National Institutes of Health website. These search engines included PubMed, MEDLINE, United States Department of Health and Human Services, Children's National Health System, medical centers websites, and Google Scholar. Original articles were used for this clinical

review; these articles were located by searching for the following key words: hematopoietic stem cell transplant, sickle cell disease, children, reduced intense conditioning, and hydroxyurea.

Preferences were given to studies done within the last 5 years, studies such as double blind, randomized, controlled trials with both large and small sample sizes and systematic reviews and meta-analyses were the focus of my research.

Literature Review

Organs of the body require adequate supply of oxygen to function effectively. Hemoglobin transports oxygen to different organs in the body. Effective supply of oxygen to these organs cause them to function maximally. Red blood cells that contain normal hemoglobin are disc shaped. This shape allows the cells to be flexible, enabling them move through large and small blood vessels to deliver oxygen (Thompson et al., 2013).

Sickle cell disease (SCD) is caused by an abnormal hemoglobin, called hemoglobin S. The defect in hemoglobin S gene causes the production of abnormal beta globin, thus changing the effective functioning of the hemoglobin. The overall effect of this defective gene leads to insufficient oxygen carrying capacity of the hemoglobin found in red blood cells. The change in hemoglobin causes normally round red blood cells to become stiff, sticky, and sickle-shaped. The deformed cells causes blockage of blood flow, causing severe pain, organ damage, and stroke. Sickle hemoglobin differs from normal hemoglobin; it forms stiff rods within the red cell, causing it to look crescent, or sickle shape. Sickle-shaped cells are not flexible and can stick to vessel walls, causing a blockage that slows or stops the flow of blood. This prevent adequate supply of oxygen to nearby tissues (Apanah & Rizzolo, 2013).

The lack of tissue oxygen causes attacks of sudden, severe pain, called pain crises. These pain attacks occur without warning; and it is often severe, resulting in patients seeking medical relief. The red cell sickling and poor oxygen delivery can also cause organ damage. Over a lifetime, SCD can lead to organ damage; most organs affected by SCD are spleen, brain, eyes, lungs, liver, heart, kidneys, penis, joints, bones, or skin (Fasano, Meier, & Hulbert, 2015).

Sickle cell disease is an inheritable disease; the disease is passed by genes from parents to their offspring. SCD patients inherit two abnormal hemoglobin genes, one from each parent. When an individual has two hemoglobin S genes, Hemoglobin SS, then it is referred to as sickle cell anemia (Fasano et al., 2015). Hemoglobin SC disease and hemoglobin Sβ thalassemia are two other common forms of SCD. But the emphasis of this review in on patients with hemoglobin SS.

The lifespan of a normal red blood cell is between 90 to 120 days, but sickle cells last only 10 to 20 days**.** The human immune system recognizes these sickled shape red blood cells as abnormal, thus causing them to hemolyze. As a defense mechanism to the early lysis of the sickled red blood cells, the body continuously makes new red blood cells to replace the old cells; however, in SCD the body is unable to produce adequate blood due to the rapid lysis of the cells. Because of this, SCD patients are often anemic (Le et al., 2015).

Sickle cell disease is a life-long illness. The severity of the disease varies widely from person to person. Our ability to predict the severity of SCD in individual patients is limited (Fasano et al., 2015).

Research Question

Hematopoietic stem cell transplant: is this the definite cure for sickle cell anemia?

CHAPTER 2

SICKLE CELL DISEASE: COMPLICATIONS AND TREATMENTS

SCD is an autosomal recessive genetic disorder. As previously stated SCD occurs when an offspring inherits defective hemoglobin S gene from both parent. When the hemoglobin S gene is inherited from only one parent and a normal hemoglobin gene is inherited from the other, this is known as have sickle cell trait. This means the patient is a carrier of defective gene but do not have the disease, thus they are generally healthy individuals. Carriers of the defective genes have the capacity to transfer the defective gene to their offspring. Individuals with two copies of the gene are considered to have SCD and may experience symptoms on various levels, starting as early as the first year of life (Fasano et al., 2015).

