



Longer Life, Better Life

Clinical research is fueling an unusual consortium's focus on sickle cell disease, including helping young patients transition to adulthood.

Each year, one in 400 African-American children is born with sickle cell disease (SCD). As recently as 30 years ago, the average life expectancy for a child with SCD was 15 years, and as many as 20 percent of children with the disease died before age 3. A genetic disorder that affects the hemoglobin of the red blood cells, SCD results in anemia and causes the cells to deform into a sickle shape that has difficulty moving through the small blood vessels. Subsequent interruption of the blood supply can harm tissue, resulting in severe pain, strokes, a pneumonialike complication called acute chest syndrome, and kidney and liver damage. Resulting damage to the spleen puts patients at risk for life-threatening infections.

In less than three decades, however, the life expectancy for children born with SCD has more than tripled, complications have become less prevalent and quality of life has improved significantly. Earlier detection coupled with comprehensive care and the development of treatment protocols and better treatment options have made these advances possible.

Basic treatment for SCD varies somewhat, depending on the severity of the disease and the particular complications, explained Peter Lane, M.D., Director of the Sickle Cell Program at the Aflac Cancer Center and Blood Disorders Service of Children's Healthcare of Atlanta, and author of SCD treatment guidelines for both the American Academy of Pediatrics and National Institutes of Health (NIH). Generally, comprehensive care includes:

- Universal newborn screening for SCD;
- Extensive education of patients and families about prevention, early recognition and appropriate treatment of acute complications;
- Prophylactic penicillin and immunizations to prevent bacteremia/ septicemia, including *Streptococcus pneumoniae* (the most common cause of death in children with SCD), as well as prompt evaluation and treatment with parenteral antibiotics for all febrile illness;
- Ongoing monitoring for early signs of chronic organ damage;
- Psychosocial assessments and services to optimize the patient's and family's adaptation to chronic illness;
- Genetic education and counseling;
- IV hydration and opioid analgesics, usually with nonsteroidal anti-inflammatory drugs (NSAIDs), for severe acute pain episodes;
- IV fluids, analgesics, antibiotics, oxygen and transfusions for acute chest syndrome;
- Exchange transfusion for ischemic stroke; and
- Hydroxyurea (Hydrea, Droxia) for patients with frequent pain events or recurrent episodes of acute chest syndrome.

Many complications of the disease may be treated or prevented with blood transfusions. However, because repeated transfusions cause iron overload, chelation therapy is necessary to prevent iron-induced damage to heart, liver and endocrine organs for any child undergoing frequent transfusions to treat SCD.

Clinical Research

Clinical research at the Aflac Cancer Center and Blood Disorders Service and Grady Health System has focused on bone-marrow transplantation (BMT) and new medications, as well as better ways to detect which patients are at greatest risk for severe complications.

STOPPING STROKES BEFORE THEY START: Patients participated in two stroke prevention trials in sickle cell anemia (STOP I and STOP II), randomized studies funded by the NIH (results published in 1998). The first study confirmed that it was possible to identify children at highest risk for strokes using transcranial Doppler (TCD) ultrasound, and found that

chest syndrome. Soon, it may also prove beneficial in preventing strokes.

Next year, Dr. Lane anticipates participating in a multicenter study that may expand the role of hydroxyurea by testing its efficacy in preventing stroke. The drug may provide an easier alternative to blood transfusions for some patients, and it is hoped that it will lessen the transfusion-related risk of organ damage from iron overload.

Basic Research: Understanding SCD

Even as clinical scientists are making strides in improving the lives and lifespans of children with SCD, basic researchers are learning more about the underlying mechanisms of the disease. Working with mice genetically engineered to have SCD, scientists are uncovering clues about mechanisms that contribute to many of the complications of the disease.

“One key area of research involves investigation into the role

Once bound to hemoglobin, nitric oxide cannot reach the endothelium to cause vasodilation.

For these reasons, scientists believe drugs that restore the balance of nitric oxide may one day be useful in treating SCD. Other potential therapies may include biologic agents that manipulate adhesion molecules, and combinations of antioxidants and anti-inflammatories, which already are being tested and which seem to have a positive effect on the mouse model of the disease.

Bone Marrow Transplants Offer Cure

While researchers are finding many ways to improve and extend life for children with SCD, there is only one way to cure the disease — through bone marrow transplantation (BMT).

The potential benefit is great, but the risks are high. Destroying the existing immune system prior to transplantation puts the child at risk for life-threatening infection. In addition, the donor marrow can react against the host, resulting in graft-versus-host disease (GVHD).

But with scrupulous attention to candidate selection, technical expertise and years of experience on the part of the multidisciplinary team, successful bone marrow transplants for SCD are the rule rather than the exception. Worldwide, the survival rate for matched sibling BMTs for SCD is 90 percent to 95 percent, and disease-free survival tends toward 85 percent. At the Aflac Cancer Center and Blood Disorders Service — the most active bone marrow transplant program for SCD in North America — both the survival and disease-free survival rates have been 100 percent, said Ann Haight, M.D., attending physician in the BMT program at Children’s.

Since the early 1990s, when the program at Children’s took part in the first clinical trial of bone marrow transplants for SCD, the center has performed 22 such transplants. Twenty have used bone marrow from matched sibling donors; the other two (including the first procedure of its type for sickle cell in the United States) used umbilical cord and placental stem cells. The Aflac Cancer Center and Blood Disorders Service has not had any significant GVHD in its matched-sibling sickle cell program, Dr. Haight said.

