May 2008 www.clinicaladvances.com Volume 6, Issue 5, Supplement 11

Guest Editor

Richard J. O'Reilly, MD

Chair, Department of Pediatrics
Chief, Pediatric Bone Marrow
Transplant Service
Memorial Sloan-Kettering Cancer Center
New York, NY

Faculty

Emanuele Angelucci, MD

Head, Department of Hematology
Cagliari Hospital
Ospedale Oncologico A Businco
Cagliari, Italy

Mark Walters, MD

Program Director
Children's Blood and Marrow
Transplant Program
Children's Hospital
and Research Center
Oakland, Calif.

Deborah Chirnomas, MD

Associate Director
Thalassemia Program
Children's Hospital
Boston, Mass.

Strategies for the Management of Iron Overload in the Transplant Setting

A Review of a Tandem Meeting from the Annual Meeting of the American Society for Blood and Marrow Transplantation
February 15, 2008
San Diego, California

A CME/CE Activity
Approved for 1.0
AMA PRA
Category 1 Credit™

Supported through an educational grant from Novartis Oncology.

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Medical College of Wisconsin CME program

Strategies for the Management of Iron Overload in the Transplant Setting

Journal Supplement

Chair: Richard J. O'Reilly, MD

Provided by:
Medical College of Wisconsin

In Partnership With:
The CBCE™ (The Center for Biomedical Continuing Education)

Date of Original Release: May 2008
Date of Expiration: May 2009
Estimated time to complete this activity: 60 minutes

Statement of Need

Patients who undergo bone marrow transplant for hematologic disorders receive numerous red blood cell transfusions during, and sometimes prior to, the transplant period. This can cause a condition called iron overload, or the accumulation of excess iron in body tissues. The underlying disease can exacerbate this condition, as is often the case with myelodysplastic syndromes (MDS). Patients with MDS have ineffective erythropoiesis and have often been dependent on transfusions in the past to manage their anemia; thus, they might already have excess iron prior to the initiation of the transplant process.

When plasma iron exceeds transferrin's binding capacity, non–transferrin-bound iron (NTBI) is deposited in tissues such as the liver, heart, and pancreas. NTBI combines with oxygen to form reactive oxygen species, which can lead to multiorgan injury. Transplant-related iron overload can be managed through iron chelation therapy, in which chelators bind excess iron within the tissues and remove it from the body. Three iron chelators that have distinct characteristics and safety profiles are approved for use in the United States, one of which is administered parenterally and the other two orally.

Participants of this program will learn about the pathophysiology and complications of iron overload, the patient populations at risk, and the appropriate management strategies that can be utilized to reduce the mortality and morbidity associated with this condition.

Target Audience

This activity is designed for physicians and allied health professionals involved in treating patients undergoing bone marrow transplant.

Educational Objectives

After reading this journal supplement, participants should be able to:

1. Describe the pathophysiology of iron overload.
2. Summarize the reasons why patients undergoing bone marrow transplants for hematologic disorders are at risk for developing iron overload.
3. Outline the numerous complications associated with iron overload.
4. Present clinical trial data investigating the use of iron chelators to treat iron overload.

Method of Participation

This journal supplement is based on highlights from a satellite symposium during the 2008 Blood and Marrow Transplantation Tandem Meetings. This supplement will engage readers and enhance the learning process.

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For further information, please contact Patti Nelson, the CME Registrar at Medical College of Wisconsin (RPC 125), 8701 Watertown Plank Road, Milwaukee, Wisconsin 53226; Telephone: (414) 456-4900; Fax: (414) 456-6623; E-mail: pnelson@mcw.edu.

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Richard J. O'Reilly, MD: Scientific Advisor: Cellerant Therapeutics, Inc., and StemCyte, Inc.

Mark Walters, MD: Consultant: StemCyte, Inc., Honorarium: ViaCell, Inc.

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Deborah Chirnomas, MD

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Strategies for the Management of Iron Overload in the Transplant Setting

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Pathophysiology of Iron Overload in the Transplant Setting

Emanuele Angelucci, MD, Head of the Department of Hematology at the Cagliari Hospital, Ospedale Oncologico A Businco in Cagliari, Italy, first discussed the biology of normal iron metabolism and then addressed the pathophysiologic effects of iron overload.

Normal Iron Metabolism

Iron is an essential element that has numerous normal metabolic functions performed via the interaction of iron with certain proteins. As an example, one of the primary metabolic functions of iron is oxygen transport, a function it performs in conjunction with the oxygen-binding proteins hemoglobin and myoglobin. Normally, humans absorb 1–2 mg of iron daily through their diet. This iron is absorbed into the body through duodenal enterocytes, after which it exists in three states: storage, utilization, and transport.[1] The liver is the primary store of iron, holding up to 1,000 mg at once. Bone marrow and muscle tissues use iron to generate hemoglobin and myoglobin, respectively. Generally, the body maintains 2,000–2,500 mg of iron bound to hemoglobin and 300–500 mg bound to myoglobin. Approximately 3 mg of iron ions are transported through the plasma by binding to the transferrin protein, which are recognized by receptors on the surface of target cells. A clathrin-mediated vesicular transport process then allows the transferrin-iron complex to be internalized, after which the iron ion is released and, in erythroid precursor cells, acts within the mitochondria to generate heme. In total, a normal human has 3,000–4,000 mg of iron within the major iron compartments.[2]