Major Complications of Sickle Cell Disease

Sickle cell disease is characterized by several complications such as, hemolytic anemia, painful vaso-occlusive crisis, stroke, avascular necrosis, pulmonary hypertension, susceptibility to infections, renal failure, and thrombosis. These complications consequently reduces life expectancy. Neurologic complications is seen to develop in 27% of children with SCD and acute chest syndrome in 25%. These tissue injuries significantly influence quality of life in most patients (Ozdogu & Boga, 2015). Listed below are further explanation to the complications associated with the disease.

Pain episodes (crises) is caused by sickle cells occluding the blood vessels, this reduces blood flow and decrease oxygen delivery. The pain is often described by patients as sharp, intense, stabbing, or throbbing. Pain crisis experienced by SCD patients has been attributed to either of the following:

- Illness
- Temperature changes
- Stress
- Dehydration
- Being at high altitudes

But often the triggers or causes of the crisis are not known.

People with SCD experience fatigue as a result of mild to moderate anemia. Severe anemia can be life threatening. Severe anemia in an infant or child with SCD can be caused by either splenic sequestration crisis or aplastic crisis (Ozdogu & Boga, 2015). Splenic sequestration crisis occurs when the red blood cell occlude blood flow to the spleen, accumulation of these sickled red blood cell is seen over time causing the enlargement of the spleen. This reduces the number of red blood cells in circulation, leads to infection and causes severe anemia. An enlarged spleen also causes pain in the left portion of the stomach and can be palpated (Ozdogu & Boga, 2015). Aplastic crisis is by parvovirus B19 infection, also called fifth disease or slapped cheek syndrome. Parvovirus B19 is a very common infection, but in SCD, it causes the bone marrow to stop producing new red cells for a while, leading to severe anemia (Ozdogu & Boga, 2015). Severe anemia in adults is caused by other factors not associated with splenic sequestration crisis and aplastic crisis. No matter the cause, severe anemia may lead to symptoms that include:

- Shortness of breath
- Being very tired
- Feeling dizzy
- Having pale skin

Since SCD damages the spleen, its functions are weakened or destroyed early in life. People with SCD who have suffered damage to their spleens are at risk for serious bacterial infections that can be life threatening.

Occlusion of blood vessels in the lungs deprives the lungs of oxygen, therefore causing damage to parts of the lung and this leads to inadequate exchange of oxygen. This condition is known as acute chest syndrome. Acute chest syndrome often starts a few days after a painful crisis begins. This condition is very serious as a lung infection may accompany this disorder.

Clinical stroke in SCD patients is a lack of blood supply to parts of the brain. The symptoms depend upon what part of the brain is affected. As many as 24 percent of people with hemoglobin SS and 10 percent of people with hemoglobin SC may suffer a clinical stroke by age 45. In children, clinical stroke occurs most commonly between the ages of two and nine, but recent prevention strategies have lowered the risk. Silent stroke is damage to the brain without any outward manifestation. This is commonly seen in SCD patients. Silent brain injury can lead to learning problems or difficulties making decisions or maintaining a job. Silent stroke is seen through brain imaging.

Sickle cell disease also damages blood vessels in the eye. The most common site of damage is the retina; SCD causes occlusion of blood vessels in the retina and can lead to hemorrhage of these blood vessels in the retina. The retina is the light-sensitive layer of tissue that lines the innermost portion of the eye and sends visual messages through the optic nerve to the brain. This can lead to detachment of the retina. Long standing damage to the retina causes blindness.

Conventional Sickle Cell Treatments

Prior to hematopoietic stem cell transplant (HSCT), the mainstay of the management of SCD had been supportive care, such as infection prophylaxis, management of pain crises, and specific treatment of acute complications with intermittent blood transfusions (Field & Nathan, 2014).

Regular Red Blood Cell Transfusion Therapy

Regular red blood cell transfusion therapy has been effective in alleviating most symptoms of SCD, and may alter the progression of the disease. However, it does not prevent the development or progression of silent infarcts in all patients, and other complications associated with SCD as listed in the above pages.

Moreover, children who received transfusions as prophylaxis for stroke has been noticed to have the risk of stroke reverted if the blood transfusions are discontinued. Other long-term complications of regular transfusions include alloimmunization and iron overload, which might lead to death. Thus, making blood transfusion inadequate as the ideal treatment for SCD and furthermore, it does not provide a definite cure for the disease (Fitzhugh, Abraham, Tisdale, & Hsieh, 2014).

