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Stem cells in the treatment of sickle cell disease

Abstract

Sickle Cell Disease (SCD) is autosomal recessive disorder that is the result of a point mutation in the coding region of the beta globin gene. Polymerization of red blood cells with the sickle hemoglobin result in painful clinical symptoms and early death due to end organ failure. Improvement of treatment has extended the survival of adolescents into adulthood and offers relief of symptoms but does not offer a cure against the diagnosis being the inevitable cause of an early death. In addition, response to therapies vary between patients depending on their responsiveness and metabolism of medications. Hematopoietic stem cell transplantation offers reduction of recipient HgbS through replacing it with HgbA from the donor. Increased use of hematopoietic stem cell transplantation (HSCT) offers a curative therapy for patients with SCD that have access to an HLA-identical donor. However, limitations to indications for HSCT result due to associated toxicities with myeloablative conditioning and risk of graft failure. Reduced intensity and non-myeloablative conditioning look at reducing associated toxicities and making HSCT readily available for the adult population through mixed chimerism. In addition, clinical trials looking at alternative donors and gene therapies expand the availability of HSCT for the vast majority of patients without an HLA-identical donor.

Keywords: sickle cell disease, stem cell, hemoglobinopathy, HSCT, allogeneic transplantation

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Introduction

Sickle Cell Disease (SCD) is a single nucleotide polymorphism that presents itself in the coding region of the HBB (β globin) gene. SCD has been documented in western medicine since 1910 when it was described as a new disease with unknown origin.[1] The molecular nature of the disease was completely unknown until 1949 and later, in 1958, its genetic origin as an amino acid substitution was determined. This amino acid substitution is a result of a point mutation of the hemoglobin gene and has a direct conformational effect on the hemoglobin molecule. In its deoxygenated state, the sickle hemoglobin adopts the characteristic sickle shape responsible for the name of this disease. Cells with this morphology easily polymerize causing symptoms identified in SCD such as anemia, vaso-occlusion, cell adhesion, and vasoconstriction[1] (Figure 1). Inability of HgbS to flow through vessels leads to hypoxia of the tissues and painful vaso-occlusive episodes (VOE)[1] Adhesion proteins found on the surface of sickled erythrocytes harm vascular endothelium which leads to vasculopathy and vasospasm.[1] Sickled erythrocytes release arginase that effectively degrades free hemoglobin which depletes nitric oxide as seen in Figure 1.[1,2] Susceptibility of HgbS RBCs to be removed by the spleen results in shortened lift spans to one tenth of that of a healthy adult hemoglobin RBC.[2] Sickled RBCs also develop specific characteristics such as their tendency to adhere to one another and abnormal migratory patterns with difficulty flowing through vessels.[3] These effects of the polymerization of HgbS are documented in Figure 1.

The complex pathophysiology of Sickle Cell Disease stems from polymerization of Hemoglobin S in times of hypoxemia, dehydration, acidosis, and pyrexia. Polymers of HgbS cause the sickle appearance of RBCs and result in hemolysis, abnormal rheology, cellular adhesion, and decreased availability of nitric oxide. These developments result in anemia, vaso-occulsion, and vasoconstriction which are causes of sickle cell related end organ damage.

