

# Advances in Hematology

Section Editor: **Craig M. Kessler, MD**

*Current Developments in the  
Management of Hematologic Disorders*

## New Treatment Options for Thalassemia

**Stanley Schrier, MD**

Professor of Medicine (Hematology)

Active Emeritus

Stanford University School of Medicine

### **What is thalassemia?**

Thalassemia is a blood disorder that initially developed 7,000 years ago as a defense against malaria. In simple terms, thalassemia is caused by a mutation in either the alpha-globin chain or the beta-globin chain which combine equally in red blood cells to form hemoglobin. These mutations lead to decreased hemoglobin production.

Mild, heterozygous thalassemia leads to mild anemia. Generally, this condition does not require treatment. Supplementing mildly anemic patients with iron generally leads to iron overload and isn't recommended. With severe thalassemia, the problems are more serious. Severe anemia can develop. In addition, the normal bone marrow expands enormously which leads to skeletal deformities. Thalassemic children must be carefully monitored for signs of endocrine disease so that it can be diagnosed early and treated appropriately.

### **What is the standard treatment for thalassemia?**

Patients with severe beta thalassemia are treated with red blood cell (RBC) transfusions every 3 weeks. However, because there are 200 mg of iron in each unit of RBCs, the repetitive transfusions lead to the build-up of iron in the body. This accumulation of iron can lead to severe heart, liver, and endocrine disease.

### **How is the problem of iron overload addressed?**

An iron-chelating agent called deferoxamine (Desferal, Novartis) is used to stem the problem. This agent is given by an 8- to 12-hour subcutaneous injection at least 5 nights per week. The treatment is expensive and inconvenient. Most beta thalassemia major patients are children, and some are especially unhappy with having to take this drug 5 nights per week.

### **Are there other iron-chelating agents in development that might be more convenient?**

Deferiprone (Ferriprox, Apotex), also known as L1, is an oral chelating agent that is approved in Europe, India, and the UK, but not in the United States or Canada. There is some concern among researchers and regulatory agencies here and in Canada that L1 might be associated with liver fibrosis, and so it has not been approved for use by the regulatory agencies in North America.

ICL670 (Novartis), another oral iron-chelating agent, is currently being evaluated in clinical trials and is showing efficacy. The manufacturer may apply for regulatory approval within a year or so; the studies are still incomplete.

### **How has transplantation been implemented into the treatment of thalassemia?**

Approximately 10 years ago, an Italian group led by Dr. Lucarelli began evaluating transplantation as a treatment for thalassemia. According to their findings, a full allogeneic bone marrow transplantation cures approximately 80% or more of thalassemic children who have a fully matched donor. Most of these children require only a single transplant, although a small number may require a second one. Many centers around the world have adopted this approach. However, only approximately one third of patients have a fully matched sibling donor.

### **Are thalassemic patients without a fully matched donor able to undergo transplantation?**

Some investigators have tried using partially matched donors. This approach is almost but not quite as successful as the fully matched transplantation. Various techniques are being explored for the partially matched transplantation, including the nonmyeloablative (mini) transplant, but it is too early in these studies to be conclusive about their efficacy.

### **What conditioning regimen is used with these transplantations?**

The Italian group that initially studied transplantations in this setting used a fairly strenuous regimen involving several agents, including busulfan and cyclophosphamide. These agents are given at very high doses because the marrow, which is hyperplastic, needs to be obliterated. However, children are generally able to tolerate the drugs fairly well.

### **What are potential treatment strategies for patients without a matched donor and for whom the partially matched transplant is not effective?**

Investigators are exploring the ability of a variety of agents to switch on the gamma globin chain in patients with severe beta thalassemia. The switching on of the gamma chain leads

to production of fetal hemoglobin, which is a combination of alpha- and gamma-globin chains. The gamma chain replaces the missing beta chain that causes the thalassemia and also binds the excess alpha chain, preventing trouble-causing alpha globin accumulation. These agents have so far shown varying degrees of success. Hydroxyurea (Par), used in the treatment of sickle cell disease, has shown efficacy in a study from Morocco, but not in a study from Greece. It is not clear why this agent works in some patients and not in others.

