

Review Article,

The Role of Hematopoietic Stem Cell Transplantation in the Treatment of Sickle Cell Disease

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Abstract:

Sickle cell disease (SCD) affects millions of people around the world and is associated with significant morbidity and premature mortality. It is a chronic, life-long illness that affects virtually every tissue in the body, worsens over time, with varying degrees of morbidity in everyone with the disease.

Before hematopoietic stem cell transplant (HCST), the mainstay of the management of SCD included early identification of the disease through newborn screening, infection prophylaxis with vaccinations and antibiotics, management of pain crises, blood transfusions, and hydroxyurea. These treatments although beneficial, do not cure SCD, stop the progressive End-organ damage associated with this disease and is lifelong. Hematopoietic stem cell transplant is the only treatment that offers a cure for SCD and stops the progressive end-organ damage. The purpose of this article is to examine traditional treatments (best medical practice) and HCST for SCD and their associated complications. The role of HCST in the treatment of sickle cell disease, as well as recent research on HSCT as a cure for SCD, risk factors, patient selection, limitations and future use of this treatment option, are also reviewed. Major issues surrounding the use of HCST for treating SCD include the optimal age for transplantation, disease severity, donor source, and the conditioning regimen before transplantation. The future of HSCT for treatment of sickle cell disease including gene editing is also presented.

Key words: Sickle Cell Disease, Hematopoietic Stem Cell Transplantation.

Introduction:

Background

Sickle cell disease (SCD), which is also known as sickle cell anemia is a grouping of inherited disorders of the red blood cells. (National Heart, Lung and Blood Institute [NHLBI], 2019). It is caused by the presence of an abnormal hemoglobin (hemoglobin S) in the red blood cells (NHLBI, 2019). If the hemoglobin S gene is inherited from only one parent and a normal hemoglobin gene is inherited from the other, the offspring will have the sickle cell trait (Centers for Disease Control [CDC] (a), 2019). Persons with the sickle cell trait carry the defective hemoglobin S gene, but will not have the disease (NHLBI, 2019). Carriers of the defective gene are usually healthy, but they can pass on the defective hemoglobin S gene to their offspring (CDC (a), 2019; NHLBI, 2019). Individuals with the disease inherit two abnormal

hemoglobin genes (hemoglobin SS), one from each parent (CDC (a), 2019; NHLBI, 2019), and therefore will have sickle cell anemia.

Hemoglobin S differs from normal hemoglobin in that it forms stiff rods within the red cells, causing the cell to look crescent, or *sickle* shaped (CDC (a), 2019). Sickle-shaped cells are not flexible and can stick to vessel walls, causing a blockage that slows or stops the flow of blood and prevents adequate oxygen supply to nearby tissues, which leads to severe pain, organ damage, and stroke (CDC (a), 2019). The defect in the hemoglobin S gene causes the production of abnormal beta globin, thus changing the effective functioning of the hemoglobin (NHLBI, 2019). The overall effect of this defective gene leads to insufficient oxygen carrying capacity of the hemoglobin found in red blood cells (NHLBI, 2019). Although there are other types of SCD, (hemoglobin SC, hemoglobin

SD, hemoglobin SE, hemoglobin S β +, and hemoglobin SB0) sickle cell anemia (hemoglobin SS) is the most common and the most severe form of the disease (NHLBI, 2019).

Major Complications of Sickle Cell Disease:

The defective sickle cell gene is present at birth, but most people will not start experiencing their first symptoms until they get to five or six months of age (CDC (a & b), 2019; NHLBI, 2019). This is because at this age (five to six months) the hemoglobin that was present in the newborn (fetal or baby hemoglobin) is replaced by the sickled hemoglobin, which leads to sickling of the red blood cells (CDC (b), 2019; NHLBI, 2019). The symptoms of sickle cell disease differ from person to person and can change over time (CDC (b), 2019). Complications usually include hand-foot syndrome (which is usually the first manifestation of the disease), painful vaso-occlusive crisis also known as acute pain crises, anemia, infections, acute chest syndrome, splenic sequestration, aplastic crisis, stroke, eye problems including vision loss, leg ulcers, deep vein thrombosis, multi-organ damage, renal failure, delayed growth and puberty, complications during pregnancy, a rare type of kidney cancer and a painful prolonged erection of the penis known as priapism and others (CDC (b), 2019; NHLBI, 2019). These tissue injuries have a significant effect on the quality of life for most patients (Özdoğu & Boğa, 2015). Hand-foot syndrome causes severe swelling of the hands and feet (CDC (b) 2019; NHLBI 2019). It is usually accompanied by fever (CDC (b) 2019; NHLBI 2019). Hand-foot syndrome is only one cause of pain for persons with SCD. Acute pain episodes (crises) are caused by sickle cells getting “stuck” in the blood vessels and occluding them, which reduces blood flow and oxygen delivery (CDC (b), 2019; NHLBI, 2019). Pain crises experienced by SCD patients have been attributed to temperature changes (Resar & Oski, 1991), dehydration, and high altitudes (Claster, Godwin & Embury, 1981) but often the triggers or causes are unknown due to the multifactorial nature of pain crises (Zhao, Schwartz, Palmer & Zennadi, (2016). Chronic pain, which is different from the acute pain that patients experience during an acute pain crisis, is also reported by many adolescents and adults who have SCD.

Anemia, which can vary from mild to severe, frequently occurs in SCD (CDC (b), 2019). This is because the red blood cells die earlier than normal red blood cells (CDC (b), 2019). People with SCD

experience fatigue and other symptoms such as delayed growth and puberty because of this anemia (CDC (b), 2019; NHLBI, 2019). Severe anemia in an infant or child with SCD can be caused by either splenic sequestration crisis or aplastic crisis (Özdoğu & Boğa, 2015). Splenic sequestration crisis, a severe complication of SCD occurs when the red blood cell occludes blood flow to the spleen; accumulation of these sickled red blood cells, over time, can cause enlargement of the spleen (CDC (b), 2019; NHLBI, 2019). 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 (Özdoğu & Boğa, 2015). Damage to the spleen as a result of SCD leads to weakening or complete destruction of splenic function early in life (CDC (b), 2019; NHLBI, 2019). People with SCD who have suffered damage to their spleens are at risk for serious bacterial infections that can be life threatening (NHLBI, 2019). Aplastic crisis, another severe complication of SCD results from parvovirus B19 infection, which causes the bone marrow to stop producing red blood cells (NHLBI, 2019). Severe anemia may lead to other symptoms such as shortness of breath, dizziness, and pale skin. Acute chest syndrome is another very serious complication of SCD. It is one of the leading causes of death in SCD patients (Field & DeBaun, 2019). It occurs when there is occlusion of the blood vessels in the lungs, which deprives the lungs of oxygen (NHLBI, 2019). The occlusion of these blood vessels causes damage to the lung tissue and inadequate oxygen exchange (NHLBI, 2019). Clinical stroke, which occurs when the sickled cells get stuck in the blood vessels leading to a lack of blood supply to parts of the brain, is common among adults and children with SCD (George, 2019). The symptoms of a stroke will vary based on which part of the brain is affected (NHLBI, 2019). Stroke prevalence in persons with SCD is reported to be as high as 24% by the time they reach 45 years of age (NHLBI, 2019; Verduzco & Nathan, 2019). In children, clinical stroke is seen most frequently between the ages of two and nine years of age (NHLBI, 2019), with an overall prevalence of 11% by the age of 20 years if there is no intervention to prevent the stroke (George, 2019). However, recent strategies to prevent stroke have lowered the risk in children (NHLBI, 2019). Silent stroke, a common occurrence in SCD patients (NHLBI, 2019), which is identified through imaging studies of the brain or

other types of mental testing, can lead to learning problems or difficulty making decisions or maintaining employment (NHLBI, 2019). SCD causes occlusion of blood vessels in the retina, which is the most common site of eye damage, and can lead to hemorrhage of these vessels (CDC (a & b), 2019). This hemorrhage within the vessels of the retina can result in detachment of the retina (NHLBI, 2019). Long term damage to the retina can ultimately lead to blindness (CDC (a & b), 2019; NHLBI, 2019). These injuries to multiple tissues significantly influence the quality of life for most SCD patients (Özdoğu & Boğa, 2015).

