

## CLINICAL THERAPEUTICS

# Hydroxyurea for the Treatment of Sickle Cell Anemia

Orah S. Platt, M.D.

*This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the author's clinical recommendations.*

**An 18-year-old woman with sickle cell anemia has had increasing symptoms, with painful crises and episodes of the acute chest syndrome. She was hospitalized three times in the past year. A hematologist recommends that hydroxyurea therapy be started.**

---

## THE CLINICAL PROBLEM

---

There are about 50,000 people in the United States who are homozygous for the sickle hemoglobin gene and thus have sickle cell anemia. Sickle cell anemia is primarily seen in persons of African heritage, about 1 in 14 of whom is an asymptomatic carrier (a heterozygote). One in 700 newborns of African heritage is affected.<sup>1</sup> Although it is the most severe of the common sickle cell diseases (which include hemoglobin SC disease and sickle  $\beta^0$ -thalassemia), patients with sickle cell anemia have a wide spectrum of clinical manifestations. All patients with this disorder have a chronic hemolytic anemia, but the rates of the most common acute vaso-occlusive events (acute painful crises and the acute chest syndrome) vary considerably.<sup>2,3</sup> Other common complications include stroke, chronic lung disease, avascular necrosis, and leg ulcers. Health-status surveys suggest that patients with sickle cell anemia have a low quality of life, similar to that of patients with arthritis or myocardial infarction.<sup>4</sup> Before the era of hydroxyurea, the average life expectancy was in the 40s.<sup>5</sup>

In 2004, there were about 113,000 hospitalizations for sickle cell disease in the United States, about 75% of which were for adults. Total hospital costs were about \$488 million.<sup>6</sup>

---

## PATHOPHYSIOLOGY AND EFFECT OF THERAPY

---

Normal adult hemoglobin, designated hemoglobin A, consists of two  $\alpha$ -globin chains and two  $\beta$ -globin chains. The cause of sickle cell anemia is a point mutation in the  $\beta$ -globin gene (Fig. 1). This genetic abnormality leads to the production of sickle hemoglobin, a protein that has the unique property of polymerizing into long fibers when deoxygenated, thereby decreasing red-cell deformability and damaging the cell membrane. Polymerization is highly dependent on the level of sickle hemoglobin in the cell and is dramatically reduced when other forms of hemoglobin, without the mutant sickle  $\beta$ -globin chains, are present.

The great majority of circulating red cells derive from mature erythroid precursors in the marrow, and although somewhat heterogeneous, the red cells of a nor-

From the Department of Laboratory Medicine, Children's Hospital Boston. Address reprint requests to Dr. Platt at the Department of Laboratory Medicine, Children's Hospital Boston, 300 Longwood Ave., Boston, MA 02115, or at orah.platt@childrens.harvard.edu.

N Engl J Med 2008;358:1362-9.  
Copyright © 2008 Massachusetts Medical Society.

mal adult generally contain almost 100% hemoglobin A and those of a person with sickle cell anemia contain almost 100% sickle hemoglobin. A smaller population of red cells comes directly from immature progenitors. These progenitors have unusually active  $\gamma$ -globin genes and produce red cells with relatively high levels of hemoglobin containing two  $\alpha$ -globin chains and two  $\gamma$ -globin chains.<sup>7</sup> This form of hemoglobin is designated fetal hemoglobin, because it predominates in fetal red cells. The fetal hemoglobin in these so-called F cells mitigates the damage caused by sickle hemoglobin; the F cells are the most nearly normal red cells in the circulation in patients with sickle cell anemia.<sup>8</sup>

