REVIEW ARTICLE

The Current State of Sickle Cell Disease Management: A Concise Review on Stem Cell Transplant as a Cure

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ABSTRACT

Treatment of sickle cell disease remains largely palliative. While it may improve the quality of life, persons with sickle cell disease still suffer from extreme sickling crises, end-organ damage, and reduced life expectancy. Increasing studies have led to the identification and advancement of stem cell transplant and gene therapy as potential curative strategies for sickle cell disease. However, there have been various factors that have hindered their clinical application. Stem cell transplantation, the more propitious of the two, is limited by restricted transplant donor pool, transplant complications, and selection criteria. The current paper reviewed the literature on sickle cell disease, current treatment options, and more particularly on the progress of stem cell transplants. It outlined various challenges of stem cell transplant and proposed ways to increase the donor pool using alternative strategies and modifications of regimen conditioning with minimal transplant-related toxicities and associated complications.

KEY WORDS: Cord blood, Haploidentical, Sickle cell disease, Stem cell transplantation.

Introduction

Sickle cell disease (SCD) is a group of inherited red blood cell disorders caused by a structural abnormality of hemoglobin leading to the characteristic shape — "the sickle". J. B. Herrick first described the medical condition in 1910 as peculiar elongated and sickle-shaped.[1] SCD occurs most frequently among people in Sub-Saharan Africa, and less regularly in parts of the Middle East, Indian subcontinent, Mediterranean regions, and people of African origin. Globally, over 300,000 children are annually born with this disease[2] with approximately 150,000 deaths per year, hence being recognized as a global health problem. The average life expectancy of persons with sickle cell disease is reported to be forty to fifty years, which is often shorter for persons with homozygous HbS or HbS/ β0 than for persons with compound heterozygous.[3]

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The sickle hemoglobin, under normal conditions, combines with oxygen or carbon dioxide forming a biconcave shape termed as premeniscocyte, which cannot be differentiated from the healthy red blood cells.[3] Premeniscocytes have randomly distributed hemoglobin and are as flexible as healthy cells. However, when the oxygen or carbon dioxide is removed, hemoglobin is transformed into an uncombined state, and premeniscocyte undergo sickling. Ingram in 1958 discovered the genetic basis of the disease and demonstrated that the disease is caused by the substitution of glutamic acid (G_A_G) to valine (G_T_G) at position six of the hemoglobin β-globin chain.[4] The amino acid substitution results from point mutation of the hemoglobin gene. SCD can occur when one inherits homozygous HbS (HbSS) or compound heterozygous with β-thalassemia mutations (HbS/ β0-thalassemia and HbS/ β+-thalassemia, and other structural β-globin variants such as HbC-African Americans, HbD-Indian/Pakistan, HbE-Asian, HbO-Arab).

Persons with SCD may suffer from acute or chronic complications. Severe complications of sickle cell

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disease include but are not limited to, painful episodes, acute chest syndrome, stroke, and hepatic and splenic sequestration. The disease may also lead to life-threatening chronic complications such as osteomyelitis, and damage or injury to the liver, lung, kidney, brain, eyes, and heart. The current disease-modifying therapies of SCD that prevent and treat these complications include red blood cell transfusion, L-glutamine, crizanlizumab, voxelotor, and hydroxyurea. However, the only promising cure, to date, remains allogeneic hematopoietic stem cell transplant which has shown excellent potential recently. Gene therapy is also a potential therapeutic strategy currently under investigation. In this paper, I outlined the advances and constraints of hematopoietic stem cell transplantation as a cure for SCD. I also highlighted strategies to improve the procedure through regimen modification to reduce transplant-related toxicities and associated complications based on meticulous considerations of current research outcomes.

Summary of the pathophysiology of sickle cell disease

SCD has a complicated pathway of contributory pathologies, and although polymerization of sickle cells is central in vaso-occlusive crises, the hypothesis that it is solely responsible for vascular obstruction and sickle cell-related painful crises is no longer valid.

In a low condition of oxygen concentration, intracellular hemoglobin becomes insoluble and polymerizes into tubulin fibers producing the sickling shape.[5] The inflexible and rigid cells aggregate and block tissue depriving cells of blood flow and oxygen, leading to ischemic damage or tissue necrosis.

