

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Update on the Diagnosis and Management of Thalassemia



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H&O When do you suspect the presence of thalassemia, and how is it diagnosed?

MW We suspect thalassemia in people who have anemia and small red blood cells that cannot be explained by iron deficiency. The clinical presentation in a severely affected infant or toddler typically includes pallor, irritability, poor feeding and weight gain, and enlargement of the liver and/or spleen. The incidence of thalassemia is highest in patients of Mediterranean, Greek, Italian, Middle Eastern, Indian, East/Southeast Asian, and African ancestry. Therefore, family and ethnic history can be very helpful in leading to a correct diagnosis. Thalassemia carrier status confers resistance to malaria, and therefore the geographic distribution of these 2 disorders overlaps.

One way to detect some forms of thalassemia is to perform hemoglobin electrophoresis or chromatography, which can detect abnormal levels of certain hemoglobins. We now also have the option of performing definitive genetic testing by analyzing the patient's DNA.

H&O What are the different forms of thalassemia?

MW In adults, hemoglobin is a 4-subunit protein (tetramer) made up of 2 copies each of 2 different subunits, α -globin and β -globin. Mutations in the genes that encode these proteins cause 2 major classes of thalassemia, α -thalassemia and β -thalassemia. Clinically, these disorders cause a spectrum of disease that varies in severity depending on the nature of the mutations and the presence of various genetic modifiers.

In α -thalassemia, α -globin gene mutations (usually deletions that remove 1 or more entire gene) inhibit

production of the corresponding protein. Consequently, there is accumulation of excess β -globin, which forms a homotetramer (β_4 , *hemoglobin H*) that can sometimes be detected by hemoglobin electrophoresis or chromatography. Thus, some forms of α -thalassemia are referred to as *hemoglobin H disease*. In neonates with α -thalassemia, accumulation of fetal (γ) globin tetramer (γ_4 , *hemoglobin Barts*), is usually detected by routine newborn screening, although the results may not be reported automatically to the pediatrician. Most cases of α -thalassemia are caused by deletion of 1 or more of the 4 α -globin genes present in healthy individuals. The severity of disease correlates with the number of α -globin genes lost. Deletions of 1 or 2 α -globin genes, termed *silent carrier state* and *α -thalassemia trait*, respectively, usually cause no symptoms. Loss of 3 genes causes mild to severe anemia that can be exacerbated by fever and/or various infections. Loss of all 4 α -globin genes, which occurs most frequently in some parts of Asia, may cause fetal death associated with a condition termed hydrops if not recognized early and treated with intrauterine transfusions.

β -Thalassemia is caused by β -globin gene mutations that inhibit production of the corresponding protein. Consequently, free α -globin accumulates, which is toxic to red blood cells and their precursors. Normally, there are 2 β -globin genes. Loss of 1 β -globin gene usually causes *β -thalassemia trait*, which is asymptomatic, although red blood cells are small. Usually, both β -globin genes must be mutated to cause symptomatic β -thalassemia. These mutations include gene deletions and (more commonly) point mutations that inhibit transcription, splicing, and translation to various degrees. β -Thalassemia is much more heterogeneous than α -thalassemia, with a broad

and continuous spectrum of clinical severity depending on the extent to which the mutations reduce β -globin gene expression. Hemoglobin E, a β -globin gene point mutation that disrupts RNA splicing and also generates an amino acid substitution, is extremely common in some regions of Southeast Asia. Individuals with compound heterozygosity for hemoglobin E and β -thalassemia can have anemia ranging from mild to severe. Genetic modifiers also influence β -thalassemia. The most important modifier is sustained expression of γ -globin, which normally shuts off after birth. In this circumstance, γ -globin substitutes for deficient β -globin to form fetal hemoglobin, which ameliorates the symptoms of β -thalassemia. Different forms of β -thalassemia, listed in increasing order of severity, are: β -thalassemia trait, β -thalassemia minor, β -thalassemia intermedia, and β -thalassemia major. However, as noted, it is more accurate to consider the disorder as a continuous clinical spectrum.