Red cells containing high levels of sickle hemoglobin contribute to the pathophysiological development of sickle cell anemia in three major ways. First, these cells lose deformability when deoxygenated, leading to vascular obstruction and ischemia. This is a critical factor underlying painful crises, the acute chest syndrome, functional asplenia, and acute stroke. Second, membrane damage shortens the life span of the red cell, causing chronic intravascular and extravascular hemolysis. Intravascular hemolysis contributes to decreased availability of nitric oxide, increased vascular tone, and pulmonary-artery hypertension.<sup>9,10</sup> Third, damaged red cells have abnormal surfaces that result in increased adherence to and damage of vascular endothelium, a process that enhances acute vaso-occlusion and also provokes a proliferative lesion involving white cells, platelets, smooth-muscle cells, cytokines, growth factors, and coagulation proteins. Such lesions underlie large-vessel stroke and possibly pulmonary-artery hypertension.

A major therapeutic approach to sickle cell anemia has been to try to shift hemoglobin production from sickle hemoglobin to fetal hemoglobin, by changing marrow-proliferation kinetics to favor F-cell production. To evaluate this concept, hydroxyurea (Fig. 2), a cytotoxic drug that had already been in use for decades to reduce the abnormally high hematocrit and platelet count in patients with polycythemia vera, was initially tested in anemic baboons.<sup>11</sup> The first patients treated with hydroxyurea had a response within 72 hours after therapy, with a burst of young F cells, and ultimately with an elevated level of fetal hemoglobin.<sup>12</sup>

Hydroxyurea belongs to a class of compounds called hydroxamic acids, which can bind metals. The primary cytotoxic effect of hydroxyurea lies in its ability to inhibit ribonucleotide reductase by binding the reductase's two iron molecules and inactivating a critical tyrosyl radical.<sup>13</sup> This cytotoxic effect of hydroxyurea reduces the production of red cells containing a high level of sickle hemoglobin, which tend to arise from rapidly dividing precursors, and favors the production of red cells containing a high fetal hemoglobin level (F cells), which arise from progenitors that divide less rapidly. This drug also reduces the numbers of white cells and platelets, potentially reducing their roles in vascular injury.

Another potentially important effect of hydroxyurea is that metabolism of the drug results in the production of nitric oxide. Soluble guanylate cyclase, an enzyme containing heme iron, is stimulated by nitric oxide, a reaction that results in the production of fetal hemoglobin, as shown *in vitro*.<sup>14</sup> The production of nitric oxide may also compensate for the loss of endogenous nitric oxide due to intravascular hemolysis.

---

#### CLINICAL EVIDENCE

---

In a landmark study, Charache et al. demonstrated the efficacy of hydroxyurea in reducing morbidity in adults with sickle cell anemia.<sup>15</sup> A total of 299 adults who had had at least three painful crises in the previous year were randomly assigned to receive either hydroxyurea or placebo. The incidence of painful crises was reduced from a median of 4.5 per year to 2.5 per year. The rates of the acute chest syndrome and blood transfusion were also reduced significantly. Observational follow-up of 233 of the original 299 subjects was performed for up to 9 years and showed a 40% reduction in mortality among those who received hydroxyurea.<sup>16</sup>

Similar large-scale randomized trials have not been conducted in children, but data from prospective treatment series have shown that hydroxyurea does not interfere with, and may actually improve, growth and development in children with sickle cell anemia.<sup>17,18</sup> Treatment with hydroxyurea in children has roughly the same effect on acute events as it does in adults<sup>18</sup> and may prevent splenic dysfunction,<sup>18</sup> cerebral-artery damage,<sup>19</sup> and secondary stroke.<sup>20,21</sup>

## CLINICAL USE

Hydroxyurea should be used to treat adults with sickle cell anemia who have moderate-to-severe disease, typically those with three or more acute painful crises or episodes of the acute chest syndrome in the previous year. It should not be given to patients with severe hypoplastic anemia, leukopenia, or thrombocytopenia. I recommend that treatment with hydroxyurea be initiated only in patients with blood counts and hemoglobin levels that are within the acceptable range (Table 1). Hydroxyurea should not be given during pregnancy or breast-feeding, and both men and women who are taking it should use contraception, since this agent is considered to be a teratogen (see discussion of adverse effects below).