The low antioxidant capacity of sickle cells caused by defective intracellular signaling pathways, less nitric oxide (NO) and adenosine triphosphate (ATP) may lead to oxidative damage. The highly reactive oxygen species may damage cellular membrane proteins and also cause hemolysis. The abnormal membrane proteins at the cell surface contribute to the interaction between sickle cells and healthy RBCs, and other blood cells. The release of hemoglobin into plasma traps NO and adversely lowers NO content since arginase-1 activity, responsible for NO production, is lower in sickle cells. The lower NO concentration causes vasoconstriction of the vessels contributing to acute chest syndrome, cardiac ischemia, and stroke.

Also, microRNAs are dysregulated in sickle cells and are partly responsible for abnormal erythropoiesis by silencing important RNA molecules. The process can lead to abnormal activation of adhesive receptors, such as RBC intercellular adhesion molecule-4 and basal cell adhesion molecule. These surface molecules mediate the interaction between sickle cell and endothelium, leukocytes, and platelets. Other adhesive proteins such as mitogen-activated protein kinase ERK $\frac{1}{2}$, E-selectin and P-selectin are upregulated in sickle cell disease and contribute to disease pathology and severity.[6]

Aside from the interaction between sickle cell and leukocytes and platelets caused by adhesive proteins on sickle cells, multiple inflammatory cytokines, such as IL-4, IL-10, macrophage inflammatory protein (MIP-1α) and tumor necrosis factor-alpha (TNF-α) are also elevated in SCD resulting in the extreme inflammation and painful episodes associated with the disease.[7,8]

As a result of the multiple contributory pathways of the disease pathology, it is challenging to strategize therapy that can address all the mechanisms and pathways. There have been short-term and long-term treatment therapies that address specific path (s) of the disease pathology. Curative strategies have also been postulated. However, there are adverse limitations of such procedures, and detailed studies ought to be carried out.

Current treatment options

Most of the treatment options for sickle cell disease remain largely palliative and while it may improve quality of life, persons with sickle cell disease may still suffer from extreme sickling crises, end-organ damage/injury, and reduced life expectancy. Current therapies for SCD include fetal hemoglobin inducing agent-hydroxyurea, RBC transfusion, L-glutamine, anti-adhesive agent — crizanlizumab, and hemoglobin oxygen-affinity modulator — voxelotor. Crizanlizumab and voxelotor were granted accelerated approval based on their effect on a surrogate endpoint, therefore further research and trials are required to verify and establish their clinical benefits.

Hydroxyurea

Hydroxyurea, also known as hydroxycarbamide, is an antineoplastic oral drug used to treat chronic myelogenous leukemia, melanoma, and inoperable ovarian cancer. The chemical compound first synthesized by Dresler and Stein in 1869, was initially

approved by US FDA as an anticancer agent in 1967.[9] The drug received approval from the FDA for use in treating adults with SCD in 1998 based on the evidence of hydroxyurea inducing HbF in the mid-1980s.[10,11] Various studies have supported the drug's effect on reducing acute painful episodes and acute chest syndrome and inducing HbF.[3–15]

Although hydroxyurea is widely believed to induce HbF synthesis, the mechanism of action for HbF induction remains not completely established. However, the well-established mechanism of action of hydroxyurea as HbF inducer is the blockage of synthesis of deoxyribonucleotides, DNA synthesis, and repair through reversible inhibition of ribonucleotide reductase.[16] The inhibition of ribonucleotide reductase in the S-phase, where DNA synthesis is highly expressed leads to the transitory arrest of erythropoiesis. The recovery from the arrested state leads to stress erythropoiesis consisting of erythropoietin induction and recruitment of early erythroid progenitors that maintain their HbF-producing ability, resulting in mature erythrocytes with actively expressing γ-gene.[17] The erythroid stress-related HbF expression may occur as a result of the changes in the erythroid environment such as a change in erythropoietic kinetics, signal transduction, or others.