Sickle Cell Disease Treatments:

Management of sickle cell disease starts with the identification of patients with the disease. In the United States babies are screened at birth for the trait or the disease. Early identification of those with the disease facilitates earlier intervention and treatment for those with the disease. Treatments for sickle cell disease fall in one of three categories – preventing complications, treating complications or curing the disease (Field & Vichinsky, 2018). Preventative treatments include vaccinations, infection prophylaxis with penicillin and red blood cell transfusions to reduce the risk of stroke (Field & Vichinsky, 2018). Since the spleen of individuals with sickle cell disease does not work as well as those without the disease, vaccinations and infection prophylaxis are important treatments to prevent diseases, infections and some illnesses (CDC (b), 2019; NHLBI, 2019). These illnesses or infections can lead to hospitalizations, trigger pain crises and can be even fatal for some patients (Field & Vichinsky, 2018). Complications of the disease are treated with narcotics for pain control, hydration, hydroxyurea and red blood cell transfusions (Field & Vichinsky, 2018).

The use of hydroxyurea, blood transfusions and other supportive care in the treatment of sickle cell disease have resulted in many sickle cell patients surviving into adulthood (Gluckman et al. 2017). These treatments do not however, prevent the organ injury related to the disease, which contributes to a mortality rate that is as high as 14% in adolescents and adults (Özdoğu & Boğa, 2015). In addition, adults with SCD live with pain, disability, and poor quality of life (Nickel, Henderson & Haight, 2014). Hemopoietic stem transplant is the only treatment that currently offers a cure for the disease (Gluckman et al., 2017). The risks and benefits associated with the use of red blood cell transfusions, hydroxyurea and

hemopoietic stem cell transplantation in the management of SCD are presented below.

Regular Red Blood Cell Transfusion Therapy:

Regular (usually monthly) red blood cell transfusion therapy has been effective in alleviating some symptoms of SCD and may alter the progression of the disease (Kassim & DeBaun, 2014). It does not, however, prevent the development or progression of silent infarcts in all patients (Fitzhugh, Abraham, Tisdale, & Hsieh, 2014). Moreover, the risk of stroke is not effectively eliminated among children receiving transfusions as prophylaxis for stroke, (Kassim & DeBaun, 2014), and the risk of stroke reverts if blood transfusions are discontinued (Abound, Yim, Musallam, & Adams, 2011). Other long-term complications of regular transfusions include alloimmunization and iron overload, conditions that can lead to death (Fitzhugh, Abraham, Tisdale, & Hsieh, 2014). Thus, blood transfusions are inadequate as the ideal treatment for SCD and do not provide a definitive cure for the disease (Fitzhugh et al., 2014).

Hydroxyurea:

Hydroxyurea is one of two medicines approved by the FDA for the treatment of SCD. It has been used as the standard of care for patients with SCD since its approval by the FDA, and is effective in reducing some complications associated with the disease due to multiple beneficial mechanisms (Field & Nathan, 2014). Hydroxyurea produces an intermittent cytotoxic effect suppressing erythropoiesis of red blood cells (RBC) containing sickle hemoglobin while simultaneously recruiting the production of RBCs containing fetal hemoglobin (HbF) (Green & Barral, 2014). Binding to ribonucleotide reductase, an enzyme necessary for DNA synthesis, hydroxyurea causes cell death, directly inhibiting RBC production and concurrently initiating paradoxical “stress erythropoiesis” (Green & Barral, 2014; Agrawal, 2014). Increased HbF offers protective properties against hemoglobin S (Field & Nathan, 2014), such as, reduction in acute coronary syndrome (Bhatia & Sheth, 2015). Hydroxyurea also reduces the numbers of white cells and platelets, potentially reducing their roles in vascular injury (Green & Barral, 2014). In addition, hydroxyurea metabolism results in the production of nitric oxide (Green & Barral, 2014) that may compensate for the loss of endogenous nitric oxide due to