Although the data regarding the use of hydroxyurea in children are somewhat more limited than those for adults, the benefits appear to be similar. I recommend that children with sickle cell anemia who have moderate-to-severe symptoms be treated according to the regimen described below for adults, ideally as part of one of the many clinical trials in progress around the world.

Alternatives to hydroxyurea that reduce morbidity are hematopoietic stem-cell transplantation and long-term transfusion therapy. These may be appropriate first-line treatments for selected persons, including those who have not had a response to a trial of hydroxyurea.

Before initiating therapy, it is important to obtain a complete blood count and to establish the patient's baseline fetal hemoglobin level, hepatic function, and renal function. Renal dysfunction is not a contraindication to treatment with hydroxyurea, but it does influence dosing (see below). There are limited data on the use of hydroxyurea in patients with clinically significant hepatic dysfunction.

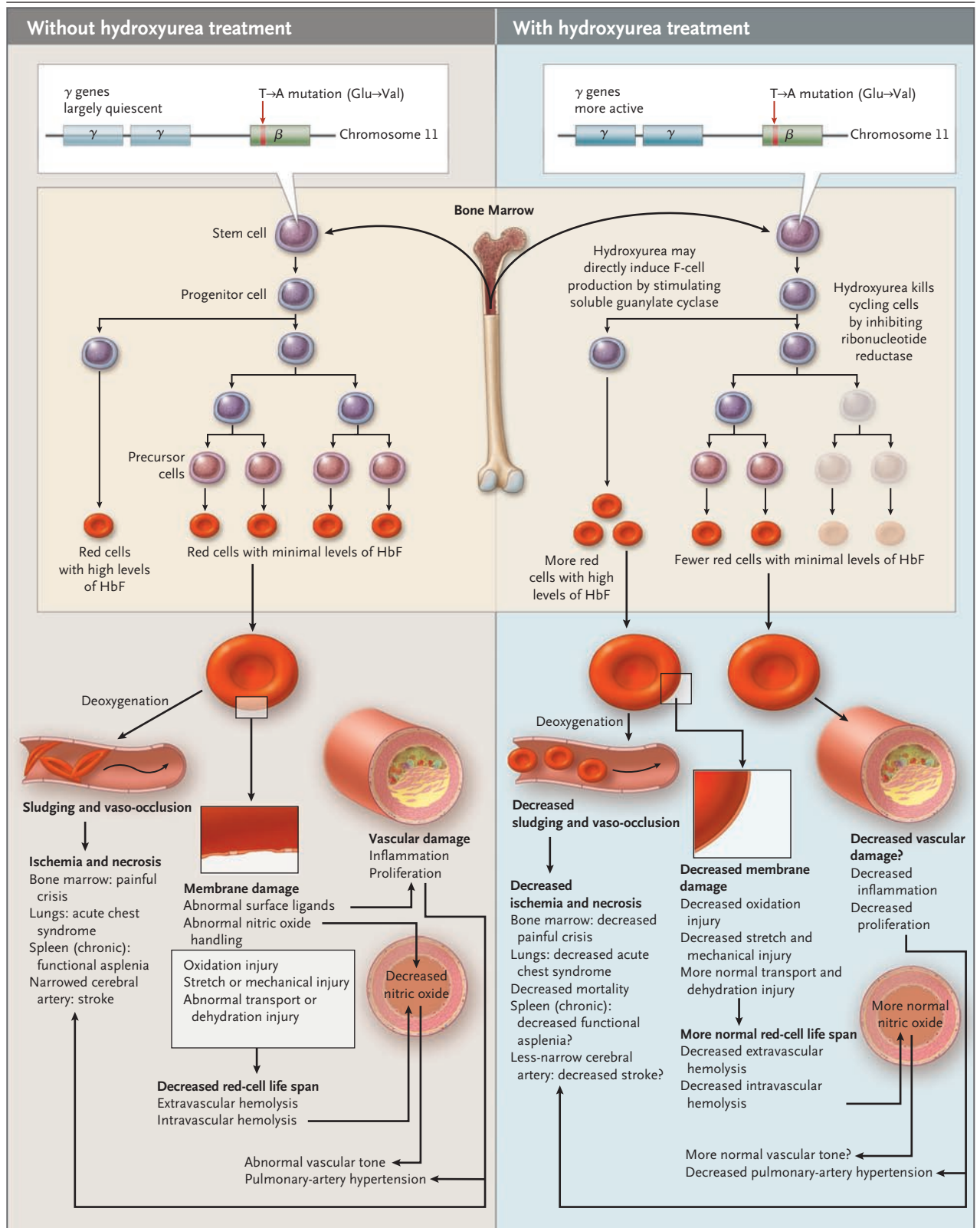
Hydroxyurea is given daily in a single oral dose. The starting dose is 15 mg per kilogram of body weight per day (unless the creatinine clearance is <60 ml per minute [1.0 ml per second], in which case the starting dose is 7.5 mg per kg per day).<sup>22</sup> At 2 weeks, the hemoglobin level and blood counts are reassessed. There should be a significant reduction in the white-cell and platelet counts and an increase in the mean cell volume of red cells. Because oral hydroxyurea is so readily absorbed,<sup>23</sup> if none of these expected blood-

