Current therapy of sickle cell disease

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Homozygous sickle cell disease (SCD) is an autosomal recessive genetic disease that results from the substitution of valine for glutamic acid at position 6 of the β-globin gene, leading to production of a defective form of hemoglobin, hemoglobin S (HbS). The prevalence of SCD is about 1-2% among African descendants in Europe and the United States and 4% or higher in West Africa. SCD shows broad phenotypic expression that varies greatly between regions, among patients and longitudinally in the same patient.[1,2] The protean clinical features of SCD result from chronic variable intravascular hemolysis, microvascular ischemia and organ damage. Vaso-occlusion is the outcome of a dynamic combination of abnormalities in hemoglobin structure and function, red blood cell membrane integrity, erythrocyte density, endothelial activation, microvascular tone, inflammatory mediators, and coagulation. These pathophysiologic events translate into clinical manifestations that fall into four general categories: anemia and its sequelae; vaso-occlusive crises and bone marrow fat embolization syndrome; infection (from functional asplenia) and organ dysfunction. Organ damage results from a combination of hemolysis and infarction and may be manifested as stroke, retinopathy, nephropathy, liver disease or pulmonary arterial hypertension. Intravascular hemolysis in SCD causes the release of hemoglobin into the plasma. When the capacity of protective hemoglobin-scavenging mechanisms (haptoglobin and hemopexin) has been saturated, levels of cell-free hemoglobin increase in the plasma resulting in the consumption of nitric oxide (NO) by hemoglobin-mediated NO scavenging.[3] In addition, arginase released by hemolyzed red cells can deplete blood plasma of arginine, the substrate for NO production by NO synthase.[4] NO plays a major role in vascular homeostasis and is a critical regulator of smooth muscle relaxation and vasomotor tone, expression of endothelial adhesion molecules and platelet activation and aggregation.[5] A deficiency in NO, due to its inactivation by cell-free plasma hemoglobin levels during intravascular hemolysis in SCD, may underlie complications associated with SCD.[6] In this editorial, we briefly review the currently available treatments for SCD. For more detail on specific topics, the reader is directed to more extensive recent review articles as cited in the references.

Prophylactic therapy

Three prophylactic measures have become widely accepted in the management of SCD; penicillin prophylaxis, immunization against pneumococcal infection and folate administration. The mortality rate due to *Streptococcus pneumoniae* pneumonia, sepsis, and meningitis was historically very high prior to the age of 6 years in children with SCD. This rate has been lowered tremendously by three maneuvers. The first is diagnostic screening for SCD in neonates, with immediate initiation of pencillin VK 125 mg twice daily, increased at the age of 3 years to 250 mg twice daily and continued until 5 years old. The second is immunization with heptavalent pneumococcal-conjugated vaccine at 2, 4, 6, and 12 months of age. The third is immunization with 23-valent pneumococcal polysaccharide vaccine at 2 and 5 years of age.[7] Due to the increased metabolic requirement for folate, this is frequently provided as a supplement at a dose of 1 mg daily, although the adequate dietary intake in the United States appears not to mandate such supplementation.[8]

Red cell transfusion

The management of SCD continues to be supportive and includes hydration, pain relief, blood transfusion and psychosocial support. The majority of patients with SCD receive transfusions at some point in their life to reduce complications of the disease. The most common complication is a vaso-occlusive crisis, but transfusion has not been shown to be acutely beneficial for this indication.[9] Indications for acute simple transfusion include symptomatic anemia, aplastic crisis, splenic or hepatic sequestration, acute chest syndrome or acute multi-organ failure with severe anemia, and preparation of patients with homozygous SCD for major surgery.[10,11] Chronic anemia usually does not require transfusion if the hemoglobin level remains above 7 g/dL. Symptoms of anemia requiring transfusion include high output cardiac failure, dyspnea, postural hypotension, angina, and cerebral dysfunction. Simple transfusion expands the normal red cell mass thereby improving oxygen-carrying capacity at the cost of increasing blood viscosity.

