

■ Article

# Management of Transfusion-Related Iron Overload in Patients With Myelodysplastic Syndromes

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Anemia is a common symptom for patients with myelodysplastic syndromes (MDS), a spectrum of hematopoietic malignancies characterized by ineffective hematopoiesis; 90% of these patients will become transfusion dependent (TD). Because of the closed nature of iron metabolism, the repeated input of packed red blood cells during transfusions inevitably leads to iron overload. Iron overload can cause iron-related toxicity as well as end-organ damage from iron deposition in tissues. Studies have shown that patients with MDS who are TD have shorter overall survival, shorter leukemia-free survival, and higher healthcare costs compared with patients who are not TD, suggesting that iron overload has a significant clinical and economic impact. Iron chelation therapy can bind and eliminate free iron from the body. Although studies in genetic anemias have shown improved clinical outcomes, clinical trials with patients with MDS are ongoing. Because iron chelation therapy can be toxic, the risks, benefits, and therapy-related costs must be weighed for each patient.

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Cytopenias, particularly anemia, are common in myelodysplastic syndromes (MDS) because of dysplastic changes in the myeloid lineage and bone marrow microenvironment abnormalities, resulting in ineffective hematopoiesis (Nimer, 2008). When MDS-associated red blood cell (RBC) dysplasia and subsequent anemia occurs, patients often require chronic RBC transfusions. Transfusion dependence (TD) is inevitable for the majority of patients with MDS during the course of their disease, with about 90% of adult patients requiring regular, repeated RBC transfusions for months or years (Kurtin, 2007). Studies have shown that when adjustments were made for age, patients with MDS and TD had more than a two-fold higher risk of death and six-fold higher risk of leukemic transformation compared with patients without TD during the initial three years after diagnosis (Goldberg et al., 2010). The negative prognostic effects of TD are partially attributable to hemosiderosis

(transfusion-related iron overload [TRIO]) and secondary organ damage (Leitch, 2011a; Pullarkat, 2009). Elevated iron levels also increase risk of infection and leukemic progression by promoting bacterial growth and inducing genetic damage. Iron overload pathophysiology, incidence, clinical impact, evaluation methods, and treatment strategies (including cost analysis) in patients with MDS are discussed in this article.

## Iron Homeostasis and the Pathophysiology of Iron Overload

Although physiologically critical, excess iron is toxic. On average, the human body maintains a pool of 3–3.5 g of total iron but has 7 g of storage capacity (List, 2010). Hemoglobin-containing RBCs hold 60% of the iron, and the rest is stored in ferritin (25% of total iron), myoglobin, heme enzymes (e.g., cytochromes,

catalases, peroxidases), and non-heme enzymes (e.g., ribonucleotide reductase). Because only 1–2 mg of iron is absorbed or eliminated daily, the iron pool represents a closed system, with homeostasis maintained by various cellular processes (Andrews, 2005).

Iron homeostasis involves a continuous exchange of iron among various physiologic compartments. Normally, iron binds to the plasma protein transferrin and then circulates in the body, allowing for distribution of transferrin-bound iron to organ tissues throughout the body, and accumulates within cells in the form of ferritin (Andrews, 2005). Daily production of new erythrocytes comprises about 80% of the iron demand and requires only 20–24 mg of iron (Wrighting & Andrews, 2008). That iron is obtained primarily through macrophage-mediated catabolization of hemoglobin from dying RBCs. Therefore, iron homeostasis is composed of a closed loop from plasma transferrin to RBCs, from RBCs to macrophages, and from macrophages to plasma transferrin.

Iron homeostasis requires a balance between absorption and macrophage-mediated recycling because of the lack of a regulated elimination mechanism for excess iron (Andrews, 2005) (see Figure 1). Intestinal cells and macrophages bind and internalize extracellular iron using the membrane protein ferroportin. Several factors influence dietary iron absorption (including body iron reserves, bone marrow erythropoietic activity, blood hemoglobin concentration, blood oxygen content, and inflammatory cytokines), which regulates liver production of the hormone hepcidin (Nemeth, 2010). Hepcidin controls both intestinal iron absorption and macrophage recycling. Hepcidin decreases plasma iron concentrations by triggering internalization and degradation of ferroportin by intestinal cells and macrophages, thus locking iron within these cells. Hepcidin deficiency, as seen in  $\beta$ -thalassemia, results in systemic iron overload in the absence of TD. Disruption of hepcidin production from other physiologic issues (e.g., hyporesponsiveness to erythropoietin, chronic inflammation) can lead to development of TD anemia (Nemeth, 2010).