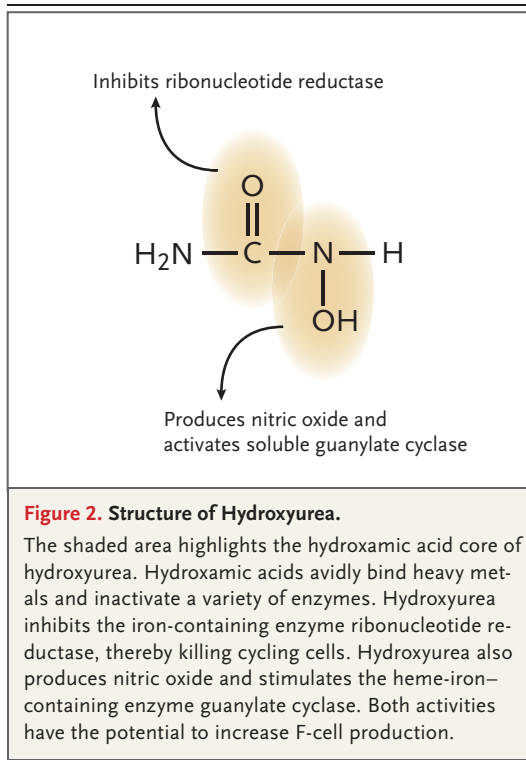
**Figure 1 (facing page). Pathophysiological Characteristics of Sickle Cell Anemia and the Effect of Hydroxyurea.**

The  $\beta$ -globin gene on chromosome 11 contains a mutation that results in the production of sickle hemoglobin. The  $\gamma$ -globin genes have a normal sequence but are quiescent in adults. In the bone marrow, most red cells are produced from mature precursor cells and contain mostly sickle hemoglobin. In rare cases, red cells called F cells are produced directly from primitive progenitors and have a high fetal hemoglobin (HbF) content. Red cells in the circulation that have a high sickle hemoglobin content undergo polymerization and morphologic sickling when deoxygenated, which can cause sludging or vaso-occlusion. Sickle hemoglobin damages the red-cell membrane in a variety of ways, leading to hemolysis and depletion of nitric oxide. Membrane damage also causes increased adherence to and damage of vascular endothelial cells. Hydroxyurea treatment allows  $\gamma$ -globin genes to be more actively expressed. By killing cycling cells, hydroxyurea changes the kinetics of erythroid proliferation, forcing more F cells to be produced from primitive progenitors. Hydroxyurea also produces nitric oxide and directly stimulates fetal hemoglobin production. Because F cells are less likely in red cells with little fetal hemoglobin to occlude vessels and cause membrane damage, hydroxyurea treatment results in fewer symptoms, less severe hemolytic anemia, and lower mortality.

count changes have occurred, it is important to recheck the dose calculation, inspect the actual pills the patient is taking, and review the dosing regimen and adherence to treatment with the patient.