intravascular hemolysis and generate beneficial anti-inflammatory properties. (Kassim & DeBaun, 2014). A review of the clinical effects of hydroxyurea therapy in children conducted by Green and Barral (2014) demonstrated a decrease in pain crises, dactylitis (also known as hand-foot syndrome), transfusions, hospitalizations, and mortality. In adults, similar effects have been seen including a decrease in pain crises, acute coronary syndrome, hospitalizations, mortality (Kassim & DeBaun, 2014), and transfusions (Bhatia & Sheth, 2015). In children with severe hemoglobin SS, hydroxyurea has reduced the number of vaso-occlusive crises or pain episodes (Nevitt, Jones & Howard 2017). Some clinicians use hydroxyurea therapy in infants who are nine months of age and older as well as in young children with SCD who have mild to moderate clinical problems, to prevent or reduce the chance of complications (Schuchard et al. 2019). Hydroxyurea is recommended for infants who are younger than 9 months of age with symptomatic SCD as well (NHLBI, 2019; Rodgers & George, 2019). Schuchard et al. (2019) found hydroxyurea to be safe and effective in children 5 to 12 months of age as a treatment for SCD in a retrospective chart review of a cohort of 35 patients who were 12 months of age and younger. There are, however, no clinical trials involving hydroxyurea use in infants less than 9 months of age (NHLBI, 2019; Rodgers & George, 2019).

Since hydroxyurea is a myelosuppressive compound, the effects on bone marrow need to be monitored by examining peripheral-blood counts. It causes a decrease in the white blood cell count and platelet count (Green & Barral, 2014). Other side effects include falsely elevated serum creatinine and other laboratory values, gastrointestinal upset, anorexia and mucocutaneous toxicity (Rodgers & George, 2019). Most of the side effects of hydroxyurea including low neutrophils, low platelet counts, anemia, rash, headache, and infrequent nausea are short-term and can be modified (Nevitt, Jones & Howard, 2017). There is no consensus at this time about the use of hydroxyurea for pregnant women, those desiring to become pregnant and for males who have the potential to father a child while using hydroxyurea. Its use during pregnancy is generally contraindicated as it is considered a teratogen for the embryo and fetus (Rodgers & George, 2019). Its use is also contraindicated in males who may be able to father children (Rodgers & George, 2019). More evidence is needed about the impact that

long term use of the drug will have on patients' virility, and their ability to conceive and have children (Nevitt, Jones & Howard, 2017). There is a delay between when hydroxyurea is initiated to when it starts working (weeks to months sometimes) so it is used to prevent complications of SCD, rather than to treat them in acute crises (Rodgers & George, 2019). The effectiveness of hydroxyurea to decrease several complications of SCD in children and adults has been established (Steinberg et al. 2010). It is not known, however, whether hydroxyurea can cause problems later in life in people with SCD who take it for many years (Kassim & DeBaun, 2014), especially children who use the medication into adulthood (Steinberg et al, 2010). Hydroxyurea is not a cure for SCD, and it does not prevent serious complications in all patients (Özdoğu & Boğa, 2015). Advances in the early recognition, prevention and the treatment of SCD have transformed this disease into a chronic condition, with more patients surviving into adulthood (Kassim & Sharma, 2017). Advances in the treatment options for SCD, including chronic blood transfusions and hydroxyurea require lifelong treatment, only alleviate the symptoms of SCD (Hsieh, Fitzhugh & Tisdale, 2011), and do not stop or turn back likely complications in the future (Arnold, Bhatia, Horan & Krishnamurti, 2016; Shenoy 2013).

Hematopoietic Stem Cell Transplantation:

Hematopoietic stem cell transplantation (HSCT or HCT) is still emerging as a treatment for SCD (Khan & Roberts, 2019). It is the only treatment option that is curative for SCD (Bhatia & Seth, 2015; Bhatia & Seth, 2008; CDC 2019; Hsieh, Fitzhugh & Tisdale, 2011; Kassim & Sharma, 2017; Shenoy, 2013). Curing SCD is an important objective because this is the only treatment option that will prevent or stop the progression of the organ damage associated with the disease (Hulbert & Shenoy, 2018). 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 can be obtained from a matching donor with identical human leukocyte antigen (HLA) such as identical twin who does not have SCD, (Negrin, 2019), or from the bone marrow of a non-SCD sibling, another relative or non-related donor in which case the cells may be HLA identical, allogenic,