L-glutamine

The USA Food and Drug Authority in 2017 announced the commercial availability of L-glutamine (under the brand "Endari") as the second drug for the treatment of SCD.[18] Glutamine is a precursor for the synthesis of glutathione, nicotinamide adenine dinucleotide and arginine, compounds central to the protection of red blood cells against oxidative stress or damage and also maintenance of normal vascular tone.[19] Sickle red blood cells absorb and utilize L-glutamine at a higher rate that exceeds the amount the body produces. The mechanistic use of the drug is to supplement the low L-glutamine levels caused by the decreased redox potential of sickle red blood cells which may lead to oxidative stress or damage to the cell. Supplementing the low levels of L-glutamine causes a subsequent increase in naturally occurring redox agents such as nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide hydrogenase which in turn prevent oxidative stress. L-glutamine has been shown to significantly decrease the frequency of vaso-occlusive episodes and incidence of acute chest syndrome with negligible side effects by neutralizing the oxidative stress in sickle red blood cells and making the cells flexible to carry oxygen throughout the body. In addition, L-glutamine acts as an antioxidant to protect red blood cell protein and lipid against oxidation, red blood cell fragility, and phosphatidylserine exposure.[20]

Crizanlizumab

On November 15, 2019, crizanlizumab was also approved for treating SCD after several reports of the drug reducing the frequency of vaso-occlusive crises in adults and young people $\geq$16 years with SCD.[21] Crizanlizumab is a humanized monoclonal antibody that binds to P-selectin expressed on the surface of endothelial cells and platelets.[22] P-selectin is expressed by these cells during activation processes such as inflammation.[23] This initiates the adherence of leukocytes to the endothelium through the P-selectin glycoprotein ligand 1 (PSGL-1) on leukocytes. Activated platelets may also bind to PSGL-1 on the surface of leukocytes. Normal RBCs do not express PSGL-1 on their surfaces. Sickle RBCs are, on the other hand, known to possess surface glycoprotein similar to PSGL-1 which adheres to activated endothelium, forming an aggregate that causes obstruction of the vasculature, vaso-occlusion, and tissue ischemia.[24] Crizanlizumab, an anti-P-selectin monoclonal antibody, inhibits the binding of (PSGL-1), thereby preventing interactions with leukocytes and sickle cells. Inhibition of these interactions also eliminates subsequent local hypoxia that may lead to the upregulation of P-selectin in endothelial cells, HbS polymerization, and severe vaso-occlusive crises.

Voxelotor

Voxelotor, a Hb oxygen-affinity modulator, was also granted accelerated approval by the US FDA on November 19, 2019, based on evidence of increasing Hb.[21] The compound inhibits HbS polymerization and the sickling of HbS-containing RBCs. The mechanism of voxelotor in reducing the sickling of RBC is through increasing the proportions of oxygenated HbS in SCD patients. Oxygenated HbS has a biconcave shape similar to normal Hb, flexible and randomly distributed, thereby preventing vaso-occlusion. The drug safety reported by Hutchaleelaha et al.[25] was fairly high with over 30% of cases of vomiting and nausea, 50% with diarrhea, and others with gastroenteritis and headache.

RBC transfusion

About ninety percent of adults with SCD must have received at least one red blood cell transfusion making blood transfusion a mainstay of treatment for SCD[26] along with hydroxyurea. RBC transfusion can be given to treat complications of sickle cell or as intermittent preventive treatment to protect against complications.[27] Blood transfusion is, in some cases, given to treat stroke in children with abnormal transcranial Doppler.[28]. Transfusion increases the oxygen capacity of the blood, especially in people with anemic-SCDs, and reduces the complications of vaso-occlusion. People with severe anemia usually require a simple transfusion in which normal blood cells are given without removal of one's blood. However, with mild anemia, exchange transfusion may be necessary to lower the concentration of HbS through dilution. RBC transfusion may follow either a restriction policy where simple transfusion is given to reach a pre-specified Hb target or a liberal policy in which transfusion reduces HbS percentage below a pre-selected threshold.[29] RBC transfusion has generally improved the quality of life of people with SCD, albeit the risk, including the transmission of transfusion-associated infections, alloimmunization, iron overload, acute or delayed hemolytic transfusion, and increased complexity of compatibility testing. Therefore, the benefits and risks must be assessed before transfusion.

Hematopoietic stem cell transplantation

Although advances have been achieved in treatment to control complications and crises of SCD, the safety and accessibility of these drugs have always been a universal issue. To date, hematopoietic stem cell transplantation (HSCT) or bone marrow transplantation remains the only cure for SCD with gene therapy also considered a promising strategy. Considering how skeptical most healthcare professionals and SCD patients are about current treatments, curative therapy should have been an accomplishing discovery. However, HSCT with its several concerns including the selection of patients (age, disease severity, and end-organ injury), risk of short-term toxicity, long-term adverse effects (graft-vs-host disease, sterility), graft failure, selection of conditioning regimen, and availability of suitable donor, have limited its prospects. This paper focuses on current advances made in HSCT, especially to overcome such limitations, recent challenges, and the way forward.