## Transfusion Dependence and Iron Overload

With TD, iron overload occurs over time from repeated, frequent transfusions (Shander & Sweeney, 2009) (see Figure 2). Each unit of packed RBCs contains about 250 mg of iron. Therefore, after receiving about 20 units of RBCs, a patient will receive a resultant 5 g of unexcretable iron (List, 2010). Death of transfused mature RBCs over time in the absence of ongoing erythropoiesis results in formation of nontransferrin-bound iron (NTBI) once transferrin-binding capacity is exceeded (List, 2010; Ozment & Turi, 2009).

NTBI increases levels of reactive oxygen species (ROS) and is associated with inflammation, fibrosis, and organ dysfunction (Leitch, 2011a). As blood levels of NTBI increase, tissue absorp-

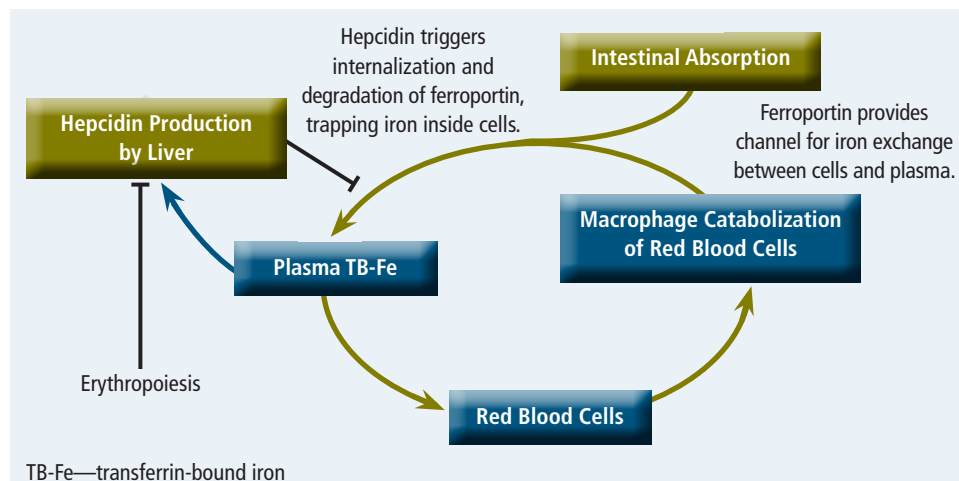


FIGURE 1. Iron Homeostasis

tion of toxic NTBI results in iron deposits in various organs (see Table 1). Although iron deposition in any organ may have detrimental effects, myocardial iron is of central concern given the increased incidence of cardiac events seen in patients with MDS and TD compared to patients without TD (Goldberg et al., 2010; Pullarkat, 2009).

A study of hepcidin levels in patients with different MDS subtypes using a quantitative mass spectrometry assay showed heterogeneous levels of hepcidin production across patients with MDS that parallels the clinical and pathologic heterogeneity of risk (Santini et al., 2011). That study found that low-risk MDS subtypes (refractory anemia [RA] with or without ringed sideroblasts [RS] and del[5q]) at risk for iron overload because of longer survival expectations have the lowest hepcidin levels, demonstrating the greatest conservation of homeostatic controls of iron levels. In contrast, high-risk MDS subtypes (RA with excess blasts and chronic myelomonocytic leukemia) with increased blast counts and related cytokines have increased hepcidin production, which may serve to protect these patients by favoring cellular entrapment of iron. The data suggest that future therapies targeting hepcidin may hold promise in treating iron overload in patients with MDS.