Clinically significant forms of thalassemia produce 2 major problems: anemia and ineffective erythropoiesis. The latter refers to a massive buildup of dying or developmentally arrested red blood cell precursors in various tissues with hematopoietic capability. This buildup causes a host of problems that include bone deformities and fractures, as well as extramedullary erythropoiesis, a condition in which red cell production occurs in the spleen, the liver, or other ectopic sites, causing organ enlargement and/or mass effects. Both anemia and ineffective erythropoiesis cause fatigue and failure to thrive.

H&O How are the most severe forms of thalassemia treated?

MW Patients who are missing all 4 α -globin genes die before birth unless they receive blood transfusions in utero and then throughout life. Patients with 3 affected α -globin genes usually have an intermediate form of thalassemia (discussed below). Patients with β -thalassemia major are generally well in the newborn period, but become symptomatic over the first year of life as fetal hemoglobin synthesis declines. These patients require blood transfusions every 3 or 4 weeks in order to function normally and remain alive.

Until approximately 50 years ago, patients with thalassemia would die of anemia in early childhood. As regular blood transfusions became recognized as an effective treatment, patients lived longer and felt better initially, but eventually died as teenagers or young adults of iron overload caused by the transfusions and also by enhanced gut absorption. Excess blood iron is deposited in organs such as the heart, liver, and pancreas, causing damage to these organs.

A breakthrough in the treatment of thalassemia came in the 1970s with the introduction of iron chela-

tors, which eliminate extra iron from the body. The first iron chelator to be approved was deferoxamine (Desferal, Novartis). This drug is lifesaving, but it must be given as a subcutaneous or intravenous transfusion for 8 to 12 hours each night in order to be effective. Understandably, this presents substantial problems for patients, and adherence to treatment is challenging. More recently, oral iron chelators have been developed, providing a major improvement for patients and their health care providers. Deferasirox (Exjade, Novartis) was approved in 2005. Deferiprone (Ferriprox, ApoPharma) was approved in 2011 for patients who cannot tolerate deferasirox or deferoxamine. Recent advances in the use of magnetic resonance imaging (MRI) to image and quantify tissue iron allows clinicians to tailor chelation therapy based on organ-specific iron loading. Of particular importance, this approach likely reduces cardiac complications of iron overload. Patients with severe thalassemia who receive regular blood transfusions with proper chelation require close medical attention, but it is possible for them to lead long, productive lives.

H&O How does treatment of severe thalassemia differ in other parts of the world?

MW There are approximately 1000 to 2000 patients with severe thalassemia in the United States. In contrast, the incidence of thalassemia is at least 10-fold higher in many other parts of the world. Such a high incidence places tremendous strains on the medical system and blood supply, which influences management approaches. For example, some countries, such as Greece and Italy, perform routine prenatal testing for thalassemia. However, abortion of affected fetuses presents ethical and religious challenges for many individuals.

Bone marrow transplantation is an effective treatment for severe forms of thalassemia. Most of the pioneering studies in this area were performed in southern European countries, predominantly Italy and Greece, where thalassemia is most common. Cure rates with bone marrow transplantation approach 90% in properly selected patients. However, there is a small but real risk of treatment-related mortality (an incidence of approximately 5%). This risk is unacceptable for many patients in the United States, where we have enough blood to provide regular transfusions for people who need them. However, in developed countries where thalassemia is endemic, the demand for blood is much higher and frequently limiting. Consequently, patients and their social/medical infrastructure are often better off accepting the risk of bone marrow transplantation. Moreover, in many underdeveloped countries, blood supplies are less reliable and there is increased risk for transmitted infectious diseases such as hepatitis C and HIV. Indeed,

efforts are underway to establish protocols for relatively safe and economical bone marrow transplants in these countries. For example, a nonprofit organization called Cure2Cure, which operates out of the United States, the United Kingdom, and Italy, provides bone marrow transplantation to children in countries such as Pakistan.

H&O How is nontransfusion-dependent thalassemia treated?