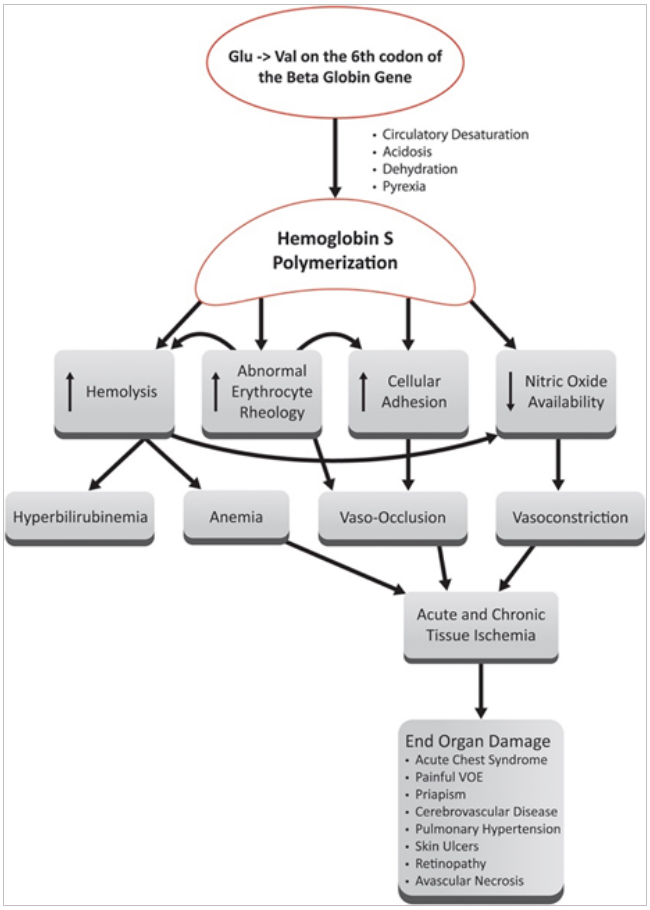

Figure 1 Pathophysiology of Sickle Cell Disease.[2]

Sickle Cell Disease is an autosomal recessive disorder that manifests itself in individuals that are homozygous for the sickle hemoglobin (HgbS). While homozygous individuals have specific clinical manifestations, individuals that are heterozygous for HgbS have sickle cell trait and act as carriers. Sickle cell trait is a benign disorder that may only be noticed in exposure to extremely low levels of oxygen.[4] However, individuals with sickle cell trait have the ability to pass the trait to their offspring. SCD is the most prominent hemoglobinopathy, with 7% of the world carrying the trait for this genetic condition.[5] This has earned SCD recognition as a global public health issue.[6] Low oxygen tension results in congregation of these mutant hemoglobin tetramers.[5] HgbS polymers change the shape of red blood cells to be rigid and have a crescent-shape. In turn, these phenotypic changes of blood cells allow for many clinical manifestations and dangerous side effects. This alteration to the erythrocytes modifies the cells' rheological properties which alters their flow in circulation and causes ischemia, stroke multi-organ damage, severe acute and chronic pain, and chronic hemolytic anemia.[5] Chronic organ complications later become the main source of mortality and morbidity in individuals that survive into their thirties.[5] In addition, efforts between transitioning of adolescent and adult care leave young adults an especially vulnerable population.[7] A better link between pediatric and adult care is needed to prevent deaths seen in this transitionary period.[8]

Current treatment

Many treatments have been offered for patients with SCD, but they primarily focus on treating symptoms and pain relief rather than treating the pathogenesis.[3] Use of penicillin prophylaxis, mandatory newborn screening, preventive vaccinations and transcranial Doppler screening have significantly helped with childhood mortality.[2,3,6,8,9] Advances in childcare for those with SCD has greatly improved to where 93.4% of children are surviving until adulthood.[8] However, children still go on to develop debilitating and painful chronic injuries into adulthood. This commonly results in death by middle age due to organ injury. While therapies have had promising results of decreasing mortality and relief of symptoms, they are not a curative method. Because presence of HgbS is the indicator for pathophysiological conditions present in a patient with SCD, the backbone of treatment plans include reducing HgbS concentration.[9]

Hydroxyurea has become the current protocol for treatment in patients with Sickle Cell Disease since the later 1980s.[3] Hydroxyurea increases the presence of fetal hemoglobin (HgbF), which in turn reduces the presence of Hemoglobin S and sickling.[3] Hydroxyurea treatment has been seen with decreased levels of VOES, ACS, hospitalizations, and blood transfusions.[10] Despite the improvement of side effects seen in patients administered hydroxyurea, this treatment is in no form a cure. One barrier preventing hydroxyurea treatment is lack of administration by providers, with only 30% of individuals potentially eligible for the drug taking it.[3] Other barriers of hydroxyurea use are unknown, however, may be linked to side effects caused due to differences in existing HgbF levels and genetic drug metabolism at the individual level.[3,10] Hydroxyurea has become the standard of care for children regardless of existing problematic side effects of SCD.[10] However, difficulty with daily adherence is often met with the pediatric population and continuation of the treatment is required for efficiency.[10,11] Patients eligible for hydroxyurea include patients with sickle cell disease that have had ≥3 moderate to severe pain episodes in a 12 month period, have a history of stroke and a contradiction to chronic transfer, children with a history of acute chest syndrome or symptomatic anemia, and infants and children >9 months that are asymptomatic or have infrequent pain episodes.[12]