Iron levels may be elevated through a variety of strategies, including increasing dietary intake, improving the efficiency of intestinal absorption, and blood transfusion. However, although traces of iron (1–2 mg) are lost each day due to the sloughing off of mucosal cells, menstruation, or other types of blood loss, humans have no physiologic ability to excrete excess iron. Because of this inability, iron levels are carefully maintained through regulation of intestinal absorption. A central mediator of this process is the small peptide hormone hepcidin, a negative regulator of duodenal iron absorption.[3] Hepcidin is sensitive to both positive and negative feedback mechanisms.[4] The "stores regulator" mechanism inhibits intestinal iron absorption through increased hepcidin expression. Although this mechanism is still not fully defined, it is thought to occur through recognition of iron-saturated levels of transferrin. In a proposed model, iron uptake in hepatocytes through the transferrin receptor increases hepcidin expression, which in turn interacts with duodenal proteins to modulate and decrease dietary iron absorption.[5,6] More recently, this model was further extended when it was demonstrated that hepcidin binds with ferroportin, a receptor located on the surface of absorptive intestinal enterocytes, hepatocytes, and other cells that release iron into the blood.[7] The consequence of hepcidin binding was shown to be ferroportin internalization and lysosomal degradation. As a result, iron is trapped within these cells, a process speculated to cause a decrease in these cells' iron uptake.[4] Pathologic states such as inflammation have also been associated with decreased iron absorption, thought to occur via interleukin-6 (IL-6)-induced hepcidin expression.[8,9] Conversely, the "erythroid regulator" mechanism senses elevated erythroid demand, triggering lowered hepcidin expression and increased duodenal absorption. In a mechanism similar but distinct from the erythroid regulator mechanism, hypoxic conditions also lead to decreased hepcidin levels and increased absorption.[8]

Pathophysiology of Iron Overload

The average unit of blood used during transfusion contains approximately 200 mg of iron.[10] Iron received during blood transfusion is taken up by the reticuloendothelial macrophages, and packaged with transferrin for transport throughout the plasma. During situations of iron overload, plasma transferrin proteins become saturated, and the remaining unstored iron circulates through the bloodstream as extracellular non–transferrin-bound iron (NTBI).[11] The majority of NTBI is then deposited in the parenchyma or in functional cells of organs such as the kidney, lungs, and heart.

NTBI ions can be toxic to cells, and ferritin is therefore an important iron storage mechanism. Ferritin is a primarily intracellular protein with two roles: iron detoxification and iron reserve.[12] Because of these dual roles, ferritin is able to store iron in a form that is readily accessible to cells and, when needed, is capable of releasing the iron in a controlled fashion. The storage capacity of a ferritin molecule is approximately 4,500 ferric iron (Fe^{3+}) ions. Although ferritin is ubiquitous and found in all tissues, it is primarily expressed in the liver, spleen, and bone marrow. A smaller percentage of ferritin, termed serum ferritin, is found in the plasma. Although the origin of serum ferritin is unknown, it has been posited as spillover from cells under conditions of high intracellular iron levels. Because serum ferritin is an acute-phase reactant, acute and chronic inflammation, as well as infections, can elevate its levels during the course of a disease. In steady-state scenarios, serum ferritin levels can be correlated with total body iron stores; therefore these levels provide a convenient laboratory measurement to estimate body iron stores. Serum ferritin levels over 1,000 ng/mL indicate excess body iron concentrations.

Uncontrolled and excessive uptake of NTBI in cells leads to iron overload pathology in the corresponding organs, such as the heart, liver, and endocrine glands. This event occurs when the cells' normal antioxidant capacity is exceeded, including the storage mechanisms ferritin and hemosiderin. Labile pools of iron (LPI) are then free to generate free radicals, especially reactive oxygen species, which leads to lipid, protein, and nucleic acid damage and ultimately to cellular destruction. In particular, tissue damage is caused by two main mechanisms initiated by lipid peroxidation following reactive oxygen species generation.[13] First, lipid peroxidation can result in the decomposition of lipid molecules, leading to a decrease in organelle integrity and eventual cell death. Concomitantly, lipid peroxidation may also increase the expression of transforming growth factor β1 (TGF-β1), which results in collagen synthesis and subsequent fibrosis (Figure 1).

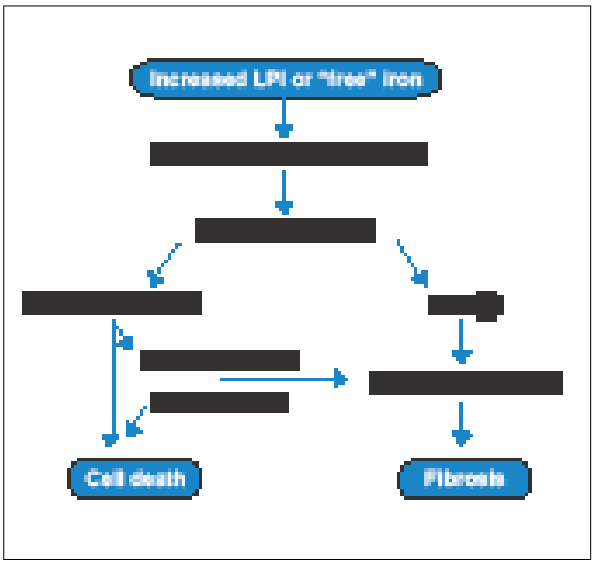

Figure 1. Consequences of iron-mediated toxicity during iron overload.

LPI=labile pools of iron; TGF=transforming growth factor.