Hydroxyurea

In recent times, hydroxyurea has been used as the standard of care for patients with SCD. It is effective in reducing some complications associated with the disease. Hydroxyurea belongs to a class of compounds called hydroxamic acids, which binds metals. The beneficial effects of hydroxyurea is its ability to inhibit ribonucleotide reductase, it does this by binding the

reductase's two iron molecules and inactivating a critical tyrosyl radical.13 This cytotoxic effect of hydroxyurea reduces the production of red cells containing a high level of sickle hemoglobin, which tend to arise from rapidly dividing precursors, and favors the production of red cells containing a high fetal hemoglobin level (F cells). This drug also reduces the numbers of white cells and platelets, potentially reducing their roles in vascular injury (Field & Nathan, 2014). Metabolism of hydroxyurea results in the production of nitric oxide. The production of nitric oxide compensates for the loss of endogenous nitric oxide due to intravascular hemolysis (Kassim, 2014).

Hydroxyurea is known to increase the amount of fetal hemoglobin in the blood, which has some protective properties against the effects of hemoglobin S. It is also has some anti-inflammatory properties. (Kassim & DeBaun, 2014).

In adults, hydroxyurea reduces the episodes of pain crises and acute chest syndrome. It also, improves anemia, decreases the need for blood transfusion and reduces the number of hospitalizations as observed in adult patients taking the medication (Kassim & DeBaun, 2014).

While in children with severe hemoglobin SS, hydroxyurea has been seen to reduce the number of vaso-occlusive crises and hospitalization. It has also been observed to also reduce the number of episodes pain crises and dactlitis. (Kassim & DeBaun, 2014).

The effectiveness of hydroxyurea has been established in decreasing several complications of SCD, most experts in the field recommend that children and adults with hemoglobin SS or $S\beta^0$ thalassemia with frequent painful episodes, recurrent chest crises, or severe anemia take hydroxyurea daily (Field & Nathan, 2014).

Also, some experts offer hydroxyurea to all infants over 9 months of age and young children with hemoglobin SS or $S\beta^0$ thalassemia, with mild to moderate clinical problems, to

prevent or reduce the chance of complications. There is no information on the effectiveness or safety of hydroxyurea in children less than 9 months of age. Hydroxyurea is contraindicated in pregnant women (Kassim & DeBaun, 2014).

Hydroxyurea is a myelosuppressive compound, and its effects on bone marrow can be conveniently monitored by examining peripheral-blood counts. It causes the blood's white cell count or platelet count to drop (Field & Nathan, 2014). In some rare cases, it worsens anemia. There is a reversal of these side effects upon termination of the medication. Also, adjusting the dosage of the medication to a lower dose can eradicate these side effects in some patients. Other short-term side effects are less common. Other rare side effect of hydroxyurea is seen with long-term use of the drug, it is suggested to cause cancer, especially leukemia with long term use. However, this fact is yet to be confirmed and it remains a subject of debate. It has not been established that hydroxyurea can cause problems later in life in people with SCD who take it for many years. Recent Studies so far suggest that it does not put people at a higher risk of cancer and does not affect growth in children. But further studies are needed to confirm this (Kassim & DeBaun, 2014).

Hydroxyurea is now the standard of care, but its limitation is that it is not a definite cure for SCD and it does not prevent serious complications in all patients.

Hematopoietic Stem Cell Transplantation

Presently, hematopoietic stem cell transplantation (HSCT) is the only cure for SCD (Bhatia & Sheth, 2015). Stem cells are cells that have the capacity to divide into multiple cells. After they divide, these cells can go on to become blood red cells, white cells, or platelets. A

person with SCD has stem cells that make sickled red blood cells. People without SCD have stem cells that make normal shaped red cells.

In HSCT, stem cells are taken from the bone marrow of a non-SCD sibling. The donor, however, may have sickle cell trait. But one without the trait is preferred. Hematopoietic stem cells may be extracted from bone marrow, peripheral blood, and cord blood. The donor is often the patient's sister or brother. This is due to the safety and high success rate associated with transplant using stem cells that are matched for HLA antigens. Since these antigens are inherited from parents, a sister or brother is the most likely person to have the same antigens as the person with SCD (Ozdogu & Boga, 2015).

