Published in final edited form as:
Biol Blood Marrow Transplant. 2010 January ; 16(1 Suppl): S64–S67. doi:10.1016/j.bbmt.2009.10.001.

SEVERE SICKLE CELL DISEASE – PATHOPHYSIOLOGY AND THERAPY

George Buchanan, MD[1], **Elliott Vichinsky, MD**[2], **Lakshmanan Krishnamurti, MD**[3], and **Shalini Shenoy**[4]

[1]University of Texas Southwestern at Dallas, TX

[2]Children's Hospital and Research Center at Oakland, CA

[3]Children's Hospital of Pittsburgh, University of Pittsburgh, PA

[4]Washington University School of Medicine and St. Louis Children's Hospital, MO

Background

Over 70,000 people live with sickle cell disease in the United States and multitudes world wide. About 2,000 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 sickle cell disease. However, the medical and psychosocial cost of supporting patients with this chronic illness is enormous and spans a lifetime. Hematopoietic stem cell transplant (HSCT) can abrogate sickle cell disease 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 database due to 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 sickle cell disease 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.

Natural History of Acute and Chronic Organ Damage in Sickle Cell Disease

Patients with sickle cell disease 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 sickle cell disease as a severe clinical entity include vaso-occlusive or pain crisis, acute chest syndrome, stroke, and priapism.

Correspondence: ShaliniShenoy, MD, Box 8116, SLCH, 1 Children's Place, St. Louis, MO 63110, Phone: 314-454-6018, Fax: 314-454-2780, shenoy@wustl.edu.

Because of the clinical heterogeneity of sickle cell disease, 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 reported for the Cooperative Study of Sickle Cell Disease that several clinical and laboratory markers during the first two years of life predict a severe clinical course (characterized by early death or recurrent pain crisis or chest syndrome) during the ensuing 10 years [1]. However, a similar study of the Dallas Newborn Cohort reported by Quinn and colleagues in 2008 refuted this finding [2]. Thus, at present, there are no reliably validated measures in the young child which can predict long term outcomes.

Although the acute events described above 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 mid-adulthood, 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 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 sickle cell disease. Many such patients seem to do well during childhood, but are vulnerable to developing irreversible organ damage due to 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 which can truly prevent or lesson 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 three 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. Since each of the three 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 Sickle Cell Disease

Improved therapy has dramatically changed the prognosis of sickle cell disease. 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 sickle cell disease and alter its progressive decline.

Annual screening with transcranial doppler enables selective chronic transfusions to be implemented that successfully prevent 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 under-reported complication requiring surgery, may be prevented by alpha/beta adrenergic agonists, gonadotropin releasing hormone, and phosphodiesterase

inhibitors. Pain management in sickle cell disease 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 sickle cell disease. 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 sickle cell disease are promising and have entered clinical trials; these include statins, pan-selectin inhibitors, anti-coagulants, glutamine, and nitric oxide modifying therapies. While gene therapy has entered Phase I trials, stem cell transplant remains the only available cure for this disease.

Stem Cell Transplantation for Sickle Cell Disease

HSCT is currently the only curative therapy for sickle cell disease (SCD). Children with HLA matched sibling donors (normal or with sickle trait) have excellent outcomes with HSCT with 85% disease free survival and 97% overall survival [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. Though 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 (less than 18%) and the lowered incidence of finding a suitably matched unrelated donor 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, transplant related mortality, infection, graft versus host disease 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 non-malignant 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 sickle cell disease have improved dramatically as described above due to better comprehensive care, pneumococcal prophylaxis, in addition to transfusion therapy and hydroxyurea. Currently, greater than 90% of newborns with sickle cell disease 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 5.8–20% 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 by 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 one organ [20]. These complications are the cause for premature mortality with a mean age of death 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 sickle cell disease gain and retain employment[28]. Since children with sickle cell disease have excellent outcomes with appropriate intervention and comprehensive care, interventions such as hematopoietic stem cell transplant remain limited in consideration/application largely due to the associated risks described above. 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 sickle cell disease 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, transplant-related mortality, 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 sickle cell disease.

Acknowledgments

EV is supported by Grant Number 2 R01 DK057778-06A1 (PIs John Brooke; Elliott P Vichinsky): Modulation of Iron Deposition in SCD and Other Hemoglobinopathies. SS is supported by Grant Number 5 U01 HL069254-07 (PI): Unrelated donor stem cell transplantation for children with severe sickle cell disease and the Children's Health Foundation, St. Louis Children's Hospital, MO.

Bibliography

1. Miller S, et al. Prediction of adverse outcomes in children with sickle cell disease. N Eng J Med 2000;342(2):83–89.
2. Quinn C, et al. Prediction of adverse outcomes in children with sickle cell anemia: a study of the Dallas Newbron Cohort. Blood 2008;111(2):544–548. [PubMed: 17909076]
3. Boyd J, et al. Asthma is associated with acute chest syndrome and pain in children with sickle cell anemia. Blood 2006;108(9):2923–2927. [PubMed: 16690969]
4. Gladwin M, Vichinsky E. Pulmonary complications of sickle cell disease. N Engl J Med 2008;359:2254–2265. [PubMed: 19020327]
5. Panepinto J, et al. Matched-related transplantation for sickle cell disease: report from the Center for International Blood and Transplant Research. Br J Haematology 2007;137:479–485.

6. Walters M, et al. Stable mixed hematopoietic chimerism after bone marrow transplantation for sickle cell anemia. Biol Blood Marrow Transplant 2001;7(12):665–673. [PubMed: 11787529]
7. Locatelli F, et al. Related umbilical cord blood transplantation in patients with thalassemia and sickle cell disease. Blood 2003;101(6):2137–2143. [PubMed: 12424197]
8. Ohene-Frempong K, Weiner S, Sleeper L. Cerebrovascular accidents in sickle cell disease rates and risk factors. Blood 1998;91:288–294. [PubMed: 9414296]
9. Scothorn D, Price C, Schwartz D. Risk of recurrent stroke in children with sickle cell disease receiving blood transfusion therapy for at least five years after initial stroke. J Peds 2002;140:348–354.
10. Mentzer W, et al. Availability of related donors for bone marrow transplantation in sickle cell anemia. Am J Pediatr Hematol Oncol 1994;16(1):27–29. [PubMed: 8311169]
11. Krishnamurti L, et al. Availability of unrelated donors for hematopoietic stem cell transplantation for hemoglobinopathies. Bone Marrow Transplant 2003;31(7):547–550. [PubMed: 12692619]
12. Walters M, et al. Neurologic complications after allogeneic marrow transplantation for sickle cell anemia. Blood 1995;85(4):879–884. [PubMed: 7849310]
13. Walters M, et al. Sibling donor cord blood transplantation for thalassemia major: experience of the sibling donor cord blood program. Ann N Y Acad Sci 2005;1054:206–213. [PubMed: 16339667]
14. Shenoy S, et al. A novel reduced-intensity stem cell transplant regimen for nonmalignant disorders. Bone Marrow Transplant 2005;35(4):345–352. [PubMed: 15592491]
15. Krishnamurti L, et al. Stable long-term donor engraftment following reduced-intensity hematopoietic cell transplantation for sickle cell disease. Biol Blood Marrow Transplant 2008;14(11):1270–1278. [PubMed: 18940682]
16. Barker J, et al. Analysis of 608 umbilical cord blood (UCB) transplants: HLA-Match is a critical determinant of transplant related mortality (TRM) in the post-engraftment period even in the absence of acute graft versus host disease (aGVHD). Blood 2005;106(11) p. Abstract #303.
17. Eapen M, et al. Higher mortality after allogeneic peripheral blood transplantation compared with bone marrow in children and adolescents: the Histocompatibility and Alternate Stem Cell Source working Committee of the International Bone Marrow transplant Registry. J Clin Oncol 2004;22(24):4872–4880. [PubMed: 15520055]
18. Walters M, et al. Barriers to bone marrow transplantation for sickle cell anemia. Biol Blood and Marrow Transplant 1996;2(2):100–104. [PubMed: 9118298]
19. Kodish E, et al. Bone marrow transplantation for sickle cell disease. A study of parents' decisions. N Eng J Med 1991;325:1349–1353.
20. Powars DR, et al. Outcome of sickle cell anemia: a 4-decade observational study of 1056 patients. Medicine (Baltimore) 2005;84(6):363–376. [PubMed: 16267411]
21. Aduloju S, Palmer S, Eckman J. Mortality in Sickle Cell Patient Transitioning from Pediatric to Adult Program: 10 Years Grady Comprehensive Sickle Cell Center Experience. Blood 2008;112(11) p. Abstract # 1426.
22. Ballas SK, Dampier C. Outcome of Transitioning Pediatric Patients with Sickle Cell Disease to Adult Programs. Blood 2004;104(11) p. Abstract 3743.
23. Gladwin MT, Vichinsky E. Pulmonary complications of sickle cell disease. N Engl J Med 2008;359(21):2254–2265. [PubMed: 19020327]
24. Klings ES, et al. Abnormal pulmonary function in adults with sickle cell anemia. Am J Respir Crit Care Med 2006;173(11):1264–1269. [PubMed: 16556694]
25. Guasch A, et al. Glomerular involvement in adults with sickle cell hemoglobinopathies: Prevalence and clinical correlates of progressive renal failure. J Am Soc Nephrol 2006;17(8):2228–2235. [PubMed: 16837635]
26. Miller RG, et al. High prevalence and correlates of low bone mineral density in young adults with sickle cell disease. Am J Hematol 2006;81(4):236–241. [PubMed: 16550513]
27. Strouse J, Haywood C, Lanzkron S. Predictors of In-Hospital Mortality and Charges in Sickle Cell Disease: Results from the California Discharge Databases 1998–2005. Blood 2007;110(11) p. Abstract #432.
28. McClish DK, et al. Health related quality of life in sickle cell patients: the PiSCES project. Health Qual Life Outcomes 2005;3:50. [PubMed: 16129027]