Several factors may be considered in the selection of patients for HSCT. The eligibility for HSCT, in contrast, is based on individual benefits-and-risks analysis. The procedure is only recommended for patients whose benefits of cure outweigh the risks of transplant-associated toxicities where a suitable donor is available. Age and suitable donors are the most significant factors of mortality and success of HSCT. Studies show that pediatric patients with human leukocyte antigen (HLA)-matched sibling donors using a myeloablative conditioning regimen is, by far, the most successful transplant.[30,31] A worldwide survey of HLA-identical sibling HSCT reported a 5-year overall survival (OS) rate of 95% and 81% for patients < 16years and those ≥16, respectively; with corresponding event-free survival (EFS) of 93% and 81%; 9% increase on hazard ratio for treatment failure (graft rejection or death) per a year increment in age; and hazard ratio for acute graft-vs-host disease (GvHD) was 4% for every 1-year increment in age.[32]

Selection of conditioning regimen

Myeloablative regimen, the standard conditioning for HSCT, has been associated with transplant-related toxicities, veno-occlusive disease of the liver, hemorrhage, secondary malignancy, graft failure, and sterility.[33–35] Attempts in preventing these adverse effects mostly seen in adults have resulted in newer regimens such as non-myeloablative and reducing-intensity conditioning regimens. HSCT using these approaches is aimed at producing mixed chimerism for stable disease control. However, an engraftment threshold that allows the improvement of the disease remains controversial. Previous studies have also heavily associated these approaches with a high rate of engraftment failure, higher incidence of GvHD, and prolonged immunosuppression which put patients at risk of infections. A study by Nickel et al.,[36] which has been replicated in other studies, prompted the use of alemtuzumab non-myeloablative regimen using HLA-matched sibling HSCT with no GvHD or transplant-related mortality and an EFS rate of 90%.[37,38]

Matched unrelated donor

With the chances of an individual finding a matched sibling donor within the 16 to 20% range, efforts have been made to expand the availability of transplant donors for most SCD patients.[35,39] Advances in HSCT have led to the use of matched unrelated, cord blood, and haploidentical donors.

A study by Shenoy et al.[40] using a reducing-intensity conditioning regimen including alemtuzumab, fludarabine, and melphalan reported a 10% graft rejection, 76% and 69% incidence of 1- and 2-year EFS, respectively, and corresponding 86% and 79% rates of OS, using matched unrelated donor. The rate of acute GvHD on day 100 was 28% and chronic GvHD was 62% in the first year. Severe GvHD-related death was also reported in the second year.

In 2019, a prospective study on adolescents and young adults, 17 – 36 years, was conducted using a reduced-intensity regimen with both HLA-identical sibling donors and HLA-allele matched unrelated donors. The progress and success of unrelated transplants were still very low. One-year OS for sibling and unrelated transplants were 94% and 80%, respectively, and corresponding EFS of 94% and 60%.[41]

Cord blood donor

The use of unrelated cord blood for the treatment of SCD is currently discouraged due to the high rate of graft rejection, GvHD, and post-transplant infections. A study conducted by Kamani and colleagues in 2012 using reduced-intensity conditioning with alemtuzumab, fludarabine, and melphalan, resulted in a 1-year EFS of 37.5%, acute GvHD of 25%, and chronic extensive GvHD of 12.5%.[42] Despite EFS not meeting the prespecified target, the reduced-intensity conditioning used in the study was reported to have a positive safety profile and therefore new approaches with improved engraftment can be adopted for unrelated cord transplants in persons with severe SCD.

In a more recent study, Abraham et al.[43] tested the previous reduced-intensity conditioning regimen with thiotepa in nine children to see the effect on engraftment. The findings showed increasing engraftment with 1-year EFS and OS rates of 78% and 100%, respectively, but the incidence of acute GvHD and viral infections of 44% and 78% were still very high.