Another approach is to use histone deacetylase inhibitors. The mechanism of action of these agents is not easy to understand. In order for a gene to be transcribed there must be a gap opened between the DNA of that gene and the covering chromatin. Acetylation of the local histones opens such a gap, thereby allowing that DNA to be transcribed. Histone deacetylases remove these acetyls, closing the gap and preventing transcription of the genes encoded by that segment of DNA. Inhibitors of histone deacetylases would keep the gap, open and for example, allow gamma-globin transcription to occur, and thus produce fetal hemoglobin. It is not yet clear whether or not this approach will be effective.

### **Is gene transfer being explored in thalassemia?**

Yes. Gene transfer strategies are being explored in animal models, with interesting results so far. The idea behind the gene transfer approach is to remove the nonproductive gene, in either alpha or beta thalassemia, and replace it with a normally functioning gene. Early studies have shown that this transfer can be done in a mouse model of thalassemia. It is possible to detect thalassemia early in the development of a fetus, and so the gene transfer is done as early in the development of the mouse as possible.

Gene transfer in humans is on the horizon, but it may be very difficult. Performing a gene transfer requires identifying the correct flanking regions and inserting the gene in the correct location, making sure that the cells are erythroid cells, not, for example, muscle cells.

### **Is there screening for thalassemia during the fetal stages?**

One of the major advances in the treatment and prevention of thalassemia, particularly in Italy, Greece, Cyprus, and Sardinia, is the development of tests to determine if a fetus is thalassemic. For high-risk families or families with a severely thalassemic child, the mother allows the fetus to be tested using chorionic villus sampling of the fetus during week 12 or 13 of the pregnancy. If the fetus is found to have a genetic background for any of the severe forms of thalassemia, the family may elect to terminate the pregnancy. In the countries in which this test is approved, approximately 90% of mothers with a high-risk pregnancy undergo this test, and approximately 90% of pregnancies that test positive for severe thalassemia are terminated. There is a 3 in 4 chance that a subsequent fetus will not have the same severe thalassemia, and so the parents often decide to prevent the birth of a thalassemic child because of the negative impact on the child's quality of life.

### **If it is possible to treat a significant percentage of severe beta thalassemia, why are these pregnancies terminated?**

In the 4 countries mentioned above, the incidence of thalassemia is much higher than in the United States. In these countries, thalassemic children are much more common and so people are familiar with the results of this disease. Advertisements about thalassemia are common; it is part of the culture, and so preventing it by terminating a pregnancy does not seem as strange a concept as it might in this country.

### **In what countries is alpha thalassemia common?**

Alpha thalassemia is common in Asia and is a substantial focus of research there. Because of the migration of Asians to the United States and Canada, the frequency of alpha thalassemia in these countries has increased. Alpha thalassemias also occur in sub-Saharan Africa.

As with beta thalassemia, there are mild and severe forms of alpha thalassemia. Homozygous alpha thalassemia/hydrops fetalis, in which a fetus develops without any adult alpha chains in the hemoglobin, is the most severe form. If both parents have the gene for alpha-zero thalassemia, there is a 1 in 4 chance that the fetus will be severely affected. In these cases, the fetus usually dies in utero of severe anemia.

### **How is alpha thalassemia treated?**

There have been approximately 10 attempts to do a bone marrow transplantation in utero. This approach is very difficult; there have been very few successes. Also, the cost of the procedure is approximately \$225,000, and so it is not a viable option for most parts of the world. Other treatments have not been very effective thus far. The gamma chain is not available to switch on in alpha thalassemia as it is in beta thalassemia. Gene transfer strategies are being explored, but data are not yet available.

### **What psychosocial problems are associated with thalassemia and how are these handled?**

In the Mediterranean countries mentioned above, thalassemia is a sensitive issue in the community. Psychosocial support is an important part of patient and family management. In Greece, families often meet with a genetic counselor. In Italy, there is a greater tendency to use family support and the church. In the United States, there is no formalized program, although some centers are developing programs.

### **Suggested Reading**

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