Chronic blood transfusions are used as stroke preventative and are also seen with decreases in hospitalizations and pain prevention.[10] Similarly, to hydroxyurea treatments, the underlying goal of this form of treatment is to reduce the presence of HgbS. However, chronic blood transfusions decrease the presence of HgbS by increasing the presence of HgbA.[1] Blood transfusions are seen with great success at reducing secondary stroke prevention that HU fails to succeed with treating.[13] However, while chronic blood transfusions reduce the risk of stroke, they do not entirely eliminate the possibility.[13,14] In addition, until 2016, transfusions were continued indefinitely due to findings in the STOP 2 study (Optimizing Primary Stroke Prevention in Sickle Cell Anemia) that showed termination of treatment resulted in a reversion back to abnormal transcranial doppler scores and possibility of overt stroke.[15] However, more recent studies support hydroxyurea therapy is an effective alternative to chronic transfusion therapy in reducing transcranial doppler scores and risk of stroke.[16] This has led to a decreased popularity of chronic blood transfusions as a treatment for SCD and increased use of HU therapy.

These disease modifying strategies have been helpful in reducing the rate of complications and improving survival: however, the only current curative treatment for sickle cell disease is hematopoietic stem cell transplantation.[17] Like HU and blood transfusions, HSCT reduces the rate of HgbS in the diseased individual. However, removal of HgbS in the recipient is accomplished through myeloablative conditioning which is then replaced with donor cells and recipient adult hemoglobin (HgbA). However, this form of treatment has not been made widely available to patients and is still controversial in nature. Transplantation is mainly reserved for patients that have suffered a stroke, have had multiple episodes of acute chest syndrome, or have had recent vaso-occlusive crisis.[17]

Discussion

The first patient to undergo hematopoietic stem cell transplantation for SCD was in 1984 at The John Hopkins Hospital.[2] This patient was undergoing HSCT for acute myelogenous anemia and was cured of SCD in the process.[18] This was the first indication that there was a cure for sickle cell disease. Since this first patient, around 1000 patients have undergone stem cell transplantation as a treatment for sickle cell disease in the past 30 years worldwide[6,19,20, 21] However, pretransplant complications and toxicities due to myeloablative conditioning limit the availability of HSCT as a treatment for patients with SCD.[22] For this reason, guidelines have been put into place identifying proper indications for allogeneic HSCT of the most threatening presentations of SCD.[23] For the most part, HSCT has remained exclusively as a treatment for the pediatric population. In an analysis of 1000 patients undergoing allogeneic HSCT, survival was typically lower in patients 16 or older (81%) than those younger than 16 (95%).[24] Not only is survival rate lower in adults, percentage of complications associated with HSCT are higher. For every year of age increase at the time of transplant, there is a 10% increased risk of death.[24] In addition, literature supports that age (< 15) is a major determinant in overall patient survival.[17]

Often times, HSCT is reserved for patients with severe presentations of the disease including overt strokes, recurrent ACS, or recurrent VOE, despite daily adherence to HU therapy.[13,14] Furthermore, there are different indications for HSCT depending on access to a matched sibling donor, match unrelated donor, or partially mismatched related donor; unrelated cord blood transplant as noted in Table 1.[13] As high levels of success are seen in HSCT with HLA-matched donors, patients are seeking HSCT as a treatment for chronic

or recurrent acute pain more frequently than in the past.[13,17] This is a change from the limitation of HSCT exclusively for patients with high risk of stroke or other life-threatening complications as seen in the 1990s.[17] It is important to note that HSCT for patients with SCD is an entirely elective procedure. For this reason, early identification of patients referred for HSCT is crucial for timely identification and search for a donor.[6] In addition, patient education and risk analysis is essential in decision making. This requires the patient to understand that the possibility of long-term disease-free survival comes at the risk of potential comorbidities associated with transplant-related toxicity and development of GvHD.[6]