Unlike unrelated cord blood, related cord blood transplant has been very successful in SCD. Reports by Lacotelli et al.[44] on patients with hemoglobinopathies that received HLA-identical sibling cord blood had a 6-year EFS and OS of 90% and 97%, respectively in SCD patients. Graft failure was observed in 10.4%, eleven of the 96 patients (11%) experienced acute GvHD and no incidence of chronic extensive GvHD. Aside from the difficulty in obtaining HLA-identical related cord blood for the majority of SCD patients, there have been reports of significant delay in the time of engraftment for neutrophils and platelets,[45,46] which place SCD patients at increased risk of viral infection.[47]

Haploidentical donor

With continuous efforts to expand the HSCT donor pool, haploidentical transplants, which use half-matched donors, have seen major improvements in the conditioning regimen with promising outcomes. Haploidentical transplants have previously been associated with high transplant morbidity, graft failure, and extensive GvHD. Also, the transplant procedure of haploidentical cells has itself been reported to cause a decline in cardiac, pulmonary, and renal functions. Haploidentical transplant uses half-matched donor cells or one HLA-matched haplotype, making donors easily accessible.

In attempts to develop a safe HLA-haploidentical peripheral blood stem cell transplant approach for patients with severe organ damage, Fitzhugh et al.[48] used alemtuzumab non-myeloablative regimen with and without post-transplant cyclophosphamide. The conditioning regimen without cyclophosphamide had all patients rejecting graft after 7 months of transplantation. In patients that received cyclophosphamide, graft failure decreased significantly to 50%, and acute and chronic GvHD was diagnosed in 16%. Two of the 21 patients died as a result of pulmonary hypertension, congestive heart failure, and infections. In a similar study with a thiotepa-augmented non-myeloablative regimen, 93% stable engraftment, and 100% OS were achieved after 6 months. Five of the 15 patients that received cyclophosphamide developed acute GvHD and 6 patients had chronic GvHD. Other complications reported in the study were mainly asymptomatic viral infection, occurring in nine patients, and one case each of typhlitis, gastritis, and gastrointestinal bleeding.[49]

A recent study by Foell et al.[50] using CD3/CD19 and $\alpha\beta$/CD19 T-cell depleted haploidentical cells achieved 100% primary engraftment. The recorded rates of EFS and OS were 100% and 88%, respectively, where all surviving patients are free of SCD-related disease and complications. The incidence of GvHD was considerably high with 28% and 16% developing acute GvHD and chronic GvHD respectively. Viral reactivation was reported in 52%,

and 4% each with macrophage activation syndrome and veno-occlusive disease of the liver.

Conclusion

Despite current advances in the management of persons with SCD, the mechanism of action, safety, and clinical benefits of these drugs remain elusive to most scientists. Universal clinical trials need to be initiated and carried out under strict conditions and analysis to firmly establish the safety and benefits of these drugs. Gene therapy as a cure for SCD is an interesting and promising field of research but its safety and efficacy are yet to be established. Allogeneic HSCT is the only curative strategy for persons with SCD. However, concerns about donor availability and transplant-related complications had limited the use of HSCT. Recent studies have discovered new approaches to expand the donor pool and prevent some transplant-associated complications. Most of these approaches met the prespecified target of event-free survival rate, however, the incidence of transplant-related diseases was considerably high.

Aside from using human leukocyte antigen (HLA)-matched sibling donors, all efforts to expand the donor pool have resulted in a high incidence of transplant-related conditions that are most deadly to recipients. However, reports from studies using haploidentical peripheral stem cells are encouraging and demonstrate a safer and feasible procedure that could be adopted as an alternative cure for SCD patients. Also, different conditioning regimens have been shown to result in transplant-related toxicities. Therefore, extensive research is needed to elucidate the best regimen for different donor cells with potential curative alternatives to SCD.

Abbreviations

ATP: Adenosine triphosphate

CD: Cluster of differentiation

DNA: Deoxyribonucleic acid

EFS: Event-free survival

ERK: Extracellular signal-regulated protein kinase

FDA: Food and Drug Authority

GvHD: Graft versus host disease

Hb: Hemoglobin

HLA: Human leukocyte antigen

HSCT: Hematopoietic stem cell transplantation

MIP: Macrophage inflammatory proteins

NO: Nitric Oxide

OS: Overall survival

PSGL-1: P-selectin glycoprotein ligand 1

RBC: Red blood cell

RNA: Ribonucleic acid

SCD: Sickle cell disease

TNF: Tumor necrosis factor

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