Transfused red cells will significantly increase blood viscosity, potentially reducing blood flow, if the hemoglobin level rises above 11 g/dL when there are greater than 20% HbS-containing cells. Therefore, if the goal is an acute reduction in the proportion of sickled red cells in addition to an increase in oxygen-carrying capacity, exchange transfusion is the therapy of choice. The indications for exchange transfusion include acute stroke, acute chest syndrome with severe hypoxia, acute multi-organ failure, and possibly acute severe priapism.[9] Partial exchange transfusion is indicated for hemoglobin SC patients undergoing major surgery.[12] Exchange transfusions offer better control of blood volume and viscosity while decreas-

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Table 1. Therapies for sickle cell disease.

Therapy	*Clinical Indications*
Accepted	
Penicillin prophylaxis Pneumococcal conjugate vaccine Pneumococcal polysaccharide vaccine	Prevention of invasive infection with *Streptococcus pneumoniae*
Simple red cell transfusion	Acute chest syndrome, severe anemia, acute splenic or hepatic sequestration, multi-organ failure, pre-operative
Red cell exchange transfusion	Acute stroke, acute chest syndrome, multi-organ failure
Hydroxyurea	Three or more hospital admissions per year for vaso-occlusive crises. Possibly for organ dysfunction, e.g., pulmonary hypertension
Deferoxamine; Deferasirox; (in Europe, also deferiprone)	Transfusional iron overload
Investigational	
Decitabine	To increase HbF expression
ICA-17043	To reduce hemolysis
Inhaled nitric oxide	Vaso-occlusive pain crisis
Sildenafil	Pulmonary hypertension
Vitamins B6, C, E or ω-3 fatty acids	Yet to be defined
Nitrite	Yet to be defined
Atorvastatin	Yet to be defined

ing the risk of transfusion-related hemochromatosis. Such transfusions are most readily accomplished via automated red cell exchange (erythrocytapheresis).[9] The drawbacks of exchange transfusions are higher cost, limited availability, and often a requirement for large central venous catheters.

Transfusion remains an essential component of care for SCD, but associated complications include iron overload, transfusion reactions, infections, acute lung injury, pain crisis, stroke, immunomodulation, anaphylaxis, and alloimmunization.[10,13] Extended red cell phenotyping (matching for the ABO, D, E, C, and Kell red cell antigens) can be instituted in North America, and is predicted to reduce the alloimmunization rate from 3 to 0.5% per unit, the number of hemolytic transfusion reactions by 90% and alloantibody formation by 53.3%.[13,14] Most North American hospital blood banks do not, however, match the red cell phenotype of non-alloimmunized sickle cell patients beyond matching for ABO and D blood goups.[15] Twenty-five percent of sickle cell patients develop alloantibodies without extended matching and 60% of chronically transfused adults become alloimmunized.[13,15] The differences between the red cell phenotypes of the predominantly Caucasian donor pool in Europe and North America and those of the sickle cell population of African descent, along with increased costs are barriers to the universal adoption of extended red cell phenotyping.

Chronic simple transfusion has been recommended for cerebrovascular disease, debilitating pain crises, severe pulmonary or cardiac disease, and complicated pregnancies. The strongest evidence in support of chronic transfusion regimens is for stroke patients with sickle cell anemia.[16] After one ischemic stroke, nearly 70% patients will have another stroke within 3 years in the absence of transfusions. Chronic transfusion therapy is also indicated for the primary prevention of stroke in children at high risk of this complication as determined by transcranial Doppler ultrasonography.[17] There is no consensus on the duration of chronic transfusion treatment required to maintain the preventive effect, but unpublished data suggest that 30 months are not sufficient.[18] Chronic exchange transfusion has been advocated to reduce iron accumulation, but it also increases donor exposure.[10] Ten mL/kg of packed red cells every 3 to 4 weeks will usually reach the therapeutic goal of less than 30% hemoglobin S and a hemoglobin concentration of 10 g/dL. While many questions remain, with the appropriate management, transfusion therapy is helping sickle cell patients live longer. Chronic transfusion may be complicated by iron overload that requires chelation therapy.[19] Allogeneic hematopoietic transplantation remains the only curative therapy but is limited by availability of matched sibling donors and transplant-related complications.[20,21]