Table 1 Current indications for HSCT in patients with severe SCD unresponsive to hydroxyurea therapy[13]

Matched sibling donor transplant	**Matched unrelated donor transplant (MUD)***	**Partially mismatched related donor (haploidentical); unrelated cord blood transplant***
Overt stroke or central nervous system event lasting >24 h	Overt stroke or any neurologic deficit lasting >24 h	Recurrent stroke despite adequate chronic blood transfusion therapy or progressive central nervous system changes
Impaired neuropsychological function with abnormal cerebral magnetic resonance imaging and angiography	Elevated TCD velocity unresponsive to hydroxyurea or chronic blood transfusion therapy	Severe SCD symptoms unresponsive to hydroxyurea therapy
Elevated TCD velocity unresponsive to hydroxyurea or chronic blood transfusion therapy	Recurrent acute chest syndrome despite hydroxyurea therapy	
Recurrent acute chest syndrome despite hydroxyurea therapy	Recurrent severe pain episodes despite hydroxyurea therapy	
Recurrent severe pain episodes despite hydroxyurea therapy	Red cell alloimmunization plus established indication for chronic blood transfusion therapy	
Red cell alloimmunization plus established indication for chronic blood transfusion therapy	Pulmonary hypertension or an echocardiographic finding of tricuspid valve regurgitant jet velocity ≥2.7 m/s	
Pulmonary hypertension or an echocardiographic finding of tricuspid valve regurgitant jet velocity ≥2.7 m/s	Bone and joint involvement	
Recurrent priapism	Recurrent priapism	
Sickle nephropathy	Sickle nephropathy	
Bone and joint involvement		
Sickle retinopathy		
Stage I or II sickle cell lung disease		

• For all genotypes, disease-related morbidity is the driving factor in pursuing a HSCT

• HSCT for adults with SCD is better tolerated with a low-intensity regimen, but may require prolonged immune suppression to maintain stable mixed-donor chimerism (recipient and donor cells)

AVN, avascular necrosis; TCD, transcranial Doppler; VOE, vaso-occlusive pain episodes; SCD, Sickle cell disease

In children with SCD, abnormally high flow capacity in the cerebral arteries is associated with ischemic stroke risk, stenoses, and silent cerebral infarcts.[9] A study used consistently high transcranial Doppler (TCD) velocities (200 cm/s or greater) as indication for HSCT.[9] HSCT was associated with extreme reduction in patient's TCD velocities (40 cm/s at one year).[9] While TCD is successful in predicting stroke in adolescents, there is no method to predict recurrent VOE or ACS which makes determination of severe SCD rather challenging.[1]

The curative option with the most supportive clinical data is match related donor allogenic hematopoietic stem cell transplantation.[11] This requires absolute removal of the diseased individual's cells to be replaced with donor cells.[11] The diseased individual must first achieve

suppression of hematopoiesis and the immune system through myeloablative conditioning to allow for more successful engraftment of donor cells. This achieved suppression of the immune system. Is why myeloablative conditioning is more traditionally used with HSCT which involves conditioning with busulfan, cyclophosphamide, and ATG.[18] Myeloablative conditioning targets the host's immune system, bone marrow, and blood cells in an attempt to maximize engraftment of the donor's stem cells and minimize rejection or GvHD. Successful engraftment and low incidence of GvHD has been observed with this treatment including stable and complete donor chimerism.[25] This results in a considerably large amount of the recipient's immune system being replaced by the donor cells and resulting in donor chimerism.[11] While children can typically tolerate the toxicities associated with myeloablative conditioning, adults have an increased risk of organ damage associated with these toxicities. For that reason, multiple studies have looked into reduced intensity and non-myeloablative conditioning followed by hematopoietic stem cell transplantation.

