

HemOnc today

CLINICAL NEWS IN ONCOLOGY AND HEMATOLOGY

COVER STORY

Sickle cell disease poised for 'golden age of treatment' amid progress toward cure

As researchers work to expand curable approaches for sickle cell disease, new options for managing its acute and chronic complications appear within reach.

Sickle cell disease — the most common inherited blood disorder in the United States — impacts millions of people around the world.

Since 1996, hydroxyurea had been the only approved therapy for sickle cell disease. That changed in 2017 with the approval of L-glutamine oral powder (Endari, Emmaus Medical) to reduce acute complications among adults and children.

Last year, the FDA expanded the approval of hydroxyurea to include use among children. Additional novel therapeutic agents in the pipeline, such as crizanlizumab (SEG101, Novartis), also are showing great promise, and investigations into

transplant and gene therapy are expanding options for potential cure.

"For a long time, we haven't had much to offer to our patients aside from opioid therapy, which really isn't satisfying to anyone," **Julie Kanter, MD**,

associate professor of hematology/oncology and director of the adult sickle cell clinic at The University of Alabama at Birmingham School of Medicine, and a *HemOnc Today* Next Gen Innovator, said in an interview. "Being able to offer them something that may not only make them feel better but might potentially alleviate some of their comorbidities would be absolutely huge."

HemOnc Today spoke with hematologists and sickle cell disease researchers about long-standing and new approaches to manage sickle cell disease-related pain, research aimed at curing this debili-

"It is my belief that the field will continue to evolve in some form of cell and or gene therapy that will be curative for this disease."

— MITCHELL S. CAIRO, MD

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Source: Mitchell S. Cairo, MD.

Sickle cell disease research over the last 6 decades has focused on symptom management rather than a cure, according to Mitchell S. Cairo, MD. "I'm more of a believer in curing the patient instead of treating the symptoms," he said. "I'm not against symptomatic treatment, but this is a disease that deserves to be cured."

COVER STORY

Growing attention to sickle cell disease paves way for new curative approaches, global access network

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tating illness, and the need for initiatives to improve access to care both in the U.S. and globally.

Dealing with pain

Patients with sickle cell disease face increased risk for blindness, leg ulcers, gallstones and priapism in men. The disease also is associated with life-threatening complications such as stroke, acute chest syndrome, pulmonary hypertension and long-term organ damage.

But, acute and chronic pain remains the most prominent and debilitating complication.

Hemoglobin S — the abnormal hemoglobin characteristic of sickle cell disease — causes damage to the membrane of red blood cells, making them sticky. As a result, the cells can stick to the inner lining of blood vessels, damaging the blood vessels and causing the cells to clump with white blood cells and platelets. Sickled red blood cells also are stiffer than normal red blood cells. These two characteristics can create a blockage of small blood vessels that prevents oxygen supply to tissues and causes injury, known as vaso-occlusive episodes, which can cause severe pain or crises.

This pain crisis can occur in any part of the body where blood flows and is the leading cause of hospitalizations for these patients. Vaso-occlusive crises (VOC) also can lead to life-threatening complications.

"Everyone is a little different when it comes to being able to tolerate pain," Ifeyinwa Osunkwo, MD, MPH, director of the Sickle Cell Disease Enterprise at Levine Cancer Institute at Atrium Health, clinical associate professor of medicine at The University of North Carolina at Chapel Hill, and a *HemOnc Today* Next Gen Innovator, told *HemOnc Today*. "We tell people that when the pain becomes unbearable and you've tried your home regimen, then you want to go to the emergency room. If you have chest pain, signs of a stroke, shortness of breath, a loss of vision, or priapism that last for more than a couple of hours ... you need to go to the emergency room."

Mental stress and fear of pain lead to decreases in microvascular blood flow, which may trigger episodes of VOC, according to data from Shah and colleagues.

In the analysis, patients with sickle cell anemia underwent a standard psychological test, during which researchers measured blood flow in small blood vessels through devices placed on their fingers. Researchers also told patients they would feel pain through a device on their arm, al-

though the device was not activated.

Investigators observed a 20% decrease in blood flow when patients experienced stress in anticipation of feeling pain.

The decreased blood flow can cause or worsen a crisis.

