

Severe Sickle Cell Disease—Pathophysiology and Therapy

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Over 70,000 people live with sickle cell disease (SCD) in the United States and multitudes worldwide. About 2000 afflicted babies are born in this country each year. In African countries such as Nigeria, over 100,000 babies are born with the disease each year. Great strides have been made in the conservative management of SCD. However, the medical and psychosocial cost of supporting patients with this chronic illness is enormous and spans a lifetime. Hematopoietic stem cell transplantation (HSCT) can abrogate SCD manifestations, and is the best option for cure today. Yet, this treatment modality is underutilized as less than 500 transplants are reported in the Center for International Blood and Marrow Transplant Research (CIBMTR) database because of its significant risk of morbidity and mortality. There is growing understanding of the pathophysiology of the disease, and this, coupled with advances in transplantation and new approaches to therapy, continue to improve care of patients with SCD both in children and during adulthood. Continuing investigation seeks to predict the course of the disease and to determine timing and modality of therapy in order to optimize outcomes.

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NATURAL HISTORY OF ACUTE AND CHRONIC ORGAN DAMAGE IN SICKLE CELL DISEASE

Patients with sickle cell disease (SCD) have an abnormal hemoglobin that polymerizes under physiologic conditions, leading to the formation of distorted and rigid red blood cells. This, in turn, causes hemolysis and obstruction of blood flow in the microcirculation, with resultant tissue ischemia and necrosis. Pain and organ injury are the sequelae.

The organs damaged by the abnormal erythrocytes vary according to patient age, the specific sickle cell genotype, other gene polymorphisms, and environmental phenomena. Organ damage can be acute or chronic, symptomatic or clinically silent, and episodic

or progressive. The most common organ-related complications that characterize SCD as a severe clinical entity include vaso-occlusive or pain crisis, acute chest syndrome, stroke, and priapism. Because of the clinical heterogeneity of SCD, there has been a great deal of interest in predicting at the earliest possible age which patients will be most severely affected. If such high-risk patients could be identified, early intervention might be prescribed to avert organ injury. In 2000, Miller and colleagues [1] reported for the Cooperative Study of Sickle Cell Disease that several clinical and laboratory markers during the first 2 years of life predict a severe clinical course (characterized by early death or recurrent pain crisis or chest syndrome) during the ensuing 10 years. However, a similar study of the Dallas Newborn Cohort reported by Quinn and colleagues [2] in 2008 refuted this finding. Thus, at present, there are no reliably validated measures in the young child that can predict long-term outcomes.

Although the acute events just described cause much morbidity during childhood as well as in adults, the toll of chronic sickling and vascular injury as well as ongoing hemolysis also promotes insidious, silent, clinically inapparent, but progressive organ damage. Such injury involves the lungs, heart, brain, kidneys, bones, and other organs. The damage may not become manifest until early or midadulthood, often after a seemingly benign clinical course during the childhood years. Some, if not much, of this organ dysfunction, results primarily from the chronic anemia or

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perhaps more specifically from intravascular hemolysis. Specific complications include pulmonary hypertension, osteonecrosis, chronic renal disease, and cognitive dysfunction. Attention is currently being given by investigators and clinicians to this progressive organ damage, for it is a major cause of morbidity and premature death in adult patients with SCD. Many such patients seem to do well during childhood, but are vulnerable to developing irreversible organ damage because of chronic hemolytic anemia and/or vascular occlusion in young adulthood. These patients are now increasingly considered candidates for the same disease-modifying interventions as those children and adults with more clinically apparent recurrent vaso-occlusive events.

At this time, the major treatments that can truly prevent or lessen the burden of recurrent pain and organ damage are hydroxyurea, chronic blood transfusions, and hematopoietic stem cell transplantation (HSCT). The real question is which of these 3 approaches (as well as novel interventions yet to be developed or perfected) is most appropriate for an individual patient. An equally important question is when such intervention should be initiated to derive optimal benefit. Because each of the 3 primary treatment modalities has substantial adverse effects, the careful assessment of the risk-benefit ratio is crucial. Some clinical trials are ongoing, and many others need to be designed and performed to generate conclusive answers to this vexing question.

MEDICAL MANAGEMENT OF SCD

Improved therapy has dramatically changed the prognosis of SCD. Once a fatal pediatric illness, it is now a chronic adult disease characterized by poor quality of life with end-organ failure and acute intermittent medical emergencies. Identification of high-risk patients, preventative therapies, and optimal management of complications can minimize the morbidity of SCD and alter its progressive decline.

Annual screening with transcranial doppler enables selective chronic transfusions to be implemented that successfully prevent central nervous system (CNS) injury. Early detection of asthma, pulmonary hypertension, and hypoxia is important for improved outcomes [3,4]. Acute chest syndrome, the most common cause of mortality, can often be prevented or minimized. Renal failure may be prevented by early treatment of proteinuria with ACE inhibitors. Avascular necrosis of the hip may affect up to 40% of patients; early detection and treatment with decompression coring procedures and aggressive physical therapy may prevent or slow progression to major surgery. Priapism, a morbid, often underreported complication requiring surgery, may be prevented by alpha/beta adrenergic agonists, gonado-

tropin releasing hormone, and phosphodiesterase inhibitors. Pain management in SCD remains inadequate, but may be improved by the day hospital model, avoidance of hyperanalgesia syndrome, and effective use of opioids. Nutritional deficiencies are common and correctable, and can improve bone density and general health.