## Incidence of Iron Overload

The actual prevalence of iron overload in patients with MDS has not been systemically documented (List, 2010). Iron overload risk is dependent on transfusion burden and intensity (Steensma, 2011). Transfusion dependence and TRIO are most common in higher-risk MDS (Leitch, 2011a; Steensma, 2011). The epidemiologic data in MDS are in a transitional state because of several factors, including an aging population, increasing familiarity with the differential diagnosis of MDS, and refinement of MDS diagnostic and prognostic criteria (Kurtin, 2011; Sekeres, 2011). The most recent MDS epidemiologic data worldwide suggest that 28%–34% of patients are in the higher-risk categories (Greenberg et al., 2011; Neukirchen et al., 2011). However, TD and TRIO also are common in the lower-risk MDS population (Sekeres, 2011). Regardless of risk status, TD is an independent predictor of poorer prognosis (Malcovati et al., 2007). As a result, the World Health

Organization's (WHO) Prognostic Scoring System and the MD Anderson Cancer Center Scoring System incorporated TD into risk stratification scoring (Garcia-Manero, 2011). The International Prognostic Scoring System (IPSS) is currently under revision and will include hemoglobin levels and serum ferritin levels as surrogates for TD (Greenberg et al., 2011).

## Clinical Consequences of Iron Overload

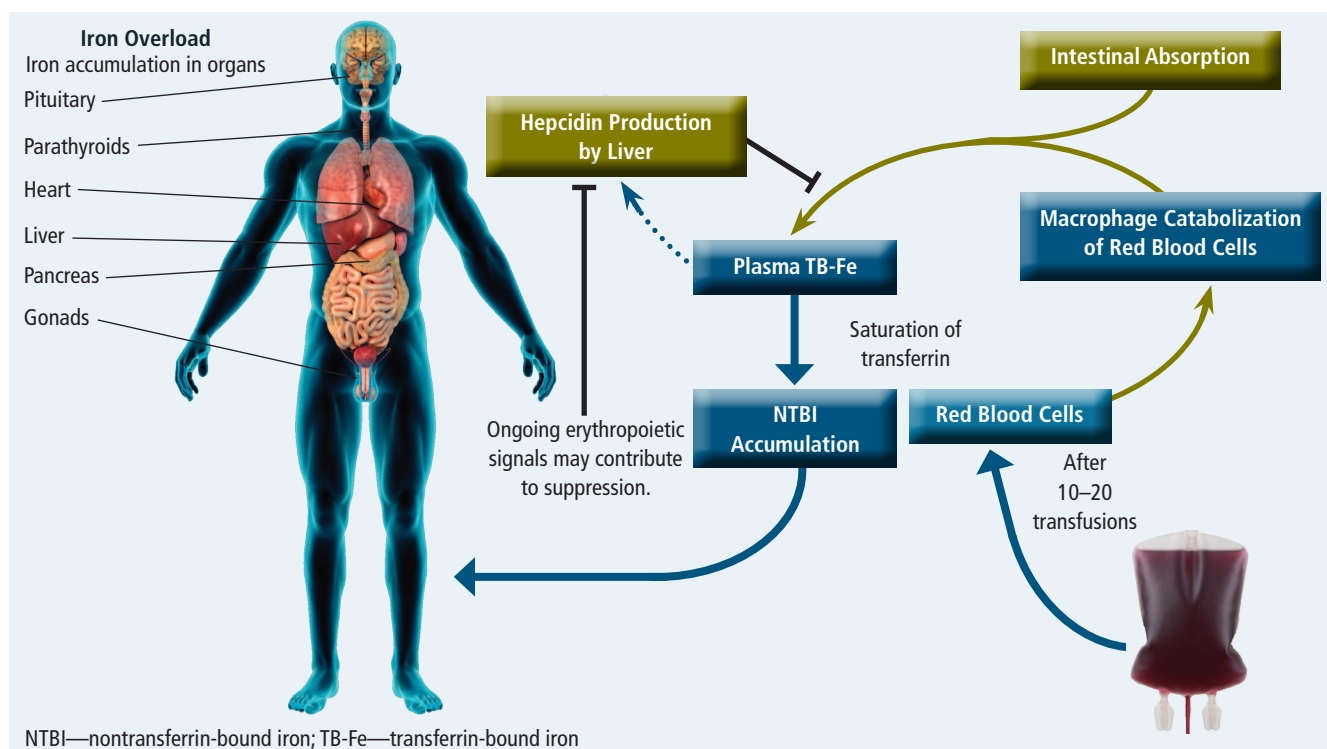
In addition to negatively impacting prognosis, anemia and TD have significant impact on the quality of life (QOL) of patients with MDS. Current therapeutic options can decrease transfusion needs as well as improve QOL (see Table 2). Achievement of transfusion independence in the absence of cytogenetic responses with disease-modifying agents (e.g., azacitidine, lenalidomide) has been associated with improved overall survival (Fenaux, Giagounidis, et al., 2009; Fenaux, Mufti, et al., 2009). Patients who receive hypomethylating agents have demonstrated improvements in QOL measures (Lübbert et al., 2011; Silverman et al., 2002). Iron overload remains a risk for patients who have continued TD even with hypomethylating therapy; therefore, iron chelation therapy (ICT) may be recommended (Harvey, 2010).