haploidentical or mismatched (Bhatia & Sheth, 2015; Negrin, 2019). Hematopoietic stem cells may also be extracted from the patient's peripheral blood (HLA identical), or the umbilical cord blood of a donor- HLA identical, allogenic, haploidentical or mismatched (Bhatia & Sheth, 2015; Negrin 2019). The harvested stem cells that make normal shaped red cells are used to replace the recipients' stem cells. Once transplanted, the goal is that the transplanted cells will completely or largely replace the abnormal hemoglobin cells (Walters, 2001). HSCT is performed in children (less than 15 or 16 years of age) who have had severe complications such as strokes, recurrent acute chest crises, recurring pain crises, kidney malfunction secondary to sickle cell disease and lung disease (Arnold et al., 2016; Bhatia & Sheth, 2015). The same guidelines are used for HSCT for children 15 years of age and older as well as adults, with the addition of tricuspid valve regurgitation velocity greater than or equal to 2.5, and chronic red blood cell transfusions to avoid pain crises (Arnold et al., 2016). These transplants are done using stem cells from a matched donor. Because less than 25% of children with SCD have a matched donor without SCD in their families (Özdoğu & Boğa, 2015), the number of people with SCD who get transplants is low (Bhatia & Sheth, 2015). HSCT is performed less frequently in adults due to resultant organ injuries (Özdoğu & Boğa, 2015), for example, ovarian failure (Dedeken et al., 2014) and a higher risk of death which may result from graft versus host disease (Oringanje, Nemecek & Oniyangi, 2013).

Risks of HSCT:

Risks associated with HSCT include severe infections (Saraf et al., 2015), neurological complications including seizures (Dedeken et al. 2014; Morin et al., 2016), infertility (Smith-Whitely, 2014), graft rejection (Bernaudin et al., 2007) and secondary cancers (Hulbert & Shenoy, 2018). Death (or transplant related mortality) is another complication but occurs in less than 5 percent of SCD patients who receive an HSCT (Özdoğu & Boğa, 2015; NHLBI, 2019). A severe complication from HSCT that occurs when the immune cells that are transplanted attack the recipient's tissues is known as graft versus host disease (GVHD) (Bhatia & Sheth, 2015). GVHD is a common cause of morbidity and mortality after allogeneic stem cell transplantation (Morin et al., 2017; Saraf et al., 2015). It has two phases, acute and chronic (Chao, 2019; Khan & Rodgers, 2019).

GVHD is a multi-system syndrome that most often affects the skin, gastrointestinal and respiratory systems, as well as the liver (Chao, 2019; Khan & Rodgers, 2019). Another complication of chronic GVHD is decreased linear growth (Bhatia & Walters, 2008; Shenoy, 2013). However, after transplantation for sickle cell disease, one group of researchers reported normal or even improved growth (Bhatia & Walters, 2008). The risk of infertility after HSCT depends mostly on the inclusion of radiation and gonadotoxic chemotherapeutic agents used following HSCT (Smith-Whitley, 2014; Walters et al., 2010). These gonadotoxic chemotherapeutic agents, such as busulfan, have a toxic effect on gonadal function (Walters et al., 2010). The stage of pubertal development of the patient at the time of HSCT is important in preventing infertility associated with HSCT (Smith-Whitley, 2014).

Mixed donor-host chimerism is another common complication of HSCT (Andreani, Testi & Lucarelli, 2014). It describes the presence of both donor and host-derived cells in the recipient after transplantation ((Andreani, Testi & Lucarelli, 2014). Mixed chimerism is a risk factor for graft rejection in HSCT, but can also lead to complete chimerism (Andreani, Testi & Lucarelli, 2014). If mixed chimerism is present for an extended time after transplantation, it is known as stable mixed donor-host hematopoietic chimerism (Andreani et al., 2014).

Factors associated with improved outcomes after HSCT:

Donor selection along with the conditioning regimen is crucial to the success of HSCT (Negrin, 2019; Özdoğu & Boğa, 2015; Wiebking et al., 2017). Age seems to be a major factor in the outcomes associated with HSCT, with younger patients generally having a higher overall survival rate than those who are transplanted when older (Arnold et al., 2016; Gluckman et al., 2017; Khan & Rodgers, 2019). Patients who have a well-matched sibling donor who receive myeloablative conditioning before transplant generally have very good overall long-term event-free survival rates (Kassim & Sharma, 2017). Bone marrow derived stems cells from a matched related donor without the sickle cell mutation or only the sickle cell trait is also considered the best donor option for HSCT and for a successful transplant (Khan & Rodgers, 2019).