Transfusion therapy has seen major advances, and is used in over 90% of patients by adulthood. Phenotypically matched units, access to cytopheresis and availability of oral iron chelators have resulted in lower alloimmunization rates and decreased iron overload. Hydroxyurea has globally altered the morbidity of SCD. New hemoglobin F modulating drugs such as decitabine and short-chain fatty acids may further improve outcomes. Emerging therapies resulting from an expanded understanding of the pathophysiology of SCD are promising, and have entered clinical trials; these include statins, pan-selectin inhibitors, anticoagulants, glutamine, and nitric oxide modifying therapies. Although gene therapy has entered Phase I trials, stem cell transplant remains the only available cure for this disease.

STEM CELL TRANSPLANTATION FOR SCD

HSCT is currently the only curative therapy for SCD. Children with HLA matched sibling donors (normal or with sickle trait) have excellent outcomes with HSCT, with 85% disease free survival (DFS) and 97% overall survival (OS) [5-7]. The majority of SCD transplants reported worldwide to date include matched sibling donor transplants in children. Unrelated donor transplantation has met with less success in SCD as has HSCT in older recipients, including transplantation in young adulthood. Although the "ideal" time to transplant is at a young age, prior to the development of irreversible vasculopathy, there are several reasons that have precluded using HSCT as curative therapy and an accepted standard of care for SCD. This is true even when the clinical history predicts a severe disease course with early fatality or significant morbidity, as in the case of multiple overt strokes. Eleven percent of patients develop a stroke by 18 years of age, and 20% of this group continue with recurrent strokes despite transfusion therapy, resulting in 5% mortality in the second decade [8,9]. From the donor perspective, obstacles to HSCT include the rarity of availability of a HLA-matched sibling donor (<18%) and the lowered incidence of finding a suitably matched unrelated donor (MUD) or umbilical cord product in this minority population [10,11]. From the recipient perspective, transplant outcomes worsen with age and presumably advanced disease [12]. HSCT is best performed in childhood prior to established disease sequelae to optimize

outcomes. However, apart from overt stroke, the best way to predict which SCD patient would benefit early from HSCT prior to the development of major complications still remains a dilemma. Recent advances in conservative therapy have provided significant early benefit in many patients with SCD leaving a smaller number with clearly progressive disease in childhood. Concern for transplant-related complications such as conditioning-related organ dysfunction, treatment-related mortality (TRM), infection, graft-versus-host disease (GVHD), and graft rejection demand that HSCT be optimized to ensure the best possible outcomes with minimal mortality. This is also true for late complications of transplant such as gonadal failure, second malignancies, and neurodevelopmental issues, especially for those patients transplanted at a young age. Advances in the field of HSCT related to high-resolution HLA typing and choice of stem cell sources, less toxic conditioning strategies, newer immune suppression medications, facilitated immune reconstitution, and improved supportive care have helped to make HSCT a more viable option in nonmalignant disorders including SCD [13-17]. The balance between the acceptability of HSCT as a cure for SCD and complications associated with the HSCT versus from the primary disease remains a question of ethical importance and an educational journey for families caring for patients with SCD [18,19].

TRAJECTORY OF DISEASE PROGRESSION IN ADULTHOOD: THE CASE FOR NOVEL INTERVENTIONS

The outcomes of children with SCD have improved dramatically as described earlier because of better comprehensive care, pneumococcal prophylaxis, in addition to transfusion therapy and hydroxyurea. Currently, >90% of newborns with SCD can expect to live beyond their 20th birthday [20]. However, this optimistic outlook begins to unravel soon after. There is a rapid progression in organ damage and morbidity with a mortality rate of 5.8% to 20% in the first 10 years after transition to adult care [21,22]. Disease progression is marked by multiple organ toxicities. Starting in late adolescence, there is an increasing incidence of pulmonary hypertension in patients with SCD, with 40% of patients affected by this condition by 40 years of age [23]. This complication is associated with a 2-year mortality of 50%. Pulmonary function tests are abnormal in 90% of adults and lung disease is predominantly (74%) restrictive in nature [24]. Renal insufficiency is present in 21% and albuminuria in 68% of adults [25]. Bone mineral density is reduced in 74% adults [26]. By the fifth decade of life, 50% of the patients have irreversible organ damage of at least 1 organ [20]. These complications are the cause for premature mortality, with a mean

age of death at merely 38 years [27]. In addition, there is substantial disease-related morbidity and poor health-related quality of life resulting in impaired societal functioning. As a result, fewer than 20% of patients with SCD gain and retain employment [28]. Because children with SCD have excellent outcomes with appropriate intervention and comprehensive care, interventions such as HSCT remain limited in consideration/application largely because of the associated risks described previously. However, the risk of interventions such as HSCT, chronic transfusion therapy, and hydroxyurea has to be balanced between excellent early disease outcomes and disease course in the later years. An emerging understanding of the severity and progression of disease in adults can alter the risk versus benefit paradigm of curative interventions such as HSCT. There is increasing interest among adult SCD patients and hematologists in clinical trials of HSCT and other treatment options that may provide benefit to the later complications of the disease. For HSCT, TRM, GVHD, and late sequelae such as infertility are still major barriers to adequately exploring this intervention. However, progress in transplant research designed to improve outcomes may make HSCT a viable intervention in patients with severe SCD.

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