"Your emotional state triggers a physiological response that makes your blood vessels squeeze, reducing blood flow and perfusion into organs. If you also have abnormal sickle-shaped red blood cells that carry along less oxygen and can further damage the blood vessels and obstruct blood flow, you are more likely to experience VOC," Osunkwo said. "When patients are stressed out, upset or afraid, the body releases more cytokines and markers that trigger symptoms. Sometimes people forget that this is also a lifelong problem, that VOC can occur repeatedly as you age."

Symptom management in practice

Hydroxyurea — which mediates induction of red blood cell fetal hemoglobin and has been the mainstay of symptom control — is recommended for all children with sickle cell anemia beginning at 9 months of age. It safely reduces incidence of acute VOC and the need for transfusions and hospitalizations, potentially reducing overall mortality.

Jeremie H. Estep, MD, assistant member of the department of hematology at St. Jude Children's Research Hospital, and colleagues found that escalating the dose of hydroxyurea to increase average fetal hemoglobin levels above 20% reduced hospitalizations among children.

"The current theory about fetal hemoglobin is increasing the concentration within the red blood cells and inhibiting sickling and polymerization," Estep told *HemOnc Today*. "Some investigators say that any increase in fetal hemoglobin is beneficial and likely the higher it is, the more benefits there will be."

In the HUSTLE trial, researchers analyzed the long-term clinical effects of hydroxyurea escalated to a maximum tolerated dose among 230 children with sickle cell anemia.

"We're targeting a neutrophil count that's 2,000 to 4,000 x 10⁶/L with a maximum daily dose of either 35 mg/kg daily or 2,000 mg," Estep said. "On average, it takes 9 to 10 months to elevate the dose to the maximum tolerated dose."

With hydroxyurea at the maximum tolerated dose, the mean fetal hemoglobin reached 26.7%, compared with 9.7% at enrollment.

When fetal hemoglobin percentage values were 20% or lower, children had twice

the odds of hospitalization for any reason ($P < .0001$) — including vaso-occlusive pain ($P < .01$) and acute chest syndrome ($P < .01$) — and more than four times the odds of admission for fever ($P < .001$).

"The higher the fetal hemoglobin, the better the outcome. It takes 3 to 6 months to get any benefit from changing the dose, so if you increase the dose when you feel sick, you are not going to feel any different ... but there is the risk for more side effects," Osunkwo said. "Hydroxyurea is a prescription medication, it's not a home remedy."

Despite the widespread use of hydroxyurea, it is not without challenges. Long-term exposure may increase risk for certain toxicities and potentially reduce sperm counts.

"Long-term studies are looking at these risks," Estep said. "The current data suggest there is not an increased risk for secondary malignancies, but the jury is out on impact on long-term fertility effects."

Role of opioids

Opioids also are commonly used to treat acute and chronic sickle cell disease-related pain.

Throughout the ongoing opioid epidemic — which has called the use of opioids in any setting into question — the in-hospital mortality rate for patients with sickle cell disease has remained steady, according to research presented at ASH Annual Meeting and Exposition.

"The risk of dying when these patients are in a hospital is very high, but it has almost nothing to do with opioids," Kanter said. "The complications in the hospital are everything from acute chest syndrome to blood clots to secondary line infections to things that are highly avoidable, but not due to opioids."

Compared with the 350% increase in opioid prescription-related death rates in the U.S. between 1999 and 2013 in the general population, Akinboro and colleagues observed no significant increase in sickle cell disease mortality among hospitalized patients.

"Opioids are safe if you use them with the right patient at the right time for the right duration and the right reason," Osunkwo said. "People shouldn't be afraid of using opioids if you are using them the right way."

"The challenge is that people are afraid of getting addicted and doctors are afraid the patient is going to accidentally die, so prescriptions of opioids have become more emotional than objective," she added. "But, research shows that opioids help with relieving the misery and suffering as-

sociated with acute pain."

Properly prescribing opioids requires a change of mindset among both physicians and patients, Kanter said.

"It's wrong for physicians to think patients are only looking for opioids to get high, but at the same time we try to teach patients that opioids aren't for chronic pain," she said. "It has to be for their severe acute pain, not for worsening of chronic pain. That is a very hard lesson to learn."

Despite that the majority of the world's patients with sickle cell disease are in Africa, Kanter noted that opioid prescription rates are higher in the U.S.

"It was fascinating to see how much more opioids we prescribe here than everywhere else," she said. "Are we doing anybody a favor by doing that? We really need to be learning with these global communities and making sure we're all looking at how we best take care of affected individuals."

Sickle cell pipeline

In 2017, the armamentarium for sickle cell disease expanded beyond hydroxyurea with the approval of L-glutamine oral powder — the first FDA-approved treatment for sickle cell disease in over 2 decades.