Despite the effects of anemia and TD on disease outcomes and patient QOL, the clinical impact of iron overload in patients with MDS remains controversial (Harvey, 2010; Pullarkat, 2009). Studies of hereditary hemoglobinopathies (e.g.,  $\beta$ -thalassemia) have shown causation for iron overload and organ toxicities (List, 2010; Pullarkat, 2009). However, evidence linking organ iron accumulation with morbidity in MDS are indirect. Small studies using magnetic resonance imaging (MRI) techniques have shown variable and infrequent incidence of

cardiac iron accumulation (Pullarkat, 2009). Regardless of organ damage, iron overload may increase infection risk by supplying readily available iron to support microorganism growth (Andrews, 2005). Additional prospective trials using accurate iron overload markers (e.g., MRI measurements of tissue iron) are required to conclusively determine the impact of iron overload on overall survival in patients with MDS.

**Low-risk myelodysplastic syndromes:** About 39% of patients with low- and intermediate-1-risk MDS are TD and at risk for iron overload complications (List, 2010). Because of the longer life expectancy in lower-risk compared with higher-risk patients, prolonged TD in lower-risk patients could contribute to increased cardiac morbidity (Messa, Cilloni, & Saglio, 2010). As a result, iron overload is an important concern and should be addressed during initial workup. Other significant factors to consider with regard to iron overload-associated risks include age, performance status, and bone marrow transplantation eligibility (particularly allotransplantation) (Armand et al., 2007; Leitch, 2011a; Pullarkat, 2009).

Several retrospective studies have suggested that TD influences subsequent overall survival and leukemic evolution (Cermak, Kacirkova, Mikulenkova, & Michalova, 2009; Malcovati et al., 2005; Sanz et al., 2008). When WHO MDS subtype was analyzed, a reduced survival rate was observed in patients with TD with RA, RARS, and isolated del(5q) compared with patients without TD but not in patients with TD and refractory cytopenia with multilineage dysplasia (RCMD) (Malcovati et al., 2005). The key difference in these two groups was a longer median overall survival (100 months for RA versus 50 months for RCMD), implying that TD-associated iron overload toxicity may only be relevant for patients with longer life expectancy.



**FIGURE 2. Pathophysiology of Iron Overload**

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Retrospective analysis found similar results, with specific risks of iron overload effects on survival in patients with TD of more than two units per month and cytopenia limited to unilineage erythroid dysplasia (Cermak et al., 2009).

Studies that use serum ferritin levels as a surrogate measure for iron overload have indicated that TD and iron overload have negative effects on overall survival and leukemia-free survival (Leitch et al., 2008; Sanz et al., 2008; Takatoku et al., 2007). A retrospective multivariate analysis of 902 patients demonstrated a strong association between high serum ferritin levels and reduced overall survival ( $p < 0.001$ ), as well as reduced leukemia-free survival ( $p < 0.0001$ ) (Sanz et al., 2008). This correlation between iron overload and risk of leukemic progression is supported by preclinical studies demonstrating increased genomic instability in hematopoietic progenitors exposed to increased ROS levels (which occur physiologically in the presence of free iron) (Koptyra et al., 2006; Naka, Muraguchi, Hoshii, & Hirao, 2008; Rassool et al., 2007). Goldberg et al. (2010) found a higher incidence of comorbidities in patients with MDS and TD compared with patients with MDS without TD, including dyspnea, cardiac events, hepatic disease, diabetes, and infections. Taken together, the data suggest a link between the higher incidence of organ comorbidities that could be caused by iron overload and decreased survival outcomes associated with TD.

