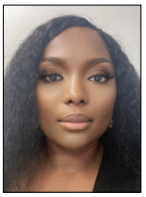
ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

Section Editor: Craig M. Kessler, MD

Treatment of Less-Common Complications of Sickle Cell Disease



Ugochi O. Ogu, MD
Associate Professor of Medicine
University of Tennessee Health Science Center
Medical Director
Diggs-Kraus Comprehensive Sickle Cell Center
Memphis, Tennessee

H&O What are the most common complications of sickle cell disease?

UO Sickle cell disease is associated with several complications, both acute and chronic. The most common complication by far is vaso-occlusive crisis, also called pain crisis, in which the occlusion of blood vessels by the sickled cells leads to severe pain. Vaso-occlusive crisis is the hallmark of sickle cell disease and is the most common reason patients seek medical attention. Another common complication is acute chest syndrome, which is the leading cause of mortality in sickle cell disease. Other common complications are acute anemia, infections, gallstones, retinopathy, and pulmonary hypertension.

H&O What is the general approach to treatment?

UO We use several modalities and drug regimens to treat patients with sickle cell disease. An important modality is blood transfusions, which can be used to both prevent and treat complications. Another important part of treating people with sickle cell disease is pain management, which may include both opioid and non-opioid regimens.

We also have 4 US Food and Drug Administration (FDA)-approved medications for sickle cell disease: hydroxyurea, L-glutamine (Endari, Emmaus Medical), crizanlizumab (Adakveo, Novartis), and voxelotor (Oxbryta, Global Blood Therapeutics/Pfizer). Hydroxyurea, which received FDA approval in 1998, was the first drug approved for sickle cell disease. This was followed much later by the approval of L-glutamine in 2017 and the approval of crizanlizumab and voxelotor in 2019.

Hydroxyurea gained approval based on the results of the MSH study, a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of hydroxyurea in 299 patients with sickle cell anemia and at least 3 vaso-occlusive crises in the prior year.[1] Patients were randomly assigned to hydroxyurea or placebo. After a mean follow-up of 21 months, patients taking hydroxyurea showed decreased rates of vaso-occlusive crisis, a longer time to first vaso-occlusive crisis, decreased rates of acute chest syndrome, and the need for fewer transfusions.

L-glutamine was approved based on the results of a phase 3, multicenter, randomized, double-blind, placebo-controlled study that enrolled 230 patients with hemoglobin SS or sickle β0-thalassemia and at least 2 vaso-occlusive crises during the previous year.[2] After 48 weeks, the patients in the L-glutamine group had significantly fewer vaso-occlusive crises and fewer hospitalizations compared with those in the placebo group.

The approval of crizanlizumab was based on the results of the phase 2 SUSTAIN study.[3] This randomized, double-blinded, placebo-controlled study enrolled 198 patients with sickle cell disease, who were randomly assigned to high-dose crizanlizumab, low-dose crizanlizumab, or placebo. Patients who received high-dose crizanlizumab had decreased rates of vaso-occlusive crisis, and a longer time to first and second crises compared with those who received the placebo.

Voxelotor was approved based on the results of the

phase 3 HOPE study.[4] This randomized, double-blinded study enrolled 274 patients with sickle cell disease and randomly assigned them to voxelotor at 1500 mg, voxelotor at 900 mg, or placebo. People in the higher-dose voxelotor group were significantly more likely to experience a hemoglobin response, defined as an increase of at least 1 g/dL in their hemoglobin at baseline to that at 24 weeks, compared with those who received a placebo.

The only established cure we have for sickle cell disease is stem cell transplant, which was discovered in the 1980s to be a cure for sickle cell disease. Gene therapy also represents a potential cure and is currently undergoing clinical trials. In addition, numerous drugs for sickle cell disease are in various stages of clinical trials. We are excited to see the results of these trials and expand the list of medications available for patients with sickle cell disease.

H&O What are the less-common complications of sickle cell disease?

UO The less-common complications of sickle cell disease include avascular necrosis, leg ulcers, stroke, priapism, splenic sequestration crisis, and multisystem organ failure.[5]

H&O What measures are used to manage each of these less-common complications?

UO Management of avascular necrosis, which most often affects the head of the femur, is usually conservative.[6] Pain management and physical therapy are the standard treatments for early-stage avascular necrosis. Surgery to replace the hip joint is often necessary if avascular necrosis progresses to an advanced stage, although procedures such as core decompression of the bone, with or without stem cell injection, are sometimes attempted to delay the need for a joint replacement.

Leg ulcers associated with sickle cell disease are most frequent around the medial and lateral malleoli.[7] These open wounds can last for several years, causing significant pain and distress. Some patients may experience an odor from the drainage, causing further social distress. Successful management of these ulcers needs to be multidisciplinary, with the hematologist focusing on getting the sickle cell disease under control and the wound care specialist handling wound debridement, dressing changes, and infection control.