MW This group includes most patients with 3 α -globin genes deleted, β -thalassemia intermedia or hemoglobin E β -thalassemia, in which the disease-causing mutations allow the expression of β -globin to some extent. These patients may require intermittent blood transfusions and various other interventions, based on symptoms such as fatigue, poor growth, or organ enlargement arising from ineffective erythropoiesis. Iron absorption from the gastrointestinal tract can be excessive and sometimes will result in iron overload requiring chelation, despite relatively few or even no prior transfusions. A panel of clinical experts led by Taher and colleagues, writing for the Thalassemia International Federation, recently formulated guidelines for the management of thalassemia intermedia patients.

Patients with thalassemia minor or thalassemia trait require no treatment. However, it is important that these individuals receive genetic counseling because their offspring may be affected more severely.

H&O What are the future directions for treatment of thalassemia?

MW Fetal hemoglobin-inducing agents, mainly hydroxyurea, work reasonably well for treating sickle cell disease but have been less successful for treating β -thalassemia. A great deal of current research focuses on developing new agents to boost fetal hemoglobin levels more effectively. Recent advances in our understanding of fetal globin gene expression facilitate such studies. In most newborns, fetal hemoglobin switches off and adult β -globin switches on, with the transition completed by about 4 to 6 months. Understanding this “globin switch” should now allow us to better inhibit or reverse it through rational, mechanism-based therapies.

Bone marrow transplantation for thalassemia is safest and most effective when patients receive their donor cells from siblings who are matched for human leukocyte antigen (HLA) genes, which regulate immune compatibilities. There is only a 1 in 4 chance that this match will occur for any sibling pair. Researchers are studying ways to improve the safety and efficacy of bone marrow transplantation from less well-matched donors, including haploidentical relatives and unrelated individuals.

Another promising strategy for treating thalassemia is gene therapy. Several academic research groups and biotechnology companies are developing gene therapies for β -thalassemia. Bluebird Bio and Memorial Sloan-Kettering Cancer Center have initiated clinical trials. Additional trials are also soon to be underway through the Cincinnati Children’s Hospital and St Jude Children’s Research Hospital. In these studies, physicians remove the patient’s own bone marrow, introduce a functional β -globin gene into hematopoietic stem cells, and reintroduce them into patients who have received some type of pretransplantation chemotherapy to improve the engraftment of modified cells. Autologous transplantation using the patients own corrected donor cells avoids many clinical problems related to standard allogeneic bone marrow transplantation, including failure to engraft or graft-vs-host disease.

Another advance that I believe will eventually apply to thalassemia is the emerging field of gene editing, in which physicians and medical scientists can use protein tools to pinpoint and correct specific disease mutations. In some cases of thalassemia, it may be possible to repair the patient’s own defective β -globin gene instead of introducing a new one. This approach is likely to revolutionize the treatment of thalassemia and other genetic disorders in the next few decades.

Overall, progress in treating thalassemia has been tremendous. Patients with what were once rapidly fatal forms of the disease can now live relatively normal lives with appropriate supportive care. Current bone marrow transplantation protocols offer high rates of cure for some patients. Rapidly advancing technologies promise to improve treatment further and cure more individuals. There are many reasons for patients and their health care providers to be optimistic.

H&O Would you like to add anything?

MW First, private foundations—such as the Cooley’s Anemia Foundation—are instrumental in advocating for patients and supporting thalassemia research.

Second, the incidence of thalassemia in the United States is likely to rise in upcoming years, owing to the influx of new immigrants from various regions of the world, particularly Southeast Asia. Medical providers must be trained accordingly to recognize the disease and treat it.

Third, much of our progress and promise for treating thalassemia derives directly from basic scientific studies initiated decades ago. Indeed, thalassemia can be considered a poster child for such research. We have been seeing some discouraging trends, however. Current research funding from federal sources like the National Institutes of Health (NIH) has dropped precipitously, owing to reduced or flattened government budgets. In addition, health-related funding sources now place a greater priority

on translational research than on basic scientific studies. Certainly, translational research is important. However, it is essential to maintain a well-funded, balanced national research portfolio that includes a strong emphasis on basic science. Reduced emphasis and funding of basic science threatens our country's long-term research pipeline, our academic infrastructure, and our dominant status as a world leader in biomedical research aimed at treating and eradicating many diseases.