Peripheral-blood counts are then monitored every 2 weeks to determine whether the dose of hydroxyurea requires adjustment over time and to establish the optimal dose for each patient. The goal is to give the highest dose that will maintain the peripheral-blood counts in a safe range, as conservatively defined (Table 1). If any of the counts or levels fall within the very low range, hydroxyurea is stopped and is not restarted (at a lower dose) until the value returns to the acceptable range. Otherwise, dosing decisions are made every 12 weeks. If after 12 weeks the counts remain in the acceptable range, the hydroxyurea dose is increased by 5 mg per kilogram per day. If the counts are in the low range, the dose is not changed. This cycle is continued until either a maximum dose of 35 mg per kilogram per day is reached or the counts fall into the very low range. Any dose that is associated with counts falling into the very low range should not be tried more than twice.





With this strategy, it typically takes less than 6 months for patients to be stabilized on a dose that defines their maximal tolerated dose. Over time, the monitoring schedule can be made more flexible. Once the maximal tolerated dose has resulted in counts that are stable, the frequency of blood-count monitoring can be reduced to monthly for 4 months and then to every 3 months for 1 year, with monitoring every 3 to 6 months in subsequent years. During the first 4 months, hepatic and renal function should be checked monthly to see whether there are idiosyncratic adverse reactions to hydroxyurea. Fetal hemoglobin levels should be checked every 3 to 4 months to assess the efficacy of the treatment.

Even before the maximal tolerated dose is established, the number of F cells increases, and the clinical-event curves that distinguish patients receiving hydroxyurea from those receiving placebo begin to diverge.<sup>15</sup> At 6 months, the fetal hemoglobin level is typically doubled, the hemoglobin level is increased by 1 g per deciliter, and the absolute reticulocyte count, bilirubin level, and lactate dehydrogenase level are reduced.<sup>24</sup> Ultimately, persons with a response to hydroxyurea have a considerable reduction in hemolysis, with a change in red-cell

survival from 34% of the normal value before treatment to 81% of the normal value with ongoing treatment.<sup>25</sup>

During the first randomized trial of hydroxyurea,<sup>15</sup> the average annual cost of the compound was about \$1,000 per year; visits and tests added about \$400 per year. This cost was offset by reduced costs for hospitalizations, emergency room visits, opiates, and transfusion. The net savings was about \$5,000 per patient per year.<sup>26</sup>

Not all patients treated with hydroxyurea have a clinically significant or sustained response to treatment. Although a variety of factors can lead to treatment failure, poor adherence to treatment is recognized as a common problem. Reasons for the high rate of noncompliance are not fully understood but seem in many cases to be related to concern about adverse effects of the drug (see below) and the expense and inconvenience associated with monitoring. Any patient who appears to have a poor or inconsistent response to hydroxyurea while receiving the maximal tolerated dose should be evaluated to determine whether treatment compliance is an issue. Other reasons for a poor therapeutic response include a decreased marrow reserve, precluding adequate dosing (in about 2% of patients),<sup>15</sup> and genetic factors.<sup>27,28</sup>

Patients in whom hydroxyurea therapy is initiated can receive the drug indefinitely, unless adverse effects occur or there are other changes (e.g., declining bone marrow function or the patient's desire to have children). The data from clinical trials confirm that the likelihood of benefit remains significant for at least 9 years,<sup>16</sup> but anecdotal reports suggest that the benefit can last longer. The first patient to be treated in the original proof-of-concept study<sup>12</sup> is still taking hydroxyurea, almost 25 years later, with a sustained response, indicating that long-term use is feasible. For patients who have to stop taking the drug for any reason, there is no evidence that abrupt discontinuation is harmful.