Myeloablative conditioning in children before transplant with well-matched sibling donors is

associated with long-term disease-free survival rate of between 90% and 92%, and a general survival rate that ranges between 92-95% (Bhatia & Sheth, 2015; Kassam & Sharma, 2017; Özdoğu & Boğa, 2015). Myeloablative conditioning before HSCT is most frequently performed in children, because of the high likelihood of morbidity and mortality in adults (Özdoğu & Boğa, 2015). The increased toxicity of myeloablative conditioning regimens in adults is most likely due to increased end organ damage resulting in a higher risk for transplant-related morbidity (Bhatia & Sheth, 2015). Recent studies using nonmyeloablative and reduced intensity regimens in HSCT have proven to be less toxic than myeloablative regimens, which has contributed to more children and even adults with several sickle cell related complications being able to benefit from HSCT (Kassim & Sharma, 2017; Saraf et al., 2015). Additionally, reduced intensity and nonmyeloablative conditioning regimens have been found to be a safe and effective regimen for young adults and adults, as well as children (Guilcher et al. 2018)

The Future of HSCT:

Investigation continues into several HSCT techniques among children and adults with SCD who do not have a matched donor in the family or who are older than typical recipients (Bhatia & Walters, 2008). The techniques include myeloablative and nonmyeloablative, reduced intensity conditioning regimens along with alternate sources for stem cells such as non-sibling haploidentical donors, cord and peripheral blood (Arnold et al., 2016; Wiebking et al., 2017). A non-myeloablative conditioning regimen is recommended for adults, and has been found to be well tolerated with good engraftment (Field & Debaun, 2019; Özdoğu & Boğa, 2015). Reduced-intensity conditioning regimes although generally well tolerated in adults, have higher rates of graft failure (Kassim & Sharma, 2017). Currently, the most appropriate reduced intensity conditioning regimen that will give the best outcome in terms of optimizing engraftment while minimizing the unwanted side effects of HSCT is uncertain (Kassim & Sharma, 2017). Additional evaluation using RIC among larger groups of patients (both children and adults) is needed to examine outcomes and create guidelines for the use of this conditioning regimen (Matthes-Martin et al., 2013; Özdoğu & Boğa, 2015; Saraf et al., 2015).

The use of alternate donor sources for HSCT may increase donor pool and the availability of this

treatment to more patients with SCD (Arnold et al., 2016; Bhatia & Walters, 2008; Gardner, 2018). There are however, multiple recommendations that HSCT using alternate donor sources should only be performed within the context of clinical trials (Bhatia & Seth, 2015; Guilcher et al., 2018; Joseph, Abraham & Fitzhugh, 2018; Khan & Rodgers, 2019). Patient selection in terms of the optimal age and timing for using HSCT for the treatment of SCD continues to be explored (Angelucci et al., 2014, Bhatia & Sheth, 2015). The current trend is for younger patients and those with severe disease to receive this treatment (Bhatia & Walters, 2008; Hulbert & Shenoy, 2018). HSCT use in adults, patients with advanced disease and children with SCD who are asymptomatic or with mild disease, is a more challenging decision (Angelucci et al., 2014; Guilcher et al., 2018).

Conclusion:

Hematopoietic stem cell transplantation (HSCT) remains the only curative option for SCD (Omondi et al., 2013). However, the risks associated with HSCT including graft rejection, graft versus host disease, impaired fertility and death have served to prevent the widespread use of this procedure and to restrict the number of patients who are offered this curative therapy (Kassim & Sharma, 2017; Özdoğu & Boğa, 2015; Saraf et al., 2016). Patient selection for transplantation including the optimal time and age as well as disease severity at time of transplantation (Bhatia & Walters, 2008; Guilcher et al., 2018; Hubert & Shenoy, 2018)), the source of the donor stem cells, as well as the optimal conditioning regimen (Kassim & Sharma, 2017) are other issues that need to be resolved.

Many efforts are now in progress that seeks to maximize HSCT for SCD (Shenoy, 2013). Achieving better transplant related outcomes and offering more transplant techniques for the treatment of SCD will allow more patients to gain from this treatment (Shenoy, 2013). Randomized controlled trials of HSCT for patients with SCD to ensure more significant findings and transplant-related conclusions are needed (Oringanje, Nemecek, Oniyangi, 2016).

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