Hydroxyurea, the only therapy specifically approved for SCD

Hydroxyurea is the most successful drug therapy for SCD. It is a cytotoxic and cytoreductive antimetabolite that acts via inhibition of DNA synthesis by inhibiting ribonucleotide reductase. Known pharmacologic effects of hydroxyurea that may contribute to this drug's efficacy in SCD include increased red cell content of hemoglobin F levels (which reduces the formation of hemoglobin S polymers), dose-related cytoreductive effects on neutrophils, increased water content of red cells, increased deformability and successful microvascular navigation of sickled cells and altered adhesion of red blood cells to endothelium by decreasing the expression of endothelial adhesion molecules. Treatment with hydroxyurea is associated with significant decreases in the yearly rate of painful crises, hospital admissions, incidence of chest syndrome, priapism, hepatic sequestration, and blood transfusion requirements by as much as 50%. Hydroxyurea treatment also reduces mortality by 40%.[22] Hydroxyurea is indicated for adults with SCD who require three or more hospital admissions for vaso-occlusive crises per year, and should also be considered for symptomatic children and for patients with organ dysfunction. Hydroxyurea may be a valid alternative to chronic transfusion support in patients with SCD and stroke, but this is controversial.[23-25] There are emerging data on the efficacy of hydroxyurea in patients with sickle-β-thalassemia and sickle cell-hemoglobin C (HbSC) disease.[26]

The starting dose of hydroxyurea is 15 mg/kg/day;

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this is then increased by 5 mg/kg/day every 12 weeks, up to a maximum dose of 35 mg/kg/day. Close monitoring is required for all patients on hydroxyurea, with blood counts every 2 weeks, in order to detect evidence of bone marrow suppression. The drug should be withheld for 1-2 weeks if signs of myelotoxicity develop (neutrophil count < 2,000/mm^3, platelet count < 80,000/mm^3, hemoglobin < 4.5 g/dL, or absolute reticulocyte count < 80,000/mm^3), and the dose should be reduced by 2.5 mg/kg/day if myelotoxicity recurs. A favorable response to hydroxyurea is indicated by an increase in fetal hemoglobin (HbF) by 5-15%, and an increase in total hemoglobin by about 1 g/dL in 4 to 12 weeks after initiation of the treatment.[27] Once a stable or maximally tolerated dose has been attained, monitoring can be performed monthly. Hydroxyurea causes red cell macrocytosis, which can be helpful in monitoring compliance. Folate deficiency, common in SCD, may be masked under hydroxyurea therapy, and all SCD patients should receive prophylactic folate supplementation. Hydroxyurea should be used with caution in patients with renal dysfunction and may pose more risk in patients with a serum creatinine concentration above 1.7 g/dL. Hydroxyurea fails to increase HbF in up to 25% of patients. The combination of hydroxyurea with erythropoietin may increase the Hb F response, and improve dose-limiting reticulocytopenia in patients with mild renal insufficiency, but this remains an investigational combination at present.[28] The combination of hydroxyurea and angiotensin-converting enzyme inhibitors in sickle nephropathy reduces urinary protein excretion.[29]

Hydroxyurea has been tolerated well over the long-term by patients with SCD and is associated with improved survival.[30] Secondary leukemia has been seen in patients with myeloproliferative disorders on long-term hydroxyurea treatment,[31] but this is controversial and has not been seen to date in SCD.[30] Hydroxyurea is a teratogen in animal models.

Although most physicians advise patients on hydroxyurea to avoid becoming pregnant, several case reports suggest that the risk of exposure to this drug during pregnancy may have been overestimated in humans.[32,33] Further studies are needed with larger numbers of patients receiving hydroxyurea during pregnancy with longer follow-up of children exposed *in utero*. Hydroxyurea is excreted in human milk and is, therefore, not recommended for lactating mothers.