#### ADVERSE EFFECTS

Hydroxyurea is a myelosuppressive compound, and its effects on bone marrow can be conveniently monitored by examining peripheral-blood counts. It is expected that all patients taking hydroxyurea will have at least one episode in which

**Table 1. Peripheral-Blood Thresholds for Adjustment of the Dose of Hydroxyurea.**

Count or Level	Very Low (Withhold Hydroxyurea until Values Are in Acceptable Range)	Low (Maintain Dose)	Acceptable (Start, Restart, or Increase Dose*)
Neutrophils (per mm <sup>3</sup> )	<2000	2000–2500	>2500
Platelets (per mm <sup>3</sup> )	<80,000	80,000–95,000	>95,000
Hemoglobin (g/dl)	<4.5	4.5–5.3	4.5–5.3
Reticulocytes (per mm <sup>3</sup> ) †	<80,000	80,000–95,000	>95,000

\* The dose should be started, restarted, or increased unless it is already at the maximum of 35 mg per kilogram of body weight.

† Reticulocyte thresholds should be taken into account unless the hemoglobin level is more than 9 g per deciliter.

myelosuppression results in the counts falling into the very low range (Table 1), requiring a temporary discontinuation of treatment and adjustment of the dose. Counts usually return to normal within 2 weeks. Interestingly, 35% of patients taking placebo in the original trial had at least one episode of bone marrow depression during the dose-adjustment phase of the study.<sup>15</sup>

The Center for the Evaluation of Risks to Human Reproduction recently reported on the reproductive toxicity of hydroxyurea.<sup>29</sup> On the basis of animal studies, the center concluded that hydroxyurea may increase the risk of fetal abnormalities if given to pregnant women and expressed concern about potential adverse effects on spermatogenesis. Reproductive counseling is a critical ongoing responsibility of physicians who provide long-term hydroxyurea therapy for the management of sickle cell anemia.

It has been suggested that such long-term use may lead to the development of cancer, especially acute leukemia. However, the existence and magnitude of such an increase in risk remains a subject of debate (see below).

#### AREAS OF UNCERTAINTY

Because hydroxyurea has been given as long-term treatment for polycythemia vera, a myeloproliferative disorder that carries an inherent risk of leukemic transformation, it has been difficult to quantify the risk, if any, that might be added by use of the drug. This issue was recently addressed in a prospective observational study of 1638 patients with polycythemia vera.<sup>30</sup> Although this study did not show any increase in the risk of leukemia that was attributable to hydroxyurea (in contrast to the

risks associated with <sup>32</sup>P, busulfan, and pipobroman), a small risk still cannot be ruled out. On the other hand, there are very few drugs that have been studied so systematically in such a leukemia-prone population. Because concern about the risk of leukemia looms so large in the perception of both patients and doctors, it remains a major impediment to the provision of optimal treatment in a high-risk patient population.<sup>31</sup>

Despite the well-demonstrated efficacy of hydroxyurea, there is growing concern that a large number of eligible patients do not have access to this therapy. In a recent study in Maryland, none of the expected effect on hospitalizations was found; in a survey of one hospital, 70% of eligible patients were not taking the drug.<sup>32</sup> The reasons for this situation are not clear, but concern on the part of both patients and their physicians about potential adverse effects is probably a major factor. Further research is needed to understand and correct such impediments to treatment.