Adapted from Cohen and Porter.[13]

Iron Overload: Transplant Populations at Risk

Richard J. O'Reilly, MD, Chair of the Department of Pediatrics and Chief of the Pediatric Bone Marrow Transplant Service at the Memorial Sloan-Kettering Cancer Center in New York, NY, spoke about those patients who were most at risk of experiencing iron overload. Dr. O'Reilly covered both the disorders that may result in iron overload and the disease complications that can lead to iron overload.

Disorders Resulting in Iron Overload

Several disorders have been associated with the development of iron overload pathology. These disorders are generally categorized into two main types, either genetic or acquired. Genetic disorders of iron metabolism are classic examples of genetic iron overload disease. Types 1, 2, 3, and 4 hereditary hemochromatosis are linked with mutations in the hemochromatosis (*HFE*), hemojuvelin (*HJV*), transferrin receptor-2 (*TfR2*), and ferroportin genes, respectively. Likewise, aceruloplasminemia is a genetic disorder in which the absence of the ceruloplasmin protein leads to iron accumulation, whereas atransferrinemia is an extremely rare disorder traced to the absence of the transferrin protein. Additionally, iron overload disorders may also be caused by genetic abnormalities in

red cell formation and survival, requiring transfusion support. Dyserythropoiesis can cause iron-loading anemia, which are treated by transfusions and can subsequently lead to iron overload. For example, thalassemia major and intermedia patients have a genetic defect that results in the formation of abnormal hemoglobin proteins and iron deficiency. Because of these resulting problems, these patients receive blood transfusions and therefore are subject to iron overload. Other dyserythropoiesis genetic disorders include congenital sideroblastic anemia and congenital dyserythropoietic anemia types I–III.

The patients most frequently presenting to transplant clinicians with iron overload are hematopoietic cell transplant candidates with acquired transfusion-induced iron overload. Specifically, these patients have β thalassemia major, aplastic anemia failing immunosuppressive therapy, and constitutional anemia, such as Diamond Blackfan and Fanconi anemia. Alternatively, other acquired disorders requiring transfusion support include myelodysplastic syndromes (MDS)-induced anemia, heavily pretreated leukemias, and myeloma-associated anemia (Table 1).

Table 1. Hematopoietic Cell Transplant Candidates Often Presenting With Transfusion-induced Iron Overload

- Patients with β thalassemia major
- Patients with aplastic anemia who fail immunosuppressive therapy
- Patients with constitutional anemias (Diamond Blackfan, Fanconi)
- Patients with long-standing anemia caused by a myelodysplastic syndrome
- Patients with heavily pretreated leukemias
- Patients with myeloma requiring treatment for associated anemia

A study recently revealed the association between acquired disorders requiring transfusion and the likelihood of developing iron overload. This retrospective analysis was of 292 Japanese patients with MDS, aplastic anemia, and other conditions requiring transfusion therapy.[14] The study found that mortality was associated with high ferritin levels (>1,000 ng/mL). An estimated 21.5 and 43.4 red blood cell (RBC) units were required to raise serum ferritin to at least 1,000 ng/mL in 50% and 75% of patients, respectively.

In a study of 467 individuals with a diagnosis of de novo MDS, a retrospective analysis revealed patient survival to be dramatically affected by transfusion dependence and iron overload in MDS.[15] Transfusion dependence was shown to be associated with shortened overall survival (OS; hazard ratio [HR]=2.16, *P*<.001) and leukemia-free survival (HR=2.02; *P*<.001) in patients with MDS. Specifically, decreases in OS were found in transfusion-dependent patients with either refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), and MDS with del(5q) (HR=3.46; *P*=.05) or refractory cytopenia with multilineage dysplasia (RCMD), and RCMD with ringed sideroblasts (RCMD-RS; HR=1.87; *P*=.04). Similarly, transfusion burden, calculated as the number of transfusions per month, was also significantly associated with decreased OS of both patients with RA, RARS, or MDS with del(5q) (HR=1.62; *P*=.007), and also those with RCMD and RCMD-RS (HR=1.51; *P*=.02). Notably, iron overload has also been correlated with adverse effects on survival in patients with both RA and RARS. Using a threshold of serum ferritin over 1,000 ng/mL, developing iron overload was associated with a significant decrease in OS (*P*<.001). An HR of 1.36 was attributed to every 500 ng/mL increase in serum ferritin over the threshold. Similar results were observed in a second study, also showing that iron overload was associated with a decrease in OS in similar patients.[16,17]

Complications Increasing the Risk of Iron Overload

Several contributing factors in multiple myeloma can lead to anemia. For example, patients often exhibit decreased erythropoietin production resulting from either cytokine-induced inhibition or renal compromise. Additionally, patients may have a decreased sensitivity to erythropoietin and shortened red blood cell survival because of hemolysis. As previously discussed, myeloma-derived IL-6 can induce hepcidin production and therefore reduced iron absorption and availability. There are also factors inherent to multiple myeloma that contribute to increased iron stores. First, the increased hepcidin induced by IL-6 can interact with cellular ferritin and impair iron export. Second, the iron derived from transfusions is preferentially stored in tissues as opposed to being recycled to the erythroid progenitor cells.