Sickle cell disease can lead to ischemic stroke through vaso-occlusion of the blood vessels in the brain.[8] When a patient with sickle cell disease has had a stroke, we provide emergency red cell exchange-transfusion, followed by chronic blood transfusions to decrease the percentage of the abnormal hemoglobin S in the blood and reduce the risk of another stroke. Children and adolescents aged 2 to 16 years who have the hemoglobin SS or sickle β0-thalassemia genotype of sickle cell disease should have regular transcranial Doppler ultrasonography to evaluate the velocity of blood flow in the intracranial blood vessels. Patients who have abnormal blood flow should be started on chronic blood transfusions, which have been shown to significantly decrease the risk of a first stroke.

I believe that we will eventually see effective combination therapies for sickle cell disease, much like what we have for conditions such as HIV and diabetes.

Priapism refers to an unwanted, persistent, and painful erection that usually does not occur in response to sexual arousal.[9] Conservative measures can be used to try to improve the flow of blood from the penis, such as light exercises, warm showers, hydration, and the use of pseudoephedrine. Patients also need to have their pain addressed. An episode of priapism that lasts for 4 hours or longer is considered a urologic emergency, and the patient needs to go to the emergency department. Emergency care for priapism usually requires aspiration of the trapped blood, followed by irrigation with saline and sometimes an alpha agonist to further improve the penile blood flow. Repeated episodes of priapism can lead to fibrosis and erectile dysfunction, so we take this complication very seriously.

Splenic sequestration crisis refers to a pooling of the red blood cells and/or platelets in the spleen of patients with sickle cell disease that leads to a drop in hemoglobin. Patients generally present with pain in the upper left quadrant of the abdomen. The diagnosis is confirmed when acute spleen enlargement is accompanied by a decrease in the hemoglobin level of 2 g/dL or more from baseline. Splenic sequestration crisis is generally seen in children, as the spleen tends to shrivel away over time in sickle cell disease, leaving most adult patients without a functioning spleen. To ensure that the patient's tissues and organs get enough blood, we treat patients with splenic

sequestration crisis with a red blood cell transfusion.

Multisystem organ failure is defined as acute decompensation of at least 2 out of the 3 following organs: the lungs, kidneys, and liver. It is treated with an urgent red-cell exchange transfusion. Patients may also need supportive care with supplemental oxygen, mechanical ventilation, or renal dialysis.

H&O What changes do you see in the future for the management of sickle cell disease?

UO Research and funding for sickle cell disease were once lacking, but we have seen a great deal of improvement. Still, a lot more needs to be done. I believe we will eventually see effective combination therapies for sickle cell disease, much like what we have for conditions such as HIV and diabetes. Regarding some of the less-common sickle cell complications, we are expecting to see results of the phase 2 SPARTAN study of crizanlizumab for priapism in sickle cell disease (NCT03938454), as well as results from a phase 2 study looking at a topical cream containing sodium nitrite as a treatment for leg ulcers in sickle cell disease (NCT02863068). I am very hopeful for the future and expect to be able to help patients with sickle cell disease lead better, healthier lives.

Disclosures

Dr Ogu has served as a consultant for Vertex Pharmaceuticals and Novo Nordisk, and is on the speakers bureau for Global Blood Therapeutics/Pfizer and Emmaus.

References

1. Charache S, Terrin ML, Moore RD, et al; Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. *N Engl J Med*. 1995;332(20):1317-1322.

2. Niihara Y, Miller ST, Kanter J, et al; Investigators of the Phase 3 Trial of L-Glutamine in Sickle Cell Disease. A phase 3 trial of L-glutamine in sickle cell disease. *N Engl J Med*. 2018;379(3):226-235.

3. Ataga KI, Kutlar A, Kanter J, et al. Crizanlizumab for the prevention of pain crises in sickle cell disease. *N Engl J Med*. 2017;376(5):429-439.

4. Vichinsky E, Hoppe CC, Ataga KI, et al; HOPE Trial Investigators. A phase 3 randomized trial of voxelotor in sickle cell disease. *N Engl J Med*. 2019;381(6):509-519.

5. Ogu UO, Badamosi NU, Camacho PE, Freire AX, Adams-Graves P. Management of sickle cell disease complications beyond acute chest syndrome. *J Blood Med*. 2021;12:101-114.

6. Martí-Carvajal AJ, Solà I, Agreda-Pérez LH. Treatment for avascular necrosis of bone in people with sickle cell disease. *Cochrane Database Syst Rev*. 2016;(8):CD004344.

7. Minniti CP, Kato GJ. Critical reviews: how we treat sickle cell patients with leg ulcers. *Am J Hematol*. 2016;91(1):22-30.

8. Kassim AA, Galadanci NA, Pruthi S, DeBaun MR. How I treat and manage strokes in sickle cell disease. *Blood*. 2015;125(22):3401-3410.

9. Anele UA, Le BV, Resar LMS, Burnett AL. How I treat priapism. *Blood*. 2015;125(23):3551-3558.