Promising results supporting reversed symptoms in patients with mixed chimerism allowed for exploration of reduced intensity and nonmyeloablative conditioning.[7,26,27] In comparison to full and absolute chimerism, mixed chimerism occurs when recipient cells remain in the bone marrow instead of fully being replaced by donor cells.[11] It is presumed that as little as 20% chimerism must be achieved in order to reverse the clinical effects of SCD.[17] Earlier studies indicated that levels as low as 11% have been seen in reversal of symptoms in patients with SCD, however, further testing is required to confirm this data.[18] While mixed chimerism is seen with reversing symptoms of SCD, it is also seen with higher rates of GvHD in recipients.[11] In addition, there was early concern with dependence on immunosuppressants and graft failure following withdrawal of immunosuppression.[18] However, more recent regimens are able to successfully remove immunosuppressants within 6 months while still achieving mixed chimerism in the recipients.[18]

While promising results support allogeneic matched HSCT, donor availability is among the major limitations behind stem cell transplantation as a curative therapy for SCD[17,28] Recommendations by the National Bone Marrow Donor Program recommend high-level matching at the HLA-A, HLA-B, HLA-C, and HLA-DRB1 loci or an 8/8 match.[17] An 8/8 matched donor is ideal for HSCT, but less than 20% of patients with symptomatic SCD will have an unaffected HLA-matched sibling.[17,25] Other sources of stem cells including umbilical cord blood and peripheral blood are available, but each source has its own risks for engraftment and GvHD.[17]

Another factor to consider with HSCT is adequate cell dosing. Cell dosing refers to the number of nucleated CD34+ cells in the graft.[17] Difficulty in engraftment with umbilical cord blood has been seen with inadequate cell dosing and technical issues associated with colony growth and survival. Poor harvesting of bone marrow or mobilized peripheral cells could account for difficulties seen with engraftment.[5] Because of risk associated with improper cell dosing, it is important to dose more than the required CD34+ cells to ensure greater success of engraftment. Questions still remain regarding proper cell dosage for each stem cell source.

Stem cell source

Bone marrow

HLA-Identical donor

The first transplant for SCD was done in 1984 at John Hopkins using bone marrow sourced stem cells.[17] Later, in 1996, Walters *et al* effectively demonstrated the ability of HLA-matched HSCT in patients with SCD with 22 patients.[29] Since then, near 1000 patients have undergone hematopoietic using HLA-identical bone marrow as the source.[29] Allogeneic stem cell transplantation remains the only curative method for sickle cell disease. Majority of stem cell treatments done thus far have relied on HLA-matched stem cells derived from bone marrow in a matched sibling donor [2]. Successful rates of engraftment, survival, and EFS have been observed in adults with an HLA-matched donor. However, the problem remains that many patients lack availability of an HLA-matched donor.

A study analyzing 736 patients with SCD that underwent HLA-identical donor transplantation between 1986 and 2017 looked at the age of transplantation.[30] At day 100, full chimerism was achieved is 63% of the patients between the ages of 0-15 and 50% in the patients >15. The four-year cumulative incidence of GvHD was 9% in patients 0-5 (group 1), 11% in patients 6-15 (group 2), and 20% in patients >15 (group 3). At the last follow-up, all of the patients age 0-5 were still alive with 21 individuals in group 1 and 15 individuals in group 3 dying (most commonly due to GvHD or infection).[30] This further success seen in allogeneic HSCT using bone marrow as the stem cell source supports the continued use of this regimen. In addition, increased incidence of GvHD and decreased chimerism is a continuing concern of HSCT in older patients.

Allogenic HSCT with an HLA-identical donor remains the only curative option for patients with SCD. Due to worldwide OS rates as high as 95% in 5-years post HSCT, it has become an increasingly popular option for those suffering from severe SCD.[6] High levels of success seen with HLA-matched donors allows for indication of HSCT for chronic or recurrent acute pain and other less critical symptoms rather than reserving this treatment for those with high TCD scores.[13] Other indications for HLA-matched HSCT can be observed in Table 1. Due to promising results in clinical trials with HLA-matched HSCT, recommendations include less severe clinical manifestations of SCD.