The prominence of iron overload in these diseases was clearly shown in a report of a series of 10 adult recipients of allogeneic stem cell transplantation.[18] In these patients, transferrin saturation occurred on day -4 in relation to transplant, reaching 99%. Over the course of the remaining follow-up period (to day 14), transferrin saturation did not fall below 80% (Figure 2). Another study showed that in a large cohort of patients, mainly receiving transplantation for acute myeloid or acute lymphoblastic leukemia, over half of the patients exhibited significant iron overload, indicated by serum ferritin levels over 1,000 ng/mL.[19]

There are many other factors that may contribute to the development of iron overload in transplant patients. A large body of evidence has established a link between

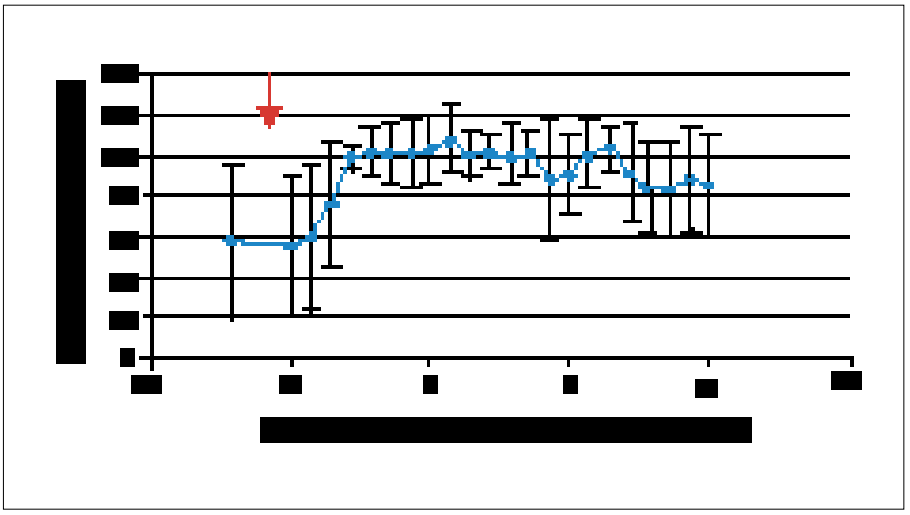

Figure 2. Alterations in transferrin saturation induced by pretransplantation cytoreduction.

Adapted from Sahlstedt et al.[18]

iron overload and patients with a C282Y mutation in the *HFE* gene. Patients homozygous for this mutation exhibit classic congenital hemochromatosis, with high levels of serum ferritin and saturated transferrin.[20] Interestingly, heterozygous patients can also accumulate significant concentrations of iron in body stores. Notably, a study of 140 MDS patients, 42 of whom were diagnosed with RARS, found a significantly higher frequency of C282Y heterozygosity compared with a race-matched control population (21% vs 9.8%, respectively, P=.03).[21] Therefore, these patients may have an increased risk of developing iron overload. Additionally, both prospective and retrospective studies of transplant recipients have shown that C282Y heterozygotes may also be at increased risk for veno-occlusive disease during the posttransplantation period, reflecting the possibility that these patients have iron overload and previously undetected hepatic damage as a result. Another factor contributing to iron overload in transplant recipients is the type of chemotherapy or radiotherapy employed. Both total body irradiation and alkylator treatments have been associated with elevated levels of NTBI (P<.02 for both) as well as decreased total radical antioxidant activity in the plasma (P<.001).[22]

Complications of Iron Overload

Mark Walters, MD, Program Director of the Children's Blood and Marrow Transplant Program at the Children's Hospital and Research Center, in Oakland, Calif., reviewed the pathophysiologic complications that may arise under iron overload conditions, as well as the benefit of iron chelation therapy on alleviating these complications.

Manifestation of Iron Overload

In circulation, ferric iron is the form of iron bound by transferrin. Because this form is biologically inactive, it is not harmful to the body. NTBI, or ferrous iron (Fe^{2+}), is the biologically active and harmful form of iron. Ferrous iron is carried through the circulation via loose binding with various molecules, including amino acids, sugars, and albumin. NTBI is involved in the production of reactive radicals. For example, ferrous iron reacts with hydrogen peroxide (H_2O_2) to form the dangerous reactive hydroxyl radical (·OH). Although there is no definitive clinical evidence that elevated NTBI levels directly induce target tissue damage, clearly, iron chelation therapy in thalassemia patients with transfusion-induced iron overload is associated with improved cardiac disease-free survival. In this way, NTBI can be responsible for major pathologies, including congestive heart failure. Likewise, the LPI present in cells can also lead to lipid peroxidation followed by cellular and tissue damage.[23]

Although there is a great variability in the distribution of iron among different tissues, it mainly targets the liver, endocrine glands, heart, and anterior pituitary.[24,25] Conversely, very little iron accumulates in the brain or skeletal muscle. The consequences of iron overload are dependent on the organ affected. For example, iron overload in the pituitary can lead to hypogonadotropic hypogonadism, whereas overload in the endocrine glands may result in diabetes, hypothyroid, hypoparathyroid, and osteoporosis. Fibrosis and cirrhosis are symptoms of iron overload of the liver, especially in patients with active hepatitis C. Iron overload in the heart tissue results in biventricular failure, arrhythmias, and enlargement of the heart, and can ultimately cause fatal congestive heart

failure in patients. A multicenter analysis of 720 patients with thalassemia was recently conducted to determine the distribution of iron overload–related complications.[26] Notably, this study included only patients born after 1970, after iron chelation therapy became more readily available. Hypogonadism was the most frequently reported complication (54.7%), followed by hypothyroidism (10.8%). Heart failure, diabetes, and arrhythmia were reported at frequencies of 6.8%, 6.4%, and 5.7%, respectively. Significantly, lower serum ferritin levels (<1,000 ng/mL) were associated with a lower probability of heart failure (HR=3.35; *P*<.005) and with prolonged survival (HR=2.45; *P*<.005).