Presently, most SCD transplants are performed in children who have had severe complications such as strokes, acute chest crises, and recurring pain crises. These transplants are done using a matched donor. Because only about 1 in 10 children with SCD has a matched donor without SCD in their families, the number of people with SCD who get transplants is low. However HSCT is rarely done in adults due its toxicity leading to organ injuries (Dedeken et al., 2014)

Based on a report from the Center for International Blood and Marrow Transplant Research and the European Society for Blood and Marrow Transplantation, approximately 1,200 patients with SCD have undergone HSCT. There has been significant reductions in infection rates, graft failure, graft versus host disease (GVHD), and long-term organ toxicity, through advances in supportive care, modified conditioning regimens and better prophylaxis for rejection and GVHD have accounted for these positive results (Bhatia & Sheth, 2015).

The focus of this clinical review is on research done on 147 patients with SCD, all under the age of 16 with matched donors (HLA-identical donor). These 147 patients had their

transplant done in multiple centers in countries such as Belgium, France and USA (Center for International Blood and Marrow Transplant Research, European Society for Blood and Marrow Transplantation personal communication, 2014). The SCD patients involved in this research had one or more of the following conditions: stroke or CNS event lasting longer than 24 hours, acute chest syndrome with recurrent hospitalizations or previous exchange transfusion, abnormal MRI scan, stage I or II pulmonary disease, sickle cell nephropathy, bilateral retinopathy, osteonecrosis of multiple joints or red cell alloimmunization.

There was a 93% success rate with event free survival of 82%. 11% had a recurrent sickle cell disease; this was a principal obstacle to achieving a 100% success rate in this particular study. Reason for the rejection was not established as there were no clear risk factors to the rejection. Although, it was noticed that patients who experienced the rejection, received the most transfusion, and thus were exposed to minor histocompatibility antigens expressed on leukocyte (Andreani, Testi, & Lucarelli, 2014).

Although bone marrow transplantation has curative potential, it has both short-term and long-term consequences. Short-term consequences include toxicities of high-dose chemotherapy, such as nausea, vomiting, mucositis, and myelosuppression, are usually short-lived, and can be treated with supportive measures until recovery. Some long term consequences include toxicities such as delays in growth and development, infertility, and secondary malignancies. These are more serious and less easily overcome. Several studies done on this topic, shows that HSCT does not cause secondary malignancies. Some patients experienced seizures, seizures occurred to SCD patients had were hypertensive, or were relatively polycythemic or had inadequate anticonvulsant blood levels (Andreani et al., 2014).

To prevent these neurologic complications, other studies ensured their patients were given anticonvulsant prophylaxis during and 6 months after transplantation, they were treated for hypertension, their hemoglobin was maintained between 9-11gm/dl and they platelets were maintained to not less than 50,000/mm.

In the above study, there were no subsequent strokes after transplantation, and most patients had stabilization or improvement of cerebral vasculopathy as seen by cerebral MRI examinations. Another benefit of HSCT observed from this study is recovery or stabilization of other organs at risk for damage from sickle vasculopathy (Andreani et al., 2014).

Following the above transplantation other findings were observed. These included disappearance of Howell-Jolly bodies and increased radionuclide uptake by the spleen seen on hepatosplenic scintigraphy. In addition, among engrafted patients in this study, there have been no reports of acute chest syndrome after transplantation and patients who had pre-existing restrictive or obstructive airway disease; their condition did not worsen after transplant. In one report, osteonecrosis improved following bone marrow transplantation.

Due to the ages of participants in this study, issues of infertility was not ascertained. Gonadotropin and sex hormone levels of patients who were more than 13 years of age were measured in those enrolled in the multicenter transplant study. The following results were observed; five females had primary amenorrhea, and five other females had elevated LH. FSH levels that were associated with decreased serum estradiol levels were observed in four females. Of the males, none had elevated serum LH/FSH levels. However, two males who were 14 and 16 years of age had low testosterone levels that were correlated with gonadotropin levels in the prepubertal range. Thus, it is anticipated that most patients will be infertile, and many will require hormonal replacement therapy (Andreani et al., 2014).

In this study, it was observed that five patients in the multicenter collaborative investigation developed persistent mixed donor-host chimerism (that is, when a person have an organ that do not match the DNA of the rest of the organism) after transplantation. This correlated with the resolution of sickle cell disease-related symptoms and anemia. After transplant, none of the 5 patients who had mixed donor-host chimerism developed acute or chronic GVHD (Andreani et al., 2014).