**High-risk myelodysplastic syndromes:** Although a greater number of patients with high-risk MDS are TD (68%) compared with lower-risk MDS (22%), high-risk patients have significantly shorter projected survival, which may limit long-term iron overload toxicity risks (Sekeris et al., 2008). Because survival outcomes of some patients with high-risk MDS are measured in months and not years, many practitioners question the relevance of iron overload and ICT in this population (Steensma, 2011). However, ICT may be relevant for certain aggressive therapies, such as allogeneic hematopoietic stem cell transplantation (HCT). Patients with MDS or acute myeloid leukemia with elevated pretransplantation serum ferritin levels had poorer posttransplantation outcomes, including increased transplantation-related mortality, compared with patients with normal levels of serum ferritin (Armand et al., 2007). Patients with serum ferritin less than 231 ng/ml had five-year overall survival rates of 54% compared with 27% for those with levels greater than 2,034 ng/ml. Subsequent studies have illustrated similar outcomes at other research centers (Steensma, 2011). The data support pretransplantation screening of serum ferritin levels and consideration of ICT to improve posttransplantation survival outcomes.

TABLE 1. Iron Deposition in Organs and Secondary Effects

Organ	Comorbidities and End Effects
Endocrine	Leads to hypogonadism, hypothyroidism, and diabetes
Heart	Increased risk of cardiac-related events, myocardial infarction, congestive heart failure, and arrhythmias
Liver	Increased risk of cirrhosis and hepatic dysfunction with elevated levels

Note. Based on information from Harvey, 2010.

TABLE 2. Mechanisms of Action of Supportive Care and Interventional Therapies That Impact Transfusion Dependence

Therapy	Mechanism
Antithymocyte globulin	Immune suppression preventing immune-mediated killing of erythroid progenitors
Erythropoiesis agents	Hematopoietic growth factor that increases proliferation and differentiation of erythroid progenitors
Hypomethylating agents (e.g., azacitidine, decitabine)	Induction of expression of silenced genes, including hemoglobin, resulting in increased erythroid differentiation
Lenalidomide	Induction of expression of fetal hemoglobin, resulting in increased erythroid differentiation and improved hemoglobin levels

Note. Based on information from Hedley et al., 2011; Heise et al., 2010; Ning et al., 2011; Sloand & Barrett, 2010; Yoo & Jones, 2006.

## Clinical Evaluation for Iron Overload

Clinical evaluation of iron overload includes both the individual patient characteristics and the expected iron overload effects in patients with TD. Symptomatic patients may present with any of the characteristic iron overload manifestations, including liver disease, hepatocellular carcinoma, diabetes, gonadal insufficiency and other endocrine disorders, arthropathy, increased skin pigmentation, and iron-induced cardiomyopathy (which may be lethal) (Goldberg et al., 2010; Steensma, 2011).

Baseline evaluation of patients with MDS focuses on disease classification and risk analysis. A careful history and physical examination including assessment of comorbidities, medications, and major organ function (e.g., bone marrow, hepatic, renal, cardiovascular) are recommended (Kurtin & Demakos, 2010). The baseline assessment is essential for identifying patients at risk for iron overload, early diagnosis of iron toxicity, and evaluation of the risks versus benefits of ICT (see Tables 3 and 4). Although many tests are available to assess iron overload, the serum ferritin level is most widely used. Ferritin levels indirectly estimate iron overload, and the tests are easy to perform repeatedly, providing trends over time in patients with variable transfusion intervals. Although a lack of consensus exists on the criteria to initiate ICT, the general recommendation is to begin monitoring serum ferritin levels in patients with lower-risk MDS and TD who are expected to live longer than one year (Leitch, 2011b). Serum ferritin levels are generally checked at the time of diagnosis and repeated every three to four months in patients with TD. Normal serum ferritin values are 12–300 ng/ml for men and 12–150 ng/ml for women. A low serum ferritin level typically means reduced iron stores. Serum ferritin levels greater than 1,000–2,500 ng/ml indicate iron overload (Steensma, 2011). In patients with MDS, serum ferritin levels have been shown to correlate with the number of RBC units received. A serum ferritin value of 1,000 ng/ml may be reached after transfusion of as few as 20 RBC units. One disadvantage to the ferritin test is that results are affected

by inflammation, infection, and ascorbic acid (vitamin C) deficiency (an acute-phase reactant) (Lipschitz, Cook, & Finch, 1974). Therefore, the ferritin level trends over an extended time period are most useful in monitoring iron overload.