Haploidentical transplantation

Allogeneic transplantation for SCD has a primary goal of achieving adequate donor engraftment to reverse the rate of HgbS and SCD phenotype while minimizing risk of developing GvHD and other therapeutic-related toxicities. While this has been achieved in patients with a matched sibling HLA-donor, less than 20% of patients with symptomatic SCD will have an unaffected HLA-matched sibling.[25] The likelihood of two siblings being HLA-identical is only 25% which accounts for the limitation in donor availability.[28] In addition, because SCD has genetic origins, it is likely that the siblings of an affected individual are also affected. Both of these phenomena contribute to the fact that donor availability is a primary barrier preventing the use of HSCT in SCD.

Haploidentical transplantation has become a common approach to patients lacking an HLA-identical donor. Haploidentical transplantation allows parents, children, and half-matched siblings to become donors. There are many benefits seen to this approach including a readily available donor pool, shorter time collecting the graft, and option for repeat collections. The main problem remains the immunologic barrier that has resulted in many incidences of GvHD and transplant-related mortality.[31] In a study at John Hopkins with 12 patients, graft rejection is seen as high as 43% but without significant toxicities.[3] A study with a slightly smaller cohort (n=8) at St. Jude's

Children Research hospital reported an overall survival rate of 75% and disease-free survival of 38% at 2 years post HSCT.[31] The two deaths observed in this study were due to complications of chronic GvHD.[31] Additional clinical trials are warranted to decrease rate of graft rejection and GvHD. Lower rates of success seen with HSCT in haploidentical donors as compared to HLA-identical limit further investigation of this donor source. Moreover, limited trials cause difficulty in further investigation of the origin responsible for graft rejection.[17,32]

Unrelated donor

Despite advancements in clinical trials looking into match unrelated donor transplantation, this source of stem cell is only recommended for individuals that do not have an HLA-matched donor.[13] Unrelated donor transplants have been less successful in patients with sickle cell disease in comparison to HLA-matched and haploidentical transplants. This is associated with relatively high GvHD and relatively low rates of event free survival and overall survival.[3] In addition, indications for HSCT from a match unrelated donor require a more severe manifestation of the disease than indications for those with an available HLA-matched related donor.[13] Despite its decreased popularity, there are clinical trials looking at the potential of match unrelated donor as an alternate donor source. A recently published phase 2 clinical trial of match unrelated donors through bone marrow HSCT included 30 children between the age of 4-19 between the years 2008 and 2014.[13] The study showed 1 and 2-year EFS of 76% and 69% and OS 86% and 79% respectively.[13,14] The 1-year incidence of GvHD was 62% with 7 deaths related to GvHD.[13,14] Another currently ongoing clinical trial (NCT01565616) is evaluating the risks and benefits of match unrelated donor transplantation in adults between the ages of 16 and 40.[13] A single antigen mismatch donor can be identified in 70% of patients and is seen as a way of expanding the field of those that qualify for transplantation.[33] However, this option has not been explored yet due to associated risks of GvHD.

Peripheral blood

Peripheral blood is less commonly used as a source of stem cells due to its abundance of T-lymphocytes and increased risk of GvHD.[34] A T-cell inhibitor allows elimination of alloreactive T-cells with simultaneous preservation of virus T-cells to decrease risk of infection. This alternative approach is one of the few options for patients with blood group incompatibility.[34] However, peripheral blood as a source of HSCT is seen with higher rates of mortality in recipients, so it is less explored in clinical trials than cord blood and bone marrow. In addition, patients are less likely to seek this form of HSCT due to the increased risk of GvHD and associated toxicities from pre-transplant conditioning. Recent discovery of use of post-transplant cyclophosphamide has allowed for expanded use of haploidentical transplantation in PBSC without increased risks of developing GvHD.[35] Modification of reduced intensity regimens improved stable donor engraftment from 40-57% to 87.5% seen with manageable levels of toxicities.[35] This is an improvement from toxicities previously associated with myeloablative conditioning including reduced renal, pulmonary, and cardiac function.[36] Lack of clinical trials using peripheral blood limit the knowledge on this stem cell source. One single center clinical trial using PBSC required additional use of umbilical cord blood or bone marrow supporting need for further investigation of adequate cell dosing required for engraftment.[36] A recent study documented 43 patients receiving peripheral blood sourced stem cells following chemotherapy.[34] This is the largest analysis of patients receiving peripheral blood sourced stem cells with 100% OS reported at 2 years.[34] These promising results look at the potential to significantly increase the donor pool through increased use of peripheral blood as a stem cell source.