A stable mixed donor-host hematopoietic chimerism is defined as the persistent coexistence of donor and host hematopoetic cells after transplantation.

This observation strongly suggests that sickle cell disease patients who develop persistent mixed chimerism after transplantation will experience a significant overall effect.(Andreani et al., 2014).

Also, a clinical review was done on three studies done in the US, Belgium, and France. The total number of participants in these countries were approximately 200, ranging from age 9 month old to 23 years old. They underwent myeloablative conditioning followed by HSCT. All three studies reported similar results, with overall survival (OS) rates of 92%–94% and an event-free survival (EFS) of 82%–86%, with an approximately 7% transplant-related mortality, mostly due to infection (Bhatia & Sheth, 2015).

HSCT is preferably done in children compared to adults, due to the associated risk observed in adults (Bhatia & Sheth, 2015). The average age of patient who had HSCT was between 9.5 to 11 year old; the range was between 2 to 21 year old. Based on several studies reviewed, all the patients had one or two veno-occlusive crises prior to HSCT. They were also pretreated with hydroxyurea prior to HSCT. And, they were also treated with conditioning after HSCT. The overall survival (OS) and event-free survival (EFS) rates estimated by previous large

cohorts ranged from 93 to 97% and 82 to 86% respectively (Bernaudin et al, 2007; Bhatia & Walters, 2008).

After a median follow-up of 4 year (range, 1–7.7), all patients are alive and disease free with 100% donor erythropoiesis. Patients transplanted from a sibling with SCD trait display the same level of HbS as the respective donors and other patients transplanted from a sibling without the SCD trait displayed the same blood type as the donor.

The success rate of HSCT can also be attributed to the use of highly immunosuppressive reduced intensity conditioning such as the use of busulfan, cyclophosphamide, with antithymocyte globulin, or antilymphocyte globulin with or without total lymphoid radiation (TLI), avoiding radiation as part of the conditioning chemotherapy after the transplant; this has significantly reduced graft versus host disease as described in the French cohort (Bernaudin et al, 2007).

Also, the use of hydroxyurea before HSCT exposure leads to an improved outcome, as seen in previous studies done. (Brachet et al, 2004). Furthermore, event-free survival following HSCT is significantly better in patients transplanted before developing SCD-associated morbidity (Bhatia & Sheth, 2015).

An important observation noticed by a study done by (Nickel et al., 2016), shows that HSCT significantly improves splenic function for most pediatric patients with SCD, but older patient age at time of HSCT and extensive chronic GVHD appear to be risk factors for poor post-HSCT splenic function. Thus, reiterating the importance age as a determining factor to the success of HSCT.

Two clinical researches were conducted using nonmyeloablative regimens in HSCT involving adults with SCD over 30 year old and the result showed significant success without

mortality (Saraf et al., 2015). Thirteen high-risk SCD adults underwent an RBC exchange transfusion using RBCs that were leukoreduced, irradiated, and matched for Rh. Hydroxyurea was permanently discontinued at day 8 before stem cell infusion. Alemtuzumab (anti-CD52 monoclonal antibody) was administered intravenously as follows: .03 mg/kg on day 7, .1 mg/kg on day 6, and .3 mg/kg/day on days 5 to 3. Total body irradiation (TBI) was given as a single dose of 300 cGy on day 2. Immunosuppressive therapy with oral sirolimus was started on day 1. In addition to standard antimicrobial prophylaxis, patients received penicillin V potassium (250 mg twice daily) until pneumococcal vaccination was completed. Platelet transfusions were given for platelet counts $<50 \times 10^{9}$ cells/L. Standard engraftment criteria for neutrophils and platelets were followed and donor cell chimerism was measured in the whole blood and in circulating $CD3^{+}$ selected cells on days +30, +60, +90, +180, +365 and annually thereafter. Transthoracic echocardiograms and pulmonary function testing were performed before HSCT and 1 year after HSCT. Patients with T cell chimerism > 50% at day +365 were considered for sirolimus withdrawal. These patients had a median follow up of 22 months (range, 12 to 44 months) and all 13 patients were alive with a disease-free survival rate of 92% (12 of 13 patients with stable donor chimerism). No patients have developed acute or chronic GVHD, and four patients have been successfully titrated off sirolimus after HSCT (Saraf et al., 2015).