#### GUIDELINES

The Division of Blood Diseases and Resources of the National Heart, Lung, and Blood Institute published a report (which is not described as a formal guideline) in 1984 to address the management of sickle cell disease. This report has been revised three times, most recently in 2002.<sup>33</sup> It includes a table outlining a protocol for the use of hydroxyurea in patients with sickle cell anemia. Treatment is indicated for patients who have “frequent pain episodes, history of acute chest syndrome, other severe vaso-occlusive events, or severe symptomatic anemia.” Treatment end points listed are “less pain, increase in Hb F [fetal hemo-

globin] to 15-20 percent, increased hemoglobin level if severely anemic, improved well-being, acceptable myelotoxicity.”

---

#### RECOMMENDATIONS

---

Because of the moderately severe clinical course of the patient in the vignette, she is an excellent candidate for hydroxyurea treatment. If she is not pregnant, has no medical contraindications, and

is fully informed about contraception and adverse effects, I recommend that she begin therapy with the use of the regimen outlined above. I anticipate that if she is provided enough support to simplify monitoring and has appropriate positive feedback along the way, she will be able to adhere to treatment and will have a decrease in symptoms. Long-term treatment should increase life expectancy.

No potential conflict of interest relevant to this article was reported.

---

#### REFERENCES

- Lorey FW, Arnopp J, Cunningham GC. Distribution of hemoglobinopathy variants by ethnicity in a multiethnic state. *Genet Epidemiol* 1996;13:501-12.
- Platt OS, Thorington BD, Brambilla DJ, et al. Pain in sickle cell disease: rates and risk factors. *N Engl J Med* 1991;325:11-6.
- Castro O, Brambilla DJ, Thorington B, et al. The acute chest syndrome in sickle cell disease: incidence and risk factors: the Cooperative Study of Sickle Cell Disease. *Blood* 1994;84:643-9.
- Ballas SK, Barton FB, Waclawiw MA, et al. Hydroxyurea and sickle cell anemia: effect on quality of life. *Health Qual Life Outcomes* 2006;4:59.
- 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;330:1639-44.
- Steiner CA, Miller JL. Sickle cell disease patients in U.S. hospitals, 2004. Statistical brief. No. 21. Rockville, Md: Agency for Healthcare Research and Quality, December 2006.
- Stamatoyannopoulos G. Control of globin gene expression during development and erythroid differentiation. *Exp Hematol* 2005;33:259-71.
- Franco RS, Yasin Z, Palascak MB, Ciralo P, Joiner CH, Rucknagel DL. The effect of fetal hemoglobin on the survival characteristics of sickle cells. *Blood* 2006;108:1073-6.
- Schechter AN, Gladwin MT. Hemoglobin and the paracrine and endocrine functions of nitric oxide. *N Engl J Med* 2003;348:1483-5.
- Gladwin MT, Sachdev V, Jison ML, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. *N Engl J Med* 2004;350:886-95.
- Letvin NL, Linch DC, Beardsley GP, McIntyre KW, Nathan DG. Augmentation of fetal-hemoglobin production in anemic monkeys by hydroxyurea. *N Engl J Med* 1984;310:869-73.
- Platt OS, Orkin SH, Dover G, Beardsley GP, Miller B, Nathan DG. Hydroxyurea enhances fetal hemoglobin production in sickle cell anemia. *J Clin Invest* 1984;74:652-6.
- Yarbro JW. Mechanism of action of hydroxyurea. *Semin Oncol* 1992;19:Suppl 9:1-10.
- Cokic VP, Smith RD, Beleslin-Cokic BB, et al. Hydroxyurea induces fetal hemoglobin by the nitric oxide-dependent activation of soluble guanylyl cyclase. *J Clin Invest* 2003;111:231-9.
- Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. *N Engl J Med* 1995;332:1317-22.