Cord blood

Related

Umbilical cord blood as a stem cell source is popular among transplantation due to its high proliferative capacity and increased volume of progenitor cells. Cord blood as a stem cell source has also been seen with lower rates of GvHD than bone marrow due to its decreased quantity of CD3+, CD4+, and CD8+ T-cells, higher CD4/CD8 ratio, and increased quantity of naïve CD45RA+ T-cells. Benefits behind Cord blood transplantation (CBT) include reduced donor morbidity, expansion of the donor pool, potential for greater HLA-mismatching, and easy availability.[25] However, CBT has been limited in pediatric populations because it is associated with delayed engraftment (in comparison with BMT and PBT) due to high dose requirements of total nucleated cells.[31] As of January 2019, 44 children or young adults have received related CBT which has been reported as successful with an overall survival of 91% and Disease-free survival (DFS) of 86%.[31] However, ten of these patients received additional stem cells sourced from peripheral blood or bone marrow from the same sibling.

The largest study to date was recently reported by Eurocord and European Blood and Marrow Transplantation Group. This study included 325 patients with -thalassemia and 160 of whom had sickle cell disease. All of the patients underwent HLA-identical sibling HSCT from either cord blood (n=30) or bone marrow (n=130).[31] The 6-year disease-free survival was observed to be similar between CB and bone marrow recipients in a study of 325 patients with (90% +/- 5) and (92% +/- 2) respectively. However, 29% of the recipients of BMT experienced chronic GvHD in comparison to none of the recipients of CBT. CBT has been observed to be as successful as BM without the risk of contracting GvHD.

Subgroup analysis of the data of CBT patients from this study found a correlation between individuals that did not receive Methotrexate and event free survival. This is likely due to the fact that methotrexate delays hematopoietic recovery and has been reported in other studies.[31] Patients who did receive methotrexate had EFS of 60 +/- 11% in comparison to those that did not receive methotrexate with an EFS of 90 +/- 11%.[31] Another factor that has been shown to significantly influence success of CBT is transplantation after 1999 (p=0.02).[31]

Unrelated

Lower success rates have been seen in individuals undergoing unrelated cord blood transplantation (UCBT).[25,37,38,39] One of the early studies involving unrelated cord blood sourced stem cells had to prematurely close due to negative patient outcomes.[2,40] As of January 2019, 41 individuals with SCD have received unrelated CBT with overall survival of 85% and DFS of 50%.[25] However, EFS was reported as low as 37.5% in a study where the patients received one or two HLA-mismatched grafts. In addition, Ruggeri et al. reported graft failure of 53% with EFS of 31% and OS of 75%.[13,41] Graft failure remains the major limitation in UCBT but other problems including technical issues (colony growth delays), development of GvHD, increased cost, and graft rejection also are seen with UCBT.[13,25] In

an analysis, it was observed that engraftment and EFS were higher in patients that received transplantations of umbilical cord blood with more than 5 x 10^7 nucleated cells/kg at the time of the infusion.[41] In addition, a recent Japanese study reported blood samples with anti-HLA antibodies at an increased rate of graft failure.[41] Limited results and differing methods fail to suggest if this could become a successful alternative for patients lacking an HLA-identical donor.

Conclusion

Promising results from clinical studies using HLA-matched donor HSCT offer a potential cure for patients with SCD. Recent experience in regard to alternate donors have been explored but are not yet safe for public use. In addition, promising results of autologous stem cell transplantation using gene therapy techniques eliminate the issue of finding a matched donor all together. Different approaches to gene therapy include replacement of the beta gene, reactivating silenced gamma genes, or augmenting HgbF production.[42,44] Success of these gene therapies would allow repopulation of corrected RBCs through a corrective anti-sickling gene agent which could allow long-term presence of corrected RBCs throughout the course of the patient's life.[42] Several open clinical trials of gene therapy (NCT02186418, NCT02247843, NCT02151526, and NCT02140554) will provide future implications for the success of this therapy as a curative treatment.