Suggested Readings

Cavazzana-Calvo M, Payen E, Negre O, et al. Transfusion independence and HMGA2 activation after gene therapy of human beta-thalassaemia. *Nature*. 2010;467(7313):318-322.

Clinicaltrials.gov. A study evaluating the safety and efficacy of the LentiGlobin® BB305 drug product in beta-thalassemia major subjects. <http://clinicaltrials.gov/show/NCT01745120>. Identifier: NCT01745120. Accessed November 20, 2013.

Nienhuis AW, Persons DA. Development of gene therapy for thalassemia. *Cold Spring Harb Perspect Med*. 2012;2(11). <http://perspectivesinmedicine.cshlp.org/content/2/11/a011833.full.pdf+html>. Published November 2012. Accessed December 8, 2013.

Propper RD, Cooper B, Rufo RR, et al. Continuous subcutaneous administration of deferoxamine in patients with iron overload. *N Engl J Med*. 1977;297(8):418-423.

Propper RD, Shurin SB, Nathan DG. Reassessment of the use of desferrioxamine B in iron overload. *N Engl J Med*. 1976;294(26):1421-1423.

Sankaran VG. Targeted therapeutic strategies for fetal hemoglobin induction. *Hematology Am Soc Hematol Educ Program*. 2011;2011(1):459-465. <http://asheducationbook.hematologylibrary.org/content/2011/1/459.full.pdf+html?sid=0cd7a46d-f987-480c-b450-85063e8fe3ac>. Published December 2011. Accessed December 8, 2013.

Taher A, Vichinsky E, Musallam K, Cappellini MD, Viprakasit V; Thalassaemia International Federation. Guidelines for the management of non transfusion dependent thalassaemia (NTDT). [http://www.thalassaemia.org.cy/wp-content/uploads/pdf/educational-programmes/Publications/Non-Transfusion%20Dependent%20Thalassaemias%20\(2013\)/NTDT%20ENGLISH.pdf](http://www.thalassaemia.org.cy/wp-content/uploads/pdf/educational-programmes/Publications/Non-Transfusion%20Dependent%20Thalassaemias%20(2013)/NTDT%20ENGLISH.pdf). Accessed December 8, 2013.

Weatherall DJ, Schechter AN, Nathan DG, eds. *Hemoglobin and Its Diseases*. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press; 2013. http://perspectivesinmedicine.cshlp.org/site/misc/hemoglobin_and_its_diseases.xhtml. Accessed December 8, 2013.

Wolfe L, Olivieri N, Sallan D, et al. Prevention of cardiac disease by subcutaneous deferoxamine in patients with thalassemia major. *N Engl J Med*. 1985;312(25):1600-1603.

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expression level of EGFR ligands amphiregulin and epiregulin. All of these are being tested in the large FIRE-3 and CALGB/SWOG C80405 clinical trials.

Suggested Readings

Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *N Engl J Med*. 2013;369(11):1023-1034.

Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus

FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol*. 2010;28(31):4697-4705.

Schwartzberg LS, Rivera F, Karthaus M, et al. PEAK (study 20070509): a randomized phase II study of mFOLFOX6 with either panitumumab (pmab) or bevacizumab (bev) as first-line treatment (tx) in patients (pts) with unresectable wild-type (WT) KRAS metastatic colorectal cancer (mCRC) [ASCO Gastrointestinal Cancers Symposium abstract 446]. *J Clin Oncol*. 2012;30(suppl 34).

Stintzing S, Jung A, Rossius L, et al. Analysis of KRAS/NRAS and BRAF mutations in FIRE-3: a randomized phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC) patients. Presented at: European Cancer Congress 2013; September 27-October 1, 2013; Amsterdam, The Netherlands. Abstract LBA17.