- Steinberg MH, Barton F, Castro O, et al. Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. *JAMA* 2003;289:1645-51. [Erratum, *JAMA* 2003;290:756.]
- Wang WC, Helms RW, Lynn HS, et al. Effect of hydroxyurea on growth in children with sickle cell anemia: results of the HUG-KIDS Study. *J Pediatr* 2002;140:225-9.
- Hankins JS, Ware RE, Rogers ZR, et al. Long-term hydroxyurea therapy for infants with sickle cell anemia: the HUSOFT extension study. *Blood* 2005;106:2269-75.
- Zimmerman SA, Schultz WH, Burgett S, Mortier NA, Ware RE. Hydroxyurea therapy lowers transcranial Doppler flow velocities in children with sickle cell anemia. *Blood* 2007;110:1043-7.
- Ware RE, Zimmerman SA, Sylvestre PB, et al. Prevention of secondary stroke and resolution of transfusional iron overload in children with sickle cell anemia using hydroxyurea and phlebotomy. *J Pediatr* 2004;145:346-52.
- Ware RE, Zimmerman SA, Schultz WH. Hydroxyurea as an alternative to blood transfusions for the prevention of recurrent stroke in children with sickle cell disease. *Blood* 1999;94:3022-6.
- Yan JH, Ataga K, Kaul S, et al. The influence of renal function on hydroxyurea pharmacokinetics in adults with sickle cell disease. *J Clin Pharmacol* 2005;45:434-45.
- de Montalembert M, Bachir D, Hulin A, et al. Pharmacokinetics of hydroxyurea 1,000 mg coated breakable tablets and 500 mg capsules in pediatric and adult patients with sickle cell disease. *Haematologica* 2006;91:1685-8.
- Kinney TR, Helms RW, O'Branski EE, et al. Safety of hydroxyurea in children with sickle cell anemia: results of the HUG-KIDS study, a phase I/II trial. *Blood* 1999;94:1550-4.
- Ballas SK, Marcolina MJ, Dover GJ, Barton FB. Erythropoietic activity in patients with sickle cell anaemia before and after treatment with hydroxyurea. *Br J Haematol* 1999;105:491-6.
- Moore RD, Charache S, Terrin ML, Barton FB, Ballas SK. Cost-effectiveness of hydroxyurea in sickle cell anemia. *Am J Hematol* 2000;64:26-31.
- Steinberg MH, Lu ZH, Barton FB, Terrin ML, Charache S, Dover GJ. Fetal hemoglobin in sickle cell anemia: determinants of response to hydroxyurea: Multicenter Study of Hydroxyurea. *Blood* 1997;89:1078-88.
- Ma Q, Wyszynski DF, Farrell JJ, et al. Fetal hemoglobin in sickle cell anemia: genetic determinants of response to hydroxyurea. *Pharmacogenomics J* 2007;7:386-94.
- Shelby MD. NTP-CERHR expert panel report on the reproductive and developmental toxicity of hydroxyurea. Research Triangle Park, NC: National Toxicology Program, 2007.
- Finazzi G, Caruso V, Marchioli R, et al. Acute leukemia in polycythemia vera: an analysis of 1638 patients enrolled in a prospective observational study. *Blood* 2005;105:2664-70.
- Zumberg MS, Reddy S, Boyette RL, Schwartz RJ, Konrad TR, Lottenberg R. Hydroxyurea therapy for sickle cell disease in community-based practices: a survey of Florida and North Carolina hema-

tologists/oncologists. *Am J Hematol* 2005; 79:107-13.

32. Lanzkron S, Haywood C Jr, Segal JB, Dover GJ. Hospitalization rates and costs of care of patients with sickle-cell anemia in the state of Maryland in the era of

hydroxyurea. *Am J Hematol* 2006;81:927-32.

33. Division of Blood Diseases and Resources. The management of sickle cell disease. 4th ed. rev. Bethesda, MD: National Heart, Lung and Blood Institute,

June 2002. (NIH publication no. 02-2117) (Accessed March 3, 2008, at [http://www.nhlbi.nih.gov/health/prof/blood/sickle/sc\\_mngt.pdf](http://www.nhlbi.nih.gov/health/prof/blood/sickle/sc_mngt.pdf).)

Copyright © 2008 Massachusetts Medical Society.