Because of the serious risks associated with bone marrow transplants, the procedure is reserved for children with severe disease and complications that have the potential to shorten their lives, said Dr. Haight. The three main complications that qualify a child for BMT are strokes, recurrent acute chest syndrome and frequent pain crises.

For other children, the risks of transplant may outweigh the benefits. Among those who meet these severity criteria, relatively few can be matched with an appropriate bone marrow donor. Research is addressing both of these issues by looking for ways to improve transplant safety and make the procedure available to more children who don’t have HLA-matched siblings.

To reduce the risk of GVHD, scientists have been studying the use of co-stimulation blockade in mice with SCD. This approach uses antibodies or fusion proteins to stop T cells from reacting. The result is a more targeted suppression of the immune system than that achieved with traditional immunosuppressives such as cyclosporine, Dr. Archer said.

Partners for Care

As life expectancies for patients with SCD have increased, physicians face a new challenge: how to ensure ongoing quality of care for adults living with the disease.

In Atlanta, the Aflac Cancer Center and Blood Disorders Service, which offers one of the largest SCD programs in the country, has joined with Grady Health System, Emory University School of Medicine and Morehouse School of Medicine to form the Atlanta Sickle Cell Provider Consortium. The largest such collaboration in the world, the consortium enables providers to coordinate care to more than 2,500 SCD patients of all ages. “Here in Atlanta, our pediatric and adolescent patients can transition into an excellent program for adult sickle cell patients. In many

cities, when kids get to be 18 or 21, there’s nowhere to send them,” said Dr. Lane.

The consortium provides more than patient care. In addition, it provides education for healthcare providers, medical students, residents and fellows and, in conjunction with community-based organizations such as the Sickle Cell Foundation of Georgia, contributes to sickle cell advocacy efforts. Consortium members also conduct both basic and clinical research, which means that young patients have the opportunity to be among the first to participate in clinical trials for new treatments.

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— Peter Lane, M.D.

chronic blood transfusions prevented strokes in such high-risk patients. The second study, recently completed, showed that blood transfusions need to be continued beyond 30 months in order to reduce the rate of stroke in children at high risk for this complication. Today, the program makes TCD screening tests routinely available to its young patients.

NEW THERAPY FOR IRON OVERLOAD: At present, the Aflac Cancer Center and Blood Disorders Service is involved in a number of new studies designed to evaluate a new oral iron chelator, ICL 670, which may take the sting and inconvenience out of preventing organ-damaging iron overload in children undergoing frequent blood transfusions.

Currently, the only way to rid a child’s body of excess iron is with deferoxamine (Desferal) which must be administered daily through a 10- to 12-hour subcutaneous injection. While the medication works well, many patients have trouble complying with the uncomfortable daily regimen. “The challenge of adhering to that medication, night after night, results in patients who aren’t appropriately chelated and who, as a result, experience damage to their organs,” said Dr. Lane.

ICL 670, which is taken by mouth once daily, is showing promise in clinical trials. A successful phase III study of the drug for thalassemia was recently completed. Phase II studies taking place now are further testing the safety and tolerability in patients with SCD.

EXPANDING THE ROLES OF EXISTING DRUGS: Many patients benefit from hydroxyurea, an antimetabolite used to treat some leukemias. In patients with SCD, hydroxyurea is effective in reducing the frequency of pain crises and acute

of oxidative stress in sickle cell,” said David Archer, Ph.D., SCD researcher and Assistant Professor of Pediatrics at Emory University School of Medicine. “Because all red blood cells in sickle cell patients have sickle hemoglobin, they all have the potential to sickle and cause complications. But it’s only under certain circumstances, when they pass through the tissues or lungs and give up their oxygen, that the hemoglobin in the cell starts polymerizing and the cells sickle and block blood flow.

“Normally, as cells pass through tissue, the length of time a cell stays in that deoxygenated state isn’t quite long enough for it to become sickled,” he added. “So now people are doing a lot of work to see what things slow the cells down, and — once they slow down — why they stay in the area long enough to become sickled and obstruct blood flow.

“The answer to the ‘what’ and ‘why’ of the disease process is probably multifactorial,” said Dr. Archer, who noted that SCD is no longer considered a disease just of blood cells, but also of blood vessels. Not surprisingly, he added, scientists are learning that SCD has an inflammatory component. “The endothelial cells in sickle mice are inflamed. They are activated so that they express more adhesion molecules on their surfaces. That makes the lining of blood vessels stickier,” Dr. Archer said. At the same time, sickled red cells are also stickier, further increasing the risk of blockage.

Although scientists don’t know the exact mechanism by which the endothelium becomes inflamed, Dr. Archer and others suspect that nitric oxide is “one of the big players.” One likely problem in SCD is that nitric oxide binds to the free hemoglobin produced when red blood cells die prematurely.

While most children with SCD will never require a bone marrow transplant, ongoing research efforts promise to one day make them more readily available — and safer — for those who do.

Dr. Haight recounted the story of a former transplant patient who was recently accepted into medical school. “They don’t have their pain crises any more, they don’t have any more strokes. They have hemoglobins of 13 and 14, instead of 7 and 8. They’re doing very well and they’re a joy to take care of.”

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