This study demonstrates that a nonmyeloablative and chemotherapy-free, HLA-matched related HSCT conditioned with alemtuzumab and low-dose TBI can normalize the hemoglobin concentration in 92% of adult patients with clinically aggressive SCD, can also reduce complications resulting from SCD, and significantly improve cardiopulmonary function and improve quality of life without transplantation-related mortality (Saraf et al., 2015).

CHAPTER 3

DISCUSSION

Risks of HSCT

HSCT is successful in about 85 percent of children when the donor is related and HLA matched (Bhatia & Sheth, 2015). This is the average success rate after reviewing several studies. Even with this high success rate, HSCT still has risks. These risks include severe infections, seizures, other clinical problems and death (in less than 5% of SCD patients). Severe complication from HSCT can occur such as transplanted cells attacking the recipient's organs; this is known as graft versus host disease (GVHD).

Infertility has remained a concern for both patients and their families. Infertility is a complication of HSCT. The risk of infertility after HSCT depends mostly on the inclusion of radiation and gonadotoxic chemotherapeutic agents used following HSCT (Andreani et al., 2014). These gonadotoxic chemotherapeutic agents such as, bulsufan has a toxic effect on gonadal function. Also, the stage of pubertal development of the patient at the time of HSCT is important in preventing infertility associated with HSCT.

GVHD is a common cause of morbidity and mortality after allogeneic stem cell transplantation (Saraf et al., 2015). It has two phases; they are acute and chronic phase. Chronic GVHD is the leading cause of late transplant-related morbidity and mortality after allogeneic stem cell transplantation. It is a systemic, multiorgan syndrome that resembles collagen vascular disorders and has features of an autoimmune disorder. It is associated with an increased risk of infection, pulmonary disease, and impaired growth and development. One complication of chronic GVHD is decreased linear growth. However, after transplantation for sickle cell disease,

several studies reported normal or even improved linear growth velocity in most patients following transplantation (Saraf et al., 2015).

Stem cell transplantation should be done earlier in the course of the disease to prevent the higher rate of graft rejection reported among patients exposed to a large number of RBC infusions. This increased rejection rate may be due to an immunologic response that interferes with engraftment. When this is done early in the course of the disease, it might prevent the high incidence of graft versus host disease. Also, this is an important reason why HSCT is done frequently in children and not adults (Fitzhugh et al., 2014).

New strategies have been suggested to induce stable mixed chimerism in patients with genetic disorders because this condition might provide a significant ameliorative effect while reducing the toxicity of transplantation. This is yet to be implemented (Andreani et al., 2014).

Medicines are given prior and after the HSCT to prevent many of the complications, but they still occur.

Limitation of Hematopoietic Stem Cell Transplantation

Allogeneic haematopoietic stem cell transplantation (HSCT) remains the only curative option for SCD. However this procedure encompasses a risk of mortality, graft rejection and late onset toxicity due to chronic graft-versus-host disease (GVHD) in addition to impaired fertility. These complications are barriers to the widespread use of HSCT. But the most significant toxicity associated with HSCT is 5-10% risk of death associated with the procedure. These concerns have at least in part restricted the number of patients who receive this potentially curative therapy (Saraf et al., 2015). Also, finding human lymphocyte antigen (HLA)-matched

donors is a limiting factor to this procedure becoming a popular treatment for this disease (Omondi et al., 2013).

Because the clinical course of SCD varies from patient to patient, it is hard to predict which patients will respond to hydroxyurea versus those who would benefit from aggressive therapy with stem cell transplantation. Studies suggest that stem cell transplantation is beneficial in patients with more severe SCD.

Future Use of HSCT

There are ongoing efforts to optimize transplant efforts for SCD. Improving HSCT outcomes and expanding transplant methods will widen the use of transplant for SCD and more patients can benefit from this intervention. A modified individualized transplant approach is the suggested method. HSCT studies will require taking host factors into consideration such as: disease severity, age and donor selection process, with twin goals of safety and success in mind. The acceptability of adverse outcomes such as treatment-related mortality, graft rejection (GR) and GVHD will continue to vary between groups, depending on the above variables (Shenoy, 2013).