Statistical analysis found myeloablative conditioning to have a 5% greater chance of engraftment than nonmyeloablative and reduced intensity regimens.[41] However, additional clinical studies are looking for alternatives to myeloablative conditioning to reduce associated toxicities for adult populations. Increased popularity of reduced-intensity and nonmyeloablative conditioning allows promising direction for increased use of HSCT in adult populations. While there are no toxicities associated with HU and chronic blood transfusions, they also offer no form of a cure for SCD and in turn increased risk of death into adult life.[40]

Socioeconomic and cultural differences and donor availability remain the main barriers in treatment of SCD with HSCT. Increased look at alternative donors and reduced intensity regimens look at promising alternatives to HLA-matched donors. In addition, gene therapy allowing for autologous HSCT allows the donor search to seize. Increased availability of HSCT worldwide promises potential of cure for those with SCD in resource constrained countries. Using HSCT as a cure for SCD is not limited to only clinical trials but has been seen in single institutions worldwide. In addition, mandatory newborn screening worldwide and standard treatment regimens have improved the quality of life of patients with SCD across the globe. However, lack of insurance and associated cost of HSCT remain a major concern for patients with SCD. Increased healthcare costs are already associated with individuals with SCD due to complications and pharmaceuticals.[45] Curing SCD with HSCT can be seen as a long-term solution to eventual reduction of healthcare costs, but the initial costs associated with the treatment remain a main barrier for individuals considering it. A study found that on average, individuals with SCD spend around $11,957 quarterly including inpatient, emergency department visits, outpatient, and pharmaceutical costs.[45] This constant burden of cost associated with SCD, leaves limited funds available to support the possibility of myeloablative HSCT with a median 100-day cost of $289,283.[46] However, overall cost related to the transplant is dependent on complications following HSCT including GvHD, readmission, and further complications support that this form of treatment is very costly. Lack of insurance or coverage from insurance companies remains a major barrier for patients with SCD who cannot afford these associated costs.

Increased use of unrelated and mismatched donors, peripheral blood, and donor lymphocyte infusions contribute to a higher risk of chronic GvHD.[47] However, the treatment available for cGvHD is suboptimal with low response rates.[47] Development of cGvHD was identified as the main predictor of poor health and adverse medical effects in patients that had received HSCT.[47] For this reason, an important aspect in the field of HSCT is developing more effective therapies for recipients that have developed cGvHD.[47] In addition to finding alternative treatments for GvHD, avoiding GvHD altogether in HSCT is another common goal. Toxicity as a result of the conditioning used in HSCT and risk of GvHD are the main reasons that patients with SCD reject treatment through HSCT when recommended by a hematologist.

Another barrier preventing HSCT for patients with SCD is lack of parent and adolescent education about the course of SCD and benefit assessment of HSCT.[48] Studies indicate that only 35% of adolescents and 46% of parents would accept HSCT if referred by their hematologist.[48] In addition, only 14% of parents believe that SCD will reduce their child's life by as few as five years.[49] This is inconsistent with the median age of death of those with SCD having their lives cut short by 20 years when compared with the average American.[49] Education of patients and parents is vital in ensuring that they are knowledgeable about their condition and able to make informed decisions about their treatment options.[49] However, education remains to be difficult due to the vast differences in clinical manifestations and severity of individual cases.

While many promising results have been found in adolescents, adults continue to be an increasingly vulnerable population.[50] Early detection and comprehensive care in adolescents have been linked to improved survival. For this reason, lack of comprehensive care for adults could contribute to the high morbidity seen in this population.[50] Increased risk associated with HSCT in adults have limited trials. However, with improved treatment of adolescents allowing as many as 93% to progress to adulthood, they have become the population of equal concern.[45] Eligibility for HSCT is an ongoing discussion with hematologists due to reduced quality of life and early morbidity seen in adults.[50,51]

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