Because of limited clinical data, risk management guidelines for iron overload in thalassemia patients have been derived from clinical experience with patients with hereditary hemochromatosis.[24] In control individuals, a normal iron level in the liver is under 3 mg/g dry liver weight. In patients with thalassemia and compliant with iron chelation therapy, the optimal liver iron range is 3–7 mg/g dry liver weight. However, liver iron ranges of 7–15 mg/g dry liver weight are associated with an increased risk of complications, and levels above 15 mg/g dry liver weight are indicative of a significant risk of cardiac failure and death. Thalassemia patients who do not receive or are not compliant with iron chelation therapy experience rapid elevations in liver iron, exceeding 30 mg/g dry liver weight or approximately 150 µM in concentration.

Benefits of Iron Chelation Therapy

Much effort has focused on determining the benefit of iron chelation therapy in thalassemia patients experiencing transfusion-induced iron overload. Specifically, birth year has been shown to influence the risk of cardiac death in patients with thalassemia, likely due to the increasing availability of chelation therapy over the past several decades. An estimation of the probability of cardiac death at age 20 shows that those individuals born 1960–1964 had a significantly higher risk compared with those born 1975–1979 (30% vs 2.5%, respectively; *P*=.00005).[26] Patients born after 1980 exhibit almost no cardiac disease-related mortality. In another study of 38 patients, those who were compliant with their iron chelation therapy experienced dramatically improved survival compared to poorly chelated patients.[27] All of the deaths in this study occurred in patients who had begun iron chelation therapy later, and at low levels relative to their transfusional iron load (*P*<.001; Figure 3).

Importantly, iron chelation therapy also has a dramatic impact on transplantation outcome, as shown in a pivotal study from 1990.[28] In that trial, progressive iron overload manifested as hepatomegaly and portal fibrosis negatively affected posttransplantation survival, event-free survival, and recurrence. Patients with neither hepatomegaly nor portal fibrosis had a 3-year probability of 94%, 94%, and 0%, respectively. However, having either hepatomegaly or portal fibrosis was sufficient to change these 3-year probabilities to 80%, 77%, and 9%, respectively. Patients having both clinical manifestations had 3-year probabilities of 61%, 53%, and 16%, respectively. In the time since this study was published, other investigators have modulated conditioning regimens so that there is not such a large disparity between these risk groups.

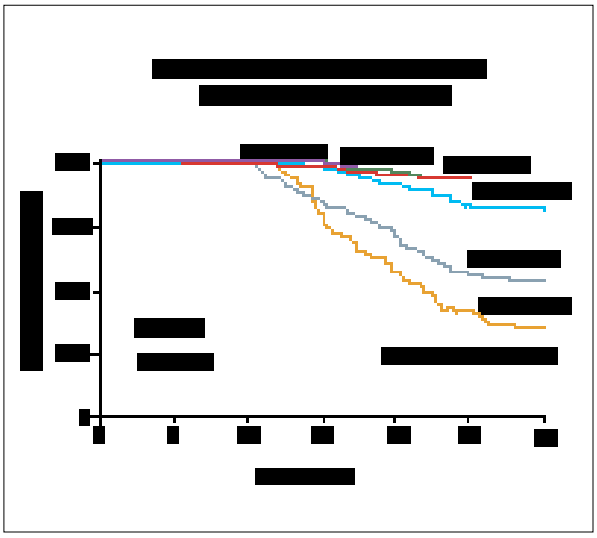

Figure 3. Survival by availability of chelation therapy.

*Deferoxamine introduced.

Adapted from Borgna-Pignatti et al.[26]

Iron overload likewise negatively affects MDS transplant patients. In a recent study comparing the impact of low versus high serum ferritin levels, survival was reduced in those patients with elevated levels.[29] One group of patients comprised those with serum ferritin levels in the lowest three quartiles, whereas the second group was composed of patients with the highest quartile of serum ferritin levels. When considering both OS and disease-free survival, patients in the group of the highest quartile of serum ferritin had significantly decreased probabilities (*P*<.001; Table 2). Elevated serum ferritin levels also conferred a higher risk of veno-occlusive disease (overall risk [OR]=1.7; 95% confidence interval [CI], 1.0–2.9; *P*=.054). Additionally, higher serum ferritin levels were associated with a higher risk of treatment-related mortality (HR=3.2; *P*=.002).

Table 2. Phase I Iron Balance Study: Deferasirox and Net Iron Excretion

- Patients (age ≥16 years) with β thalassemia and transfusional iron overload
- Randomized, double-blind, placebo-controlled, dose-escalation study
- 12-day treatment at each of 3 escalating doses (10, 20, and 40 mg/kg/day)
- 24 patients randomized
  - 18 to deferasirox; 6 to placebo
- Assessments: safety, tolerability, pharmacokinetics, cumulative iron balance

Data from Nisbet-Brown et al.[39]

Complications of Iron Overload

The association of hepatic iron overload with the risk of invasive fungal infections following liver transplantation was recently studied in a cohort of 153 patients.[30] Iron in the hepatic explant was assessed using Perl Prussian blue stain. Significantly, in a multivariate analysis, stainable iron was shown to be strongly and independently associated with fungal infections after transplantation (HR=3.09; 95% CI, 1.45–6.56; *P*=.003). Overall, 18% of patients had invasive fungal infections, but this percentage increased to 33% when only patients with stainable iron were considered. Patients with stainable iron also had a decreased probability of 1-year survival, compared with those with no stainable iron (67% vs 92%, respectively).

A second study also addressed the association between iron overload and risk of invasive fungal infection.[31] This study concluded that in patients who die following hematopoietic stem-cell transplantation, iron overload is frequent and is associated with invasive *Aspergillus* infection.

Iron overload was also found to be a major risk factor for the development of severe infections following autologous stem-cell transplantation in a study of multiple myeloma patients.[32] Statistical analysis of 367 patients with newly diagnosed multiple myeloma showed that elevated bone marrow iron stores significantly predicted an increased risk for serious infection following high-dose melphalan and autologous stem-cell transplantation. Elevated bone marrow iron stores were a significant risk factor for infection in univariate analysis (OR=2.686; 95% CI, 1.707–4.226; *P*<.0001) and remained significant in multivariate analysis, which showed the OR to be 2.716 (95% CI, 1.720–4.287; *P*<.0001).

Current Management Strategies for Transfusional Iron Overload

Deborah Chirnomas, MD, Associate Director of the Thalassemia Program at Children's Hospital in Boston, Mass., presented an overview of the goals of iron reduction therapy, then reviewed the clinical characteristics of the currently used iron chelating agents.

Goals of Iron Reduction Therapy

There are two major strategies for iron reduction therapy. In transfusion-independent patients, the most common and effective strategy is phlebotomy. Conversely, iron chelation therapy is the treatment of choice in transfusion-dependent patients. There are three goals of iron chelation therapy. The first and main goal is to maintain iron levels within a safe range in tissues.[33] Each day, chelation and removal of 0.3–0.63 mg/kg iron is necessary to offset the iron influx from transfusions. Removal of iron from body stores is a slow process, mainly because there is only a small fraction of iron available in chelatable iron pools. The second goal of iron chelation therapy is iron detoxification. To be effective, chelation complexes must coordinate with all six interaction sites on the iron ion to prevent free radical generation by either NTBI or LPI.[34] Additionally, effective chelation agents should provide protection from NTBI that is maintained between doses.[35] The third goal of iron chelation therapy is a wide therapeutic safety margin for each agent. Currently, there are three iron chelation agents available.

Current Chelation Therapies

Deferoxamine (DFO) is the gold standard iron chelating agent worldwide. However, because of compliance issues and socioeconomic limitations, its use is limited in some countries where thalassemia is endemic. DFO is a naturally occurring siderophore that has been in use since the mid-1970s.[34] As a hexavalent chelator, it has a high affinity for iron and binds it in a 1:1 molar ratio.[35] Once it binds to the iron ion in the plasma, the chelation complex is excreted from the body in the urine. Pharmacokinetically, it has an extremely short plasma half-life (20 minutes), and it is unavailable orally. Therefore, DFO is administered by an overnight subcutaneous or intravenous administration, generally multiple times per week. Because of its established efficacy as an iron chelator, it is often used as an active control for trials of novel chelation agents. DFO has been shown to maintain its safety and efficacy over long-term use, over the course of several decades.[36]

As a result of its widespread use, DFO has been linked with multiple clinical benefits, including prevention and reversal of cardiac disease, prevention of hepatic fibrosis,

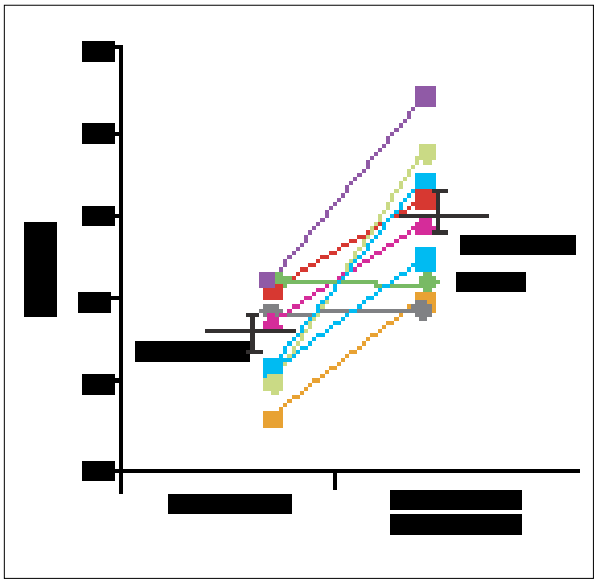

Figure 4. LVEF of congestive heart failure patients improves with continuous intravenous deferoxamine.

DFO=intravenous deferoxamine; LVEF=left ventricular ejection fraction.

Adapted from Davis and Porter.[37]

and reduced risk of diabetes.[36] Additionally, DFO has also been shown to result in the prevention and improvement of hypothyroidism, the reduced risk of hypoparathyroidism, and a decreased incidence of hypogonadotropic hypogonadism. Ultimately, DFO leads to increased survival in treatment-compliant patients. Several limitations are attributed to DFO. Chief among these is patient adherence, limited both by the necessity of an inconvenient parenteral administration, as well as pain from needle insertion, inflammation, and localized sclerosis. However, patient adherence is particularly important, as the survival benefit associated with DFO therapy is highly dependent on patient compliance, and it is most effective when taken more than 80% correctly.[24,36] Of note, there are retinal toxicities associated with DFO use that require careful monitoring. At high chronic DFO doses, osteopenia may also be observed. Because of its short half-life, if not administered properly, patients may not be fully protected against the deleterious effects of NTBI.

One example of the positive effect of DFO on cardiac disease was shown in a study of 9 patients with transfusion-dependent thalassemia with concurrent cardiac disease.[37] These patients all received continuous 24-hour DFO infusions for 6–7 days/week, and left ventricular ejection fraction (LVEF) was monitored prior to and 6–12 months following DFO therapy. LVEF was improved significantly in 7 of 9 patients and was stabilized in the remaining 2 individuals. The mean initial LVEF prior to DFO for all 9 patients increased significantly from 36% to 49% after DFO therapy (P=.002; Figure 4).

Deferasirox (ICL670) was approved for use in the United States in 2005, and it is also available in Europe and South America. It is a tridentate chelator with a high specificity and binding affinity for iron.[38] Deferasirox binds iron in a 2:1 molar ratio, meaning two deferasirox molecules form a complete complex with one iron ion. It is orally available and administered as a once-daily liquid. Deferasirox has a long plasma half-life, and over 90% of iron that is chelated by deferasirox is excreted in the feces.

An initial phase I dose-escalation study established the safety, tolerability, and pharmacokinetics of deferasirox, as well as the cumulative iron balance of the study participants.[39] This trial of 24 patients with thalassemia randomized individuals to either deferasirox or placebo. Deferasirox was administered as 12-day treatments of each of 3 escalating doses—10, 20, and 40 mg/kg/day. There was a clear dose-response relationship in the net iron excretion, and iron excretion was found to be within the therapeutic range (0.1–0.5 mg/kg/day) for deferasirox doses of 10–40 mg. Chronically transfused patients often require iron excretion of 0.4–0.6 mg/kg/day, which was achieved only by either 20 or 40 mg deferasirox. However, even in these doses, some patients did not achieve adequate iron excretion (Figure 5).

The phase III study that evaluated deferasirox was a noninferiority study comparing it to DFO.[40] A total of 298 patients were randomized to receive either deferasirox (n=296) or DFO (n=291) over the course of 1 year. The trial had several inherent flaws, including that the doses of deferasirox used were chosen before the completion of the phase I trial, and therefore patients were started at low doses (5–10 mg). Also, the dosing was chosen based on the current iron load of the patient, and not based on the dose of DFO required to keep that patient at that iron balance. Once-daily oral administration over 1 year of deferasirox was indeed found to result in a significant reduction in the liver iron content, and parallel decreases in serum ferritin levels. This effect was shown to be dose-dependent, as, in most patients, only doses of 20–30 mg induced stable or decreasing liver iron content, and doses of 5–10 mg were too low to elicit an effect.

Although deferiprone (L1) has been available since the mid-1990s, it is not approved for use in either the United States or Canada. Deferiprone is a bidentate chelator, and therefore binds iron in a 3:1 molar ratio. It is orally available and administered thrice daily because of a strong concentration dependence for efficient chelation. Multiple

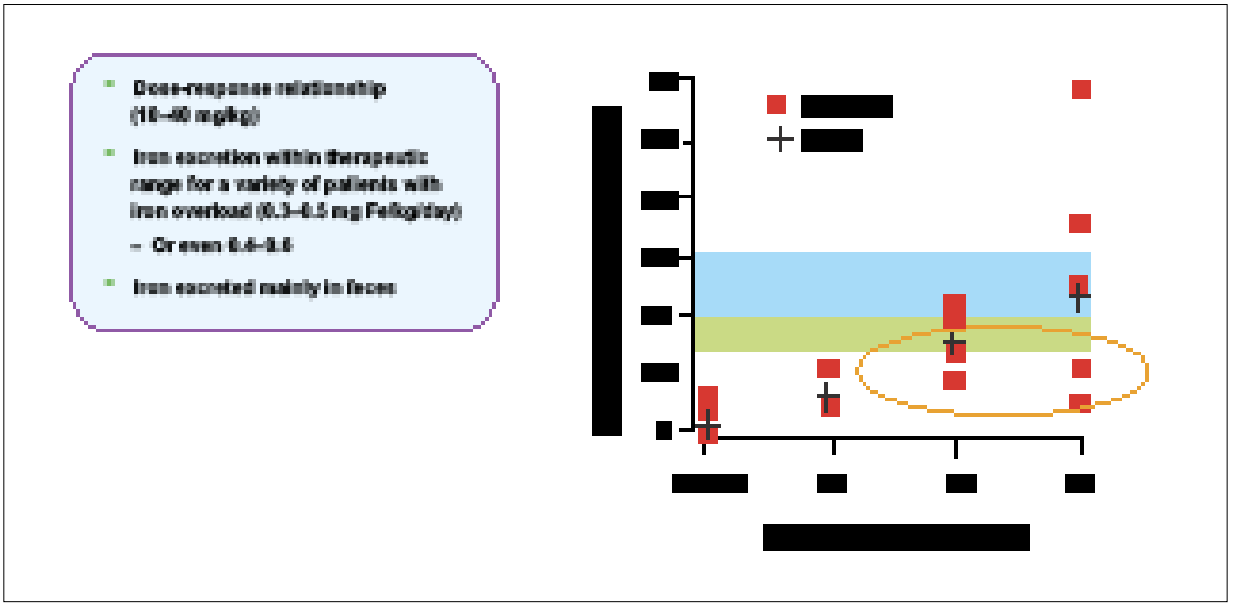

Figure 5. Phase I iron balance study: deferasirox-induced net iron excretion at tolerable doses.

Horizontal bar=range of iron received by patients as a result of transfusion regimens.

Adapted from Nisbet-Brown et al.[39]

studies have established that deferiprone produces similar benefits as DFO and deferasirox, including maintenance of iron balance, reduction in liver iron concentration, and prevention and reversal of cardiac toxicity.[38,41-46] Notably, a recent study found that thalassemia patients who were switched from DFO to deferiprone experienced greater cardiac protection and survival compared with patients only receiving DFO.[47]

Two studies in particular have evaluated the benefit of deferiprone compared with DFO to improve cardiac siderosis. In the first study, 61 thalassemia patients with asymptomatic myocardial siderosis were randomized to receive either agent alone over 1 year.[48] A significantly greater improvement in myocardial T2(*) was observed in patients receiving deferiprone over those receiving DFO (27% vs 13%, respectively; *P*=.023). Likewise, LVEF was also significantly increased in the deferiprone group (3.1% vs 0.3%, respectively; *P*=.003). However, no significant differences were noted in either liver iron concentrations or serum ferritin levels between the two groups. In the second study, 65 patients with thalassemia and mild-to-moderate cardiac disease were randomized to receive either DFO alone or DFO plus deferiprone. Patients receiving the combined therapy experienced significant improvements in myocardial T2(*), LVEF, and endothelial function. Based on these encouraging results, an ongoing trial is being conducted to evaluate the efficacy of this agent in the setting of severe cardiac disease.

In clinical studies, several toxicities have been attributed to deferiprone, including nausea and vomiting, liver function fluctuation, and zinc deficiency.[49] More rare toxicities include potentially fatal idiosyncratic agranulocytosis (~1%) and neutropenia (4%).[50,51] Additionally, erosive arthropathy was observed in 6–39% of patients over the course of several years.

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Strategies for the Management of Iron Overload in the Transplant Setting

CME/CE Post-Test: *Circle the correct answer for each question below.*

1 Under normal conditions, humans absorb _____ of iron through daily dietary intake.

a. 0.5–1 mg
b. 1–2 mg
c. 3 mg
d. 5 mg

2. Hepcidin interaction with _____ on the surface of intestinal enterocytes induces its internalization and lysosomal degradation, ultimately leading to a decrease in iron uptake.

a. ferroportin
b. transferrin
c. IL-6 receptors
d. hepcidin receptors

3. Iron-induced lipid peroxidation can lead to fibrosis through increased expression of _____.

a. IL-6
b. transferrin
c. ferroportin
d. transforming growth factor β1

4. In a study of 467 patients with de novo myelodysplastic syndrome described by Dr. O'Reilly, transfusion dependence was associated with decreases in both _____ and _____.

a. overall survival; progression-free survival
b. overall survival; leukemia-free survival
c. progression-free survival, leukemia-free survival
d. time-to-event; leukemia-free survival

5. An analysis of 140 patients with MDS showed that _____ displayed C282Y heterozygosity, compared with 9.8% in a control population.

a. 7%
b. 16%
c. 21%
d. 32%

6. Which of the following areas is NOT a main target for iron accumulation?

a. liver
b. heart
c. endocrine glands
d. brain

7. In chelated patients with thalassemia, the target iron range in the liver is _____.

a. <3 mg/g dry liver weight
b. 3–7 mg/g dry liver weight
c. 7–15 mg/g dry liver weight
d. >15 mg/g dry liver weight

8. Thalassemia patients born in 1960-1964, before the introduction of chelation therapy, have a _____ risk of developing cardiac disease, significantly higher than those born in 1975–1979, according to a study presented by Dr. Walters.

a. 2.5%
b. 15%
c. 30%
d. 32%

9. In a trial of 9 patients with transfusion-dependent thalassemia and concurrent cardiac disease, deferoxamine therapy significantly improved the mean LVEF from 36% to _____.

a. 49%
b. 51%
c. 53%
d. 55%

10. Deferasirox, approved in the U.S. in 2005, requires doses of _____ to achieve 0.4–0.6 mg/kg/d iron excretion in chronically transfused patients.

a. 5 mg/kg/day
b. 10 mg/kg/day
c. 20–40 mg/kg/day
d. 50 mg/kg/day

TO RECEIVE CREDIT, PLEASE COMPLETE AND RETURN THE POST-TEST AND EVALUATION OF ACTIVITY FORM TO::

Patti Nelson, Medical College of Wisconsin (RPC 125), 8701 Watertown Plank Road, Milwaukee, Wisconsin 53226; Telephone: (414) 456-4900; Fax: (414) 456-6623; E-mail: pnelson@mcw.edu.

Name and degree(s)_____

Institution _____

Address (for Certificate)_____

Phone _____ Fax_____

E-mail (if applicable)_____ Credits claimed (if less than maximum) _____

Indicate whether you need: ❑ CME credits for physicians ❑ Contact Hour credits for allied health professionals

Strategies for the Management of Iron Overload in the Transplant Setting

Evaluation of Activity

Objectives

1. Describe the pathophysiology of iron overload.
2. Summarize the reasons why patients undergoing bone marrow transplants for hematologic disorders are at risk for developing iron overload.
3. Outline the numerous complications associated with iron overload.
4. Present clinical trial data investigating the use of iron chelators to treat iron overload.

1. This activity (please check all that apply):

- ❑ Met the four (4) stated educational objectives.
- ❑ Contained content that was fair, balanced, and free from commercial bias.
- ❑ Contained content relevant to my current patient care responsibilities.
- ❑ Impacted my practice of medicine or improved my ability to render quality patient care.

2. The speakers' level of expertise regarding content presented was: ❑ Excellent ❑ Very Good ❑ Good ❑ Fair ❑ Poor

3. The audiovisuals/handouts (if applicable) were: ❑ Excellent ❑ Very Good ❑ Good ❑ Fair ❑ Poor

4. The learning environment was: ❑ Excellent ❑ Very Good ❑ Good ❑ Fair ❑ Poor

What information or techniques did you acquire that you plan to use on the job: _____
_____
_____

The best feature of the activity was: _____
_____
_____

My suggestions for improvement include: _____
_____
_____

What topics would you recommend be included in future educational program planning: _____
_____
_____

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