If the intensity of conditioning is reduced and it is still possible to ensure successful engraftment of donor cells, it is likely that more patients will be considered for transplantation and not just patients with severe SCD. The reduction of transplant-related toxicity might also facilitate treatment of patients before they develop disease related complications. This was done in recent studies; patients were treated with hydroxyurea before transplantation and treated with antithymocyte globulin after transplantation. These treatments were beneficial in reducing the toxicities seen after HSCT (Saraf et al., 2015).

It is also important for outcome and safety perspectives to perform SCD transplants and expand applicability in a trial setting. A multicenter team approach as opposed to individual centers pursuing different transplant methods is ideal. At individual centers, hematologists, healthcare staff, transplant teams, and patients/families need to work together to utilize transplant in a timely fashion in those who might benefit from this intervention.

There are several medical centers researching new SCD HSCT techniques in children and adults who do not have a matched donor in the family or who are older than typical recipients. Hopefully, more people with SCD will be able to receive a transplant in the future, using these new methods regardless of their age or severity of their disease. But for now, it is restricted to children with severe SCD complications with matched donor. More research is warranted before this treatment approach can be recommended as a standard of care for all patients with SCD.

CHAPTER 4

CONCLUSION

In conclusion, current conventional non-HSCT treatments are not effective in reducing morbidity and mortality associated with SCD, they are only supportive care (Shenoy, 2013). There are also significant barriers and side effects seen in transfusion therapy, toxicities and organ damage seen in prolong use of hydroxyurea (Vermylen, 2013).

Current treatment options have lengthened the lifespan of patients with SCD. Hydroxyurea is the standard of care for the management of SCD, but it does not prevent serious complications in all patients (Le et al., 2015). For those patients with severe disease, stem cell transplantation may be an appropriate curative option. Nonetheless, it is important to weigh the risks and benefits when considering the use of stem cell transplantation for SCD. Furthermore, the severe morbidity and increased mortality of homozygous SCD justifies more aggressive treatments with curative intent such as the use of HSCT as a definite cure of SCD (Ozdogu & Boga, 2015). However, since SCD is a genetic disorder, finding a disease-free HLA-matched sibling or relative will continue to pose a challenge (Jae et al., 2011; Justus, Perez-Albuerne, Dioguardi, Jacobsohn, & Abraham, 2015).

HSCT use in the treatment of SCD should be expanded and should include all patients less than 18 years old, irrespective of whether they have a less severe disease or have had one or more of the devastating complications of SCD. And, it is also recommended to be done before any significant organ damage (Nickel, Hendrickson, & Haight, 2014).

The overall risk of mortality with HSCT is lower than the risk of mortality before age 18 without HSCT. This should encourage the widespread use of HSCT in a well-equipped setting, as its benefits exceed its risk. However, alternative donor HSCT and other modifications of the

standard protocol must still be considered experimental and should be performed in an investigational setting (Ozdogu & Boga, 2015).

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Abstract

Hematopoietic stem cell transplantation is the only definite treatment currently in use for patients with sickle cell disease (SCD). The first successful hematopoietic stem cell transplantation was performed in 1984. To date, approximately 1,200 transplants have been reported. Given the high prevalence of this disorder in Africa, and its emergence in the developed world through immigration, this number is relatively small (Bhatia & Sheth, 2015). There were many reasons for this; primarily among them were the availability of a donor, the several risks associated with this complex procedure, and the cost and availability of resources in the developing world. The risks associated with this procedure have steadily decreased to the point where, if currently performed in a center with experience using a matched sibling donor, overall survival is close to 100% and event-free survival is over 90%. There were little to no controversy as to the use of hematopoietic stem cell transplantation in the treatment of symptomatic SCD patients with a matched sibling donor, but there were controversies as to the use of this procedure in less severe patients and in adults. Prior to the HSCT, current conventional non-HSCT treatments were not effective in reducing morbidity and mortality associated with SCD, they were only supportive care (Shenoy, 2013). There are also significant barriers and side effects seen in transfusion therapy, toxicities and organ damage seen in prolong use of hydroxyurea. Understanding of the pathology and treatment of SCD is important in explaining the importance of using hematopoietic stem cell transplant only in patients with a severe form of SCD and not on those with a less severe form and on the patients with matched siblings. In this review, we discussed the effectiveness, limitation and future use of hematopoietic stem cell transplant as the definite cure of SCD. The importance of this procedure done in a researched center facility was duly emphasized.