Thalassemia – State-of-the-Art, 2007

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CONFERENCIA

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ABSTRACT

Thalassemia is a hereditary anemia resulting from defects in hemoglobin production.

β or α -Thalassemia, which is caused by a decrease in the production of α or β-globin chains, affects multiple organs and is associated with considerable morbidity and mortality. Accordingly, lifelong care is required, and financial expenditures for proper treatment are substantial.

Thalassemia is among the most common genetic disorders worldwide; 4.83 percent

of the world's population carry globin variants, including 1.67 percent of the population who are heterozygous for α-thalassemia and β-thalassemia.

β-Thalassemia is caused by any of more than 200 point mutations and, rarely, by deletions, while in α-thalassemia 50 deletions and about 100 point mutations have been identified. Thalassemia is clinically heterogeneous because various genetic lesions variably impair globin-chain synthesis. However, genotypic variability at known loci is often insufficient to explain the disparate phenotypes of individual patients with the same genotype. Disparity between genotypes and phenotypes is particularly marked in β thalassemia intermedia where patients are not regularly transfused like those with β-thalassemia major, and hemoglobin E thalassemia.

Hemolysis and ineffective erythropoiesis together cause the anemia that occurs in thalassemia. The relative contributions of these two pathologic processes differ in various forms of thalassemia and is mainly related to the quantity of the remaining globin chains. In β-thalassemia, the unstable α globin chains precipitates much faster than excess β globin chains in α thalassemia which results in premature denaturation of the affected red blood cells, with al the deleterious consequences.

Regular transfusion therapy to maintain hemoglobin levels of at least 9 to 10 g per deciliter allows for improved growth and development and also reduces hepatosplenomegaly due to extramedullary hematopoiesis as well as bone deformities.

Impairment of growth and endocrinopathies, particularly hypogonadism and "bronze diabetes", are common features of thalassemia particularly in older patients or in those where iron chelation therapy is insufficient. Considerable morbidity in older patients results from bone disease due to osteopenia and osteoporosis, which is often accompanied by disabling pain and fractures. The pathogenesis is complex and multifactorial. Bone marrow expansion due to ineffective erythropoiesis, endocrine dysfunction, and complications of treatment all contribute to the condition.

Iron overload causes most of the mortality and morbidity associated with thalassemia. Iron deposition occurs in visceral organs (mainly in the heart, liver, and endocrine glands), causing tissue damage and ultimately organ dysfunction and failure. Cardiac events due to iron overload are still the primary cause of death. Both transfusional iron overload and excess gastrointestinal absorption are contributory.

Accurate, preferably noninvasive measurement of iron stores is crucial for the evaluation and management of chelation therapy. Serum ferritin is most commonly measured as an indicator of iron stores. Ferritin levels below 2500 ng per milliliter are associated with improved survival. The application of T2 gradient-echo sequencing is more sensitive to hemosiderin de-

position and appears to be useful for the measurement mainly of myocardial and liver iron in thalassemia. Elevated tissue iron stores are only one component of the damaging effects of iron overload. A highly toxic form of iron, non–transferrin-bound iron, is formed when the iron-binding capacity of transferrin has been exceeded. Non–transferrin bound iron is highly toxic because it can catalyze the formation of reactive oxygen species through the Fenton reaction. Evidence for oxidative stress has been found in all 3 blood cell components and in major organs.

Iron-chelation therapy is largely responsible for doubling the life expectancy of patients with thalassemia major. Deferoxamine continues to be the most common iron-chelating agent in use, despite the less convenient parenteral administration. Deferiprone, an oral iron chelator, has a number of advantages over deferoxamine. It can penetrate the cell membrane and chelate toxic intracellular iron species and may be more effective than deferoxiamine in the removal of myocardial iron. An encouraging new approach to chelation therapy is the sequential combined administration of deferiprone and deferoxamine, which removes more iron than each one of the drugs by itself.

Deferasirox (ICL670), another oral iron chelator, is particularly promising for its efficacy, which may be similar to that of deferoxamine. Deferasirox is administered once daily and appears to have an acceptable side-effect profile.

Bone marrow transplantation had excellent results in low-risk patients, those with thalassemia termed class 1 or class 2 by the Lucarelli classification, which is used to assess risk factors that predict outcome and prognosis and addresses the degree of hepatomegaly, the presence of portal fibrosis on liver biopsy, and the effectiveness of chelation therapy before transplantation. However, patients with class 3 disease (with extensive liver damage from iron overload) have had poor results in the past, primarily because of the 30 percent rate of graft rejection due to attenuated conditioning.

The use of related or unrelated umbilical-cord blood further increases the donor pool. However, cord-blood transplantations have often been unsuccessful in the treatment of thalassemia because large numbers of transplanted cells need to be administered to sustain hematopoiesis and prevent graft rejection.

Initial efforts at gene therapy were directed against diseases of the β-globin gene. This therapeutic strategy involves the insertion of a normally functioning γ-globin or β-globin gene into the patient's autologous hematopoietic stem cells. Although the concept is relatively straightforward, it has met with two decades of seemingly insurmountable hurdles and is still in experimental stage.

Polymerase-chain-reaction (PCR) technology has been used for more than a decade for prenatal diagnosis to detect point mutations or deletions in chorionic-villus samples, enabling first-trimester, DNA-based testing for thalassemia. However, because pregnancy termination is unacceptable to some persons (even when the fetus is affected), methods were developed beginning in the early 1990s, to perform diagnostic testing before implantation, but they are still not commonly used.

In developed parts of the world, such as the United States and Europe, there are approximately 10,000 homozygous patients with thalassemia, and the number of new cases has been progressively decreasing because of effective prevention methods.

In contrast, the treatment of thalassemia is entirely different in less developed countries, where most of the patients with this disease reside. Safe transfusion (with the use of filtration and the viral testing of blood) and chelation are not universally available. Consequently, many patients with thalassemia in underdeveloped nations die in childhood or adolescence.

The challenge for the future is to ensure that people who are born with a severe form of thalassemia will continue to thrive, while effective prevention eventually decreases the number of severely affected patients worldwide.

β-THALASSEMIA

Thalassemia is a hereditary anemia resulting from defects in hemoglobin production.1 β-Thalassemia, which is caused by a decrease in the production of β-globin chains (Fig. 1), affects multiple organs and is associated with considerable morbidity and mortality. 2 Accordingly, lifelong care is required,3 and financial expenditures for proper treatment are substantial.4

Thalassemia is among the most common genetic disorders worldwide; 4.83 percent of the world's population carry globin variants, including 1.67 percent of the population who are heterozygous for α-thalassemia and β-thalassemia. In addition, 1.92 percent carry sickle hemoglobin, 0.95 percent carry hemoglobin E, and 0.29 percent carry hemoglobin C. Thus, the worldwide birth rate of people who are homozygous or compound heterozygous for symptomatic globin disorders, including α-thalassemia and β-thalassemia, is no less than 2.4 per 1000 births, of which 1.96 have sickle cell disease and 0.44 have thalassemias.5

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