The efficacy of hydroxyurea in children with SCD appears to be at least as high as that in adults, and additional studies are underway in especially young children.[34,35] Initiation treatment with hydroxyurea at a young age may decrease long-term organ complications and the mortality rate associated with SCD.[36,37] Long-term treatment with hydroxyurea for children and adults with SCD is well tolerated, effective, and has sustained hematologic efficacy with apparent long-term safety.[38,39] This drug is unfortunately underutilized in SCD due to lack of experience among non-hematologists/oncologists and toxicity concerns among patients and some physicians.[40] Favorable long-term safety data from a large European cohort of children with SCD published in this issue of the journal may help to promote more widespread use of hydroxyurea.[41]

Experimental treatments for SCD

There are increasing data on the efficacy of newer agents including decitabine, a Gardos channel inhibitor (ICA-17043), butyrate and nitric oxide in SCD. Decitabine (2'-deoxy-5-azacytidine) is an antimetabolite cytosine analog derived from cytarabine with potent anti-leukemic activity. In preliminary studies it increased the amount of HbF by hypomethylating DNA at the γ-globin (HbF) gene promoter in patients with β-thalassemia and SCD. A small study indicated that decitabine may induce HbF in patients with sickle cell anemia who failed to increase HbF in response to hydroxyurea. The long-term safety and efficacy of decitabine in SCD remains to be proven.[42]

The Gardos channel, the erythrocyte intermediate conductance Ca-activated K channel, is responsible for Ca^{2+}-dependent K^+ efflux from human erythrocytes (the Gardos effect). SCD is characterized by the presence of dense dehydrated erythrocytes that have lost most of their potassium content. Inhibition of the Gardos channel appears to reduce polymerization and hemolysis. Studies with the imidazole antimycotic clotrimazole have shown a reduction of sickle cell dehydration *in vivo* in a small number of patients with SCD; dose-limiting gastrointestinal and liver toxicities were observed.[43] Based on the chemical structure of clotrimazole metabolites, a novel Gardos channel inhibitor, ICA-17043, has been developed and shown to be safe, tolerable and effective in increasing total hemoglobin and reducing hemolytic rates in SCD.[44]

Hb F levels increase in most patients with SCD following intermittent butyrate therapy.[45] The mechanisms responsible for induction of HbF by butyrate include an increase in the synthesis of reticulocyte γ globin chain as a result of increasing the efficiency of translation of γ-globin mRNA.[46]

Nitric oxide, essential for maintaining vascular tone, is produced from arginine by NO synthase. Plasma arginine levels are low in sickle cell anemia and supplementation may be beneficial; trials on this issue are in progress.[47] In a small pilot study, inhaled NO reduced the duration and severity of acute vaso-occlusive crises in children, and additional studies are in progress.[48] Sildenafil, which potentiates the effect of NO has shown promising results in SCD-related pulmonary hypertension.[49]

Other agents under investigation for SCD are too numerous to review here, but a few highlights are provided below. Deficiencies of various nutrients are reported in patients with SCD, including folate, vitamins B6, C, D, and E, arginine, zinc and magnesium.[8]

However, detailed large studies are needed to determine the clinical efficacies of these and other dietary supplements, such as omega-3 fatty acids.[50] Clinical trials of agents specifically directed at reducing cell

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adhesion have not yet been reported in humans. Our group is investigating the potential clinical efficacies of atorvastatin and nitrite.[51] These are all important areas for more extensive future research.

Conclusions

Patients with SCD now more frequently survive beyond about 50 years, but with increasing chronic organ complications. Current data suggest that hydroxyurea therapy should be initiated early for adults with SCD requiring three or more hospital admissions per year, and possibly also for patients with sickle cell-induced organ dysfunction. A growing body of literature supports the safety and efficacy of initiating hydroxyurea therapy in childhood. Long-term treatment with hydroxyurea is safe, effective and affordable. The future of drug therapy for SCD lies in developing more effective HbF-inducing agents, other drugs to reduce hemolysis and vasculopathy, and early identification and treatment of end organ complications, especially pulmonary hypertension. Curing SCD by novel allogeneic transplantation regimens and gene therapy are important future directions. Genetic counseling and public education remain critical for decreasing the current burden of SCD.

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