"As we have a better understanding of sickle cell disease, it allows for more targeted approaches," Estep said. "[Also,] the push at a governmental level has really incentivized drug companies to look at orphan diseases."

A randomized trial showed patients treated with L-glutamine experienced fewer median hospital visits for sickle cell crises (3 vs. 4), fewer median hospitalizations for sickle cell pain (2 vs. 3), fewer median days in the hospital (6.5 days vs. 11 days) and fewer occurrences of acute chest syndrome (8.6% vs. 23.1%) than patients assigned placebo.

Other drugs still in the pipeline also are showing promise for managing symptoms.

In January, the FDA granted breakthrough therapy designation to crizanlizumab for the prevention of VOC among patients with sickle cell disease.

Crizanlizumab inhibits interactions between red blood cells, sickled red blood cells, endothelial cells, platelets and leukocytes, preventing these cells from being able to bind to P-selectin, a key driver of the vaso-occlusive process.

"We have focused so long on the red blood cell. Obviously, the red cell is at the heart of the problem, but so much of the pathology that we see is due to vasculopathy in terms of the poor outcomes," Kanter said. "The majority of the organ damage is due to

blood vessel damage, not so much to other causes. So, it's important that we look at therapies that are affecting the blood vessel.

"Because crizanlizumab is an anti-P selectin drug, it helps the sickled cell not stick to the inside of the endothelium," Kanter added. "That should help prevent pain crises, which was proven in the original trial. But, ideally, it should also decrease or stop ongoing scarring of the endothelium, which likely is what's causing so much of the organ pathology. It may be a drug that again not only decreases the rate of pain, but secondarily will decrease some of the bad outcomes."

The phase 2 SUSTAIN trial showed crizanlizumab reduced the median annual rate of VOC that led to health care visits by 45.3% compared with placebo (1.63 vs. 2.98; $P = .01$). A significantly higher percentage of crizanlizumab-treated patients did not experience any VOC during treatment (35.8% vs. 16.9%; $P = .01$).

"I'm very optimistic about crizanli-

zumab with the reported dramatic reduction in pain observed in adults with sickle cell disease," Estep said. "I suspect we will see it used in combination with hydroxyurea and as a single therapy in a subset of individuals that choose not to use hydroxyurea or who do not respond well to hydroxyurea therapy."

It is also important that the drug was tested in every sickle cell genotype, Osunkwo said.

"I'm most excited about crizanlizumab because it showed benefit in all genotypes, including SC and SB+ — they have not had any study focus on them and this is the first option that is truly evidence-based," she said.

The pipeline also includes voxelotor (GBT440, Global Blood Therapeutics) — a novel hemoglobin S polymerization inhibitor — which works by increasing hemoglobin's affinity for oxygen, thereby blocking sickling of red blood cells.

In Part A of the HOPE study, 154 pa-

tients aged 12 years and older with sickle cell disease were randomly assigned to receive 900 mg or 1,500 mg voxelotor or placebo.

Updated results presented at ASH in December showed that 65% of patients in the 1,500-mg voxelotor arm and 33% of patients in the 900-mg arm experienced an increase in hemoglobin of more than 1 g/dL at 24 weeks compared with 10% of patients in the placebo arm.

The drug's manufacturer announced it will submit a new drug application to the FDA for voxelotor through an accelerated approval pathway. Voxelotor also received fast track, orphan drug, rare pediatric disease and breakthrough therapy designations from the FDA.

The path toward cure

Although many therapies in the pipeline target symptoms of sickle cell disease, experts say research on transplants and gene editing has the potential to expand

the pool of patients who can be cured.

"I'm more of a believer in curing the patient instead of treating the symptoms," Mitchell S. Cairo, MD, chief of pediatric hematology, oncology and stem cell transplantation; director of the Children and Adolescent Cancer & Blood Diseases Center; associate chairman of the department of pediatrics; and professor of pediatrics, medicine, pathology, microbiology and immunology, and cell biology and anatomy at New York Medical College, told *HemOnc Today*. "Unfortunately, symptom management has been the focus for the last 60 years. I'm not against symptomatic treatment, but this is a disease that deserves to be cured."

The only known cure for patients with sickle cell disease is allogeneic hematopoietic stem cell transplantation from an HLA-matched sibling after myeloablative or reduced-toxicity conditioning. However, that cure is only available to 15% of pa-

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