Liver iron concentration obtained by tissue biopsy is the most precise iron overload measure, but is rarely used in the MDS population because of the older age of most patients and the common concurrent cytopenias (Leitch & Vickars, 2009). Noninvasive alternatives have been explored including T2\* MRI for either cardiac or hepatic iron. These technologies are expensive, difficult for claustrophobic patients, and not yet widely available. In addition, retrospective clinical trials have failed to show correlation between T2\* cardiac MRI and elevated ferritin levels (Steensma, 2011). A prospective, randomized clinical trial (ClinicalTrials.gov, 2011) will evaluate the benefit of ICT in 600 patients with low-risk MDS over a five-year period and will include serial serum ferritin levels, morbidity, and mortality, and will help to clarify the validity of serum ferritin levels and the risk-benefit ratio of ICT.

### Chelation Therapy

In the face of growing evidence that TD and iron overload reduce overall survival and leukemia-free survival in patients with MDS, approaches are needed to reduce iron burden in patients with MDS and TD. The main goals of ICT are prevention of increased NTBI concentrations and organ damage (e.g., heart, liver) by reducing iron deposition (Agarwal, 2010). Iron chelators bind to free iron in the bloodstream and mediate excretion through urine and stool (Neufeld, 2006). By reducing levels of toxic NTBI and labile plasma iron, iron chelation agents may reduce iron deposition in organs, limiting secondary organ effects, reducing infection risk, delaying disease progression, and potentially improving hematopoiesis (Gattermann & Rachmilewitz, 2011; Leitch, 2011a; Pullarkat, 2009).

Guidelines for the use of ICT in the MDS population vary globally and are updated regularly based on scientific developments. Effective ICT may require months to years in patients who achieve transfusion independence from active therapies and should be continued indefinitely in patients who remain TD but who continue to benefit from disease-modifying therapies (Leitch, 2011b). Published guidelines recommend ICT consideration in patients with low-risk MDS (low- and intermediate-1-risk by IPSS or WHO RA, RARS, or del[5q]) who require at least two units of packed RBCs per month, have ferritin levels greater than 1,000 ng/ml, and have a life expectancy of one year or longer (National Comprehensive Cancer Network, 2011). In addition, patients at increased risk for secondary organ damage (underlying comorbidities), those considered eligible for HCT, and those with high-risk disease benefitting from disease-modifying therapies also should be considered for ICT.

### Current Therapies

Three agents are available commercially for the treatment of iron overload. Deferoxamine, deferasirox, and deferiprone are all approved in the United States and Europe for disease states other than MDS, although deferiprone is just entering the U.S. market following its approval in October 2011. Each drug has a different iron-binding capacity and requires baseline and ongoing monitoring of renal, hepatic, hematologic, auditory, and ophthalmic function (List, 2010). An overview of key efficacy and safety data, an economic comparison of treatment costs for each agent are provided in this article, and drug profile summaries are listed in Table 5.

#### Deferoxamine

Introduced more than 40 years ago, deferoxamine has been proven effective in patients with thalassemia. It has been shown to reduce the incidence of organ dysfunction and improve

TABLE 3. Clinical Evaluation of Iron Overload

Test or Clinical Evaluation	Advantages	Disadvantages
Ferritin test (most common method)	Noninvasive, widely available, useful in deciding when to initiate therapy, and useful in monitoring treatment effectiveness	Measurement values altered by inflammation, infection, and ascorbic acid (vitamin C) deficiency; does not correlate well with total body iron
Liver biopsy for liver iron concentration (limited use because of risk)	Correlates well with total body iron burden; allows for assessment of liver histology; and high levels predict risk for cardiac disease, endocrine complications, and death	Invasive, accuracy affected by sample size, sampling errors from fibrosis and uneven distribution of iron, and cardiac disease may be present when liver iron levels are low
MRI (used to evaluate abnormal liver enzyme levels in patients with elevated ferritin levels)	Noninvasive, widely available, and correlates well with liver iron concentration by biopsy	Expensive, variety of techniques and analytical programs may limit comparability, cardiac disease may be present when liver iron levels are low
Cardiac iron loading by MRI (used primarily to evaluate cardiac symptoms in patients with elevated ferritin levels)	Noninvasive and correlates with risk for cardiac disease	Expensive and difficult to validate with biopsy specimen

MRI—magnetic resonance imaging

*Note.* From "Anemia, Blood Transfusions, Iron Overload, and Myelodysplastic Syndromes: A Handbook for Adult MDS Patients," by the MDS Foundation, 2011. Retrieved from <http://www.mds-foundation.org/pdf/AnemiaBloodTransfusionsIronOverloadAndMDS-5-16-11.pdf>. Copyright 2011 by the MDS Foundation. Reprinted with permission.

**TABLE 4. Testing at Baseline and Throughout Iron Chelation Therapy**

Test <sup>a</sup>	Frequency of Testing During Iron Chelation Therapy		
	Every Month	Every 3 Months	Once Per Year
Auditory testing			X
Granulocytes	X		
Liver iron stores (T2* MRI)			X
Myocardial iron stores (T2* MRI)			X
Ophthalmic testing			X
Physical examination and review of medications	X	X	X
Serum creatinine	X		
Serum ferritin		X	
Serum transaminase	X		

<sup>a</sup>All tests were performed at baseline.

MRI—magnetic resonance imaging

*Note.* From "Anemia, Blood Transfusions, Iron Overload, and Myelodysplastic Syndromes: A Handbook for Adult MDS Patients," by the MDS Foundation, 2011. Retrieved from <http://www.mds-foundation.org/pdf/AnemiaBloodTransfusionsIronOverloadAndMDS-5-16-11.pdf>. Copyright 2011 by the MDS Foundation. Reprinted with permission.

survival outcomes in these patients (Messa et al., 2010). Chronic deferoxamine use slows hepatic iron accumulation and decreases or prevents the progression of hepatic fibrosis. Deferoxamine is primarily eliminated through the kidneys and is contraindicated in patients with severe renal impairment. Ocular and auditory adverse effects have been observed with deferoxamine, with postmarketing reports indicating a potential increased risk in older adults (Novartis Pharmaceuticals, 2007). Visual acuity tests and audiometry tests are recommended.

Because of its poor oral bioavailability and short half-life, deferoxamine requires five to seven overnight subcutaneous transfusions per week (Neufeld, 2010). That inconvenience often results in poor adherence and is a major limitation for its use (Hershko, 2005). Costs for deferoxamine vary based on mechanism of infusion (balloon versus pump) and body weight, in addition to normal monitoring costs (McLeod et al., 2009). A 500 mg vial costs \$17.37 (Stumpf, 2007). Drug-related equipment and treatment drug alone contribute to 43% and 19% of annual deferoxamine costs, respectively (Payne et al., 2008).

## Deferasirox

An oral ICT, deferasirox was approved by the U.S. Food and Drug Administration (FDA) in 2005. A one-year study of 341 patients with MDS showed that deferasirox significantly reduced serum ferritin levels by 253 mcg/L from a median baseline level of 2,730 mcg/L (Gattermann et al., 2008). A phase

II trial showed that deferasirox significantly reduced liver iron concentration in patients with MDS who required frequent RBC transfusions (Novartis Pharmaceuticals, 2011).

Deferasirox was generally well tolerated in clinical trials. The most frequent adverse events were mild (e.g., transient nausea, vomiting, abdominal pain, skin rash), dose dependent, and subsided over time with continuous treatment (Cappellini, 2008; Cappellini et al., 2011). Mild nonprogressive serum creatinine level increases and reversible elevations of liver transaminases have been observed. The FDA has issued a black box warning stating that deferasirox may cause renal or hepatic impairment, including failure, or gastrointestinal hemorrhage (Novartis Pharmaceuticals, 2011). Those events occurred more frequently in older adults, patients with high-risk MDS, those with predisposing renal or hepatic impairment, or those with low platelet counts (less than  $50 \times 10^9/L$ ). Renal and hepatic function should be closely monitored in patients taking deferasirox (Porter et al., 2008). Costs for deferasirox treatment also vary with body weight and includes costs for creatinine and renal monitoring. A 125 mg tablet costs \$13.42 (Stumpf, 2007).

## Deferiprone

Deferiprone has been available for more than 25 years in 59 countries for iron overload treatment in patients with thalassemia. Based on the analysis of results from 12 clinical trials, deferiprone was approved for use in the United States for the treatment of patients with thalassemia with iron overload who have had inadequate responses to prior chelation therapies (FDA, 2011).

The iron-binding efficiency, drug-to-iron ratio, is 3:1, which is less efficient than deferoxamine and deferasirox (Hershko, 2005). In 48 patients with MDS, deferiprone maintained or decreased iron stores in 73% of patients with serum ferritin levels less than 2,000 mcg/L and in 46% of patients with serum ferritin levels greater than 2,000 mcg/L. Gastrointestinal adverse events (38% of patients) were most common (Cermak et al., 2011). Deferiprone also was effective in decreasing cardiac and hepatic iron stores in patients with thalassemia (Messa et al., 2010). Agranulocytosis was reported, but was a rare occurrence. Deferiprone treatment necessitates neutrophil monitoring, and costs vary based on body weight. Based on listings in New Zealand, deferiprone costs \$5.33 per 500 mg tablet (Pharmaceutical Management Agency, 2010).

## Cost Comparison of Available Iron Chelation Therapies

Appropriate ICT choice for patients is a balance of both efficacy and cost. Although deferasirox and deferiprone are more ideal chelators based on oral administration and better access to intracellular pools because of their charged nature, deferoxamine can dramatically reduce iron overload-associated cardiac toxicity when administered via central catheter and remains the standard therapy for cardiac iron overload (Neufeld, 2006). Cost comparisons of the three drugs are complicated by international price differences and prescribing patterns. A meta-analysis conducted to analyze clinical trial data as well as economic evaluations for all three agents found no differences in iron removal efficacy from liver and blood, although the authors acknowledged limitations based

on heterogeneity of study designs and relatively few comparisons with deferiprone (McLeod et al., 2009). Because of the lack of long-term data for the efficacy of deferasirox, a short-term, one-year model was used to compare the costs and benefits of ICT in patients with TD sickle-cell anemia and  $\beta$ -thalassemia for deferasirox versus deferoxamine and deferiprone. That analysis included cost estimates of drug-specific monitoring beyond any testing common to all three drugs. Although deferiprone has the least expensive annual costs, its side effect profile likely means that it will remain a second-line ICT for patients with an inadequate response to other treatments (Neufeld, 2006). Additional controlled studies comparing the annual cost, efficacy, QOL impact, and cost of side effect management are needed to better define the cost effectiveness of each ICT.

Phlebotomy

Because toxicity risks with some chelating agents are increased in patients with only slightly elevated iron burdens, continued chelation is not recommended for patients once serum ferritin levels drop within an acceptable range (less than 500 ng/ml) (Fausel, 2010). For patients with favorable hematologic response to disease-modifying therapies, phlebotomy may be an option for continued management of iron overload (Kurtin & Demakos, 2010).

Evaluation of Response to Chelation Therapy

During ongoing chelation therapy, serum ferritin level monitoring should continue to ensure that patients are responding to the chosen ICT (Fausel, 2010). Ideally, the objective of ICT is to reduce iron overload to the extent that serum ferritin concentrations are maintained at levels less than 1,000 ng/ml. Iron chelation therapy should be continued as long as RBC transfusions are received or as long as evidence exists of continued iron overload based on accepted measures. Discontinuation of ICT is recommended for patients who are intolerant or in those no longer requiring transfusions who have maintained serum ferritin less than 1,000 ng/ml (Leitch, 2011b).

Global Impact of Iron Overload

In addition to direct effects on both physiologic outcomes and resource use from iron overload-related comorbidