ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

Section Editor: Craig M. Kessler, MD

Sickle Cell Disease in Children

Winfred C. Wang, MD
Department of Hematology
St. Jude Children's Research Hospital
Memphis, Tennessee

H&O Could you provide some background on sickle cell disease?

WW In the United States, approximately 100,000 persons have sickle cell disease (SCD). The most common type is HbSS, which accounts for approximately 65% of the total cases. In African-Americans, the frequency of SCD is approximately 1 in 350–400 births.

Newborn screening is performed in all 50 states to identify infants with SCD. Those who are confirmed to have SCD are usually followed in sickle cell programs in major medical centers. Typically, these infants are first seen by 2–3 months of age, and then are followed throughout childhood.

The most characteristic complication of SCD is the acute pain event or pain crisis. Other common problems include acute chest syndrome, pulmonary hypertension, splenic sequestration, gallstones, priapism, leg ulcers, avascular necrosis of the hip, stroke, neuropsychologic dysfunction, and retinopathy. In the past, the leading cause of mortality was pneumococcal sepsis, due to the loss of splenic function. However, penicillin prophylaxis and pneumococcal vaccination have significantly reduced the incidence of sepsis in the past two decades. Recently published data from the Dallas Newborn Cohort have shown a reduction in childhood mortality to approximately 6% for HbSS/HbSβ^0-thalassemia and 2% for other types of SCD. Mortality now is infrequent until the late teens and early adulthood.

H&O How are patients with sickle cell disease currently treated?

WW Three treatments for SCD are generally considered. Hydroxyurea is the only agent approved by the US Food and Drug Administration and is indicated for adults with HbSS and a history of severe complications. Another treatment is chronic transfusion, which is used in patients with a history of stroke and which is 80–85% effective in preventing recurrent stroke. At present, however, in larger sickle cell centers, the most common indication for chronic transfusion is the prevention of primary stroke in a child at very high risk based on the transcranial Doppler ultrasound (TCD) finding of abnormally increased blood flow velocity in the major cerebral arteries. Chronic transfusion reduces the risk of stroke in these patients by 80–90%.

The third treatment approach is hematopoietic stem cell transplantation (HSCT). The use of this therapy has been limited in the United States in part because of the infrequent availability of an HLA-matched sibling donor source of the stem cells. This approach also has had limited acceptance among patients and families, in part because of its associated morbidity and a mortality of about 5%. A recent development has been the use of nonmyeloablative transplant conditioning regimens with reduced toxicity.

H&O Why are new treatments necessary for children with sickle cell disease?

WW Morbidity and mortality are major concerns in SCD, particularly in adulthood. The treatments that I have mentioned are all associated with limitations in terms of availability or toxicity. HSCT is associated with significant treatment-related morbidity and mortality. Chronic transfusion eventually results in iron overload, which now can be neutralized with oral iron chelation using deferasirox, which, however, is expensive and sometimes poorly tolerated. In addition, transfusions

are associated with allergic reactions; autoantibodies and alloantibodies; and, rarely, the transmission of infections such as hepatitis. The use of hydroxyurea has been limited by inadequate or incorrect information about its benefits and risks, and sometimes by cost (which is actually very low) or availability.

H&O What were the objectives of the Pediatric Hydroxyurea Phase III Clinical Trial?

WW My colleagues and I recently published the results of this study, referred to as the BABY HUG trial. We examined the use of hydroxyurea (20 mg/kg/day given as a liquid formulation) compared with a similar-appearing placebo in infants with sickle cell anemia unselected for severity, who were 9–18 months old at onset of treatment. In this double-blinded trial, which was conducted in 13 centers across the United States, 193 infants were randomized to receive either hydroxyurea or placebo.

The primary objective of this trial was to evaluate whether hydroxyurea prevented early organ toxicity seen in very young children with SCD. The primary endpoints were spleen function (qualitative interpretation of technetium sulfur colloid uptake on spleen scan) and renal function (glomerular filtration rate [GFR] using diethylenetriamine pentaacetic acid [DTPA] clearance). Other important endpoints of the trial were adverse events, particularly vaso-occlusive complications of SCD, toxicities from hydroxyurea, and hematologic effects.

H&O What were the study results?

WW Hydroxyurea was beneficial in reducing vaso-occlusive events, particularly pain and dactylitis. The frequency of pain was about half as much and dactylitis about a fifth as much in those receiving hydroxyurea compared with those on placebo. In addition, hydroxyurea reduced the frequency of acute chest syndrome, hospitalizations, and transfusions. There were no differences in the primary endpoints of spleen function and renal function, but hydroxyurea had beneficial effects on some secondary measures of organ function of the spleen, kidneys, and central nervous system, including slightly lower transcranial Doppler ultrasound velocities. No significant toxicity was associated with hydroxyurea other than mild to moderate neutropenia, which was expected. Neutropenia resulted in a modest decrease in dose for 9 patients in the hydroxyurea arm (and 5 on placebo). Hydroxyurea was associated with improved hematologic values, including higher hemoglobin and fetal hemoglobin levels, and lower white blood cell and reticulocyte counts—all of which have been associated with beneficial effects on the clinical course of patients with SCD.

The patients in the BABY HUG study were not selected for severity, and yet those in the hydroxyurea arm received significant benefit. Based on hydroxyurea's ability to reduce vaso-occlusive events as well as its limited toxicity, the main conclusions from the BABY HUG trial were that hydroxyurea should be considered for all sickle cell patients, regardless of age, and that it should not be limited only to patients with severe complications.

In an editorial that accompanied publication of the study in the *Lancet*, Weatherall suggested that hydroxyurea could be a very useful drug in sub-Saharan Africa, where the number of persons affected by SCD is approximately 100 times the number in North America or Europe. Hydroxyurea would be particularly suited to this population because it has limited toxicity and is relatively inexpensive.

H&O What is the presumed mechanism of action of hydroxyurea in these patients?

WW Hydroxyurea increases fetal hemoglobin as observed in the BABY HUG study. Increased fetal hemoglobin has been associated with reduction of pain, acute chest syndrome, and other complications of SCD. In addition, hydroxyurea is known to decrease adherence of sickle red cells to vascular endothelium, and to improve nitric oxide metabolism, promoting vasodilatation. Finally, hydroxyurea improves blood counts, causing increased hemoglobin levels and reduced white blood cell counts, both of which are associated with clinical benefit in SCD.

H&O What are some other areas of research in children with sickle cell disease?

WW Several other drugs are being studied as possible alternatives or adjuncts to hydroxyurea. Decitabine (Dacogen, Eisai) has been shown in small trials to benefit patients who have been refractory to hydroxyurea. When combined with hydroxyurea, drugs that work by different mechanisms of action might yield increased benefit with no increase in toxicity, if they are chosen appropriately. Combination pharmacotherapy has been utilized successfully for decades in the treatment of many other conditions, such as cancer, HIV, and tuberculosis.

Newer approaches to HSCT have explored nonmyeloablative conditioning regimens as well as the use of alternative donors (other than matched siblings). Gene therapy approaches in which genetic programs for normal beta or gamma globin production are inserted into hema-

topoietic stem cells are now just beginning to be tested in human subjects.

Suggested Readings

Wang WC, Ware RE, Miller ST, et al. Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). *Lancet*. 2011;377:1663-1672.

Weatherall DJ. Hydroxycarbamide for sickle-cell anaemia in infancy. *Lancet*. 2011;377:1628-1630.

Platt OS, Thorington BD, Brambilla DJ, et al. Pain in sickle cell disease. Rates and risk factors. *N Engl J Med*. 1991;325:11-16.

Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. *N Engl J Med*. 1994;330:1639-1644.

Ware RE. How I use hydroxyurea to treat young patients with sickle cell anemia. *Blood*. 2010;115:5300-5311.

Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. *N Engl J Med*. 1995;332:1317-1322.

Quinn CT, Rogers ZR, McCavit TL, Buchanan GR. Improved survival of children and adolescents with sickle cell disease. *Blood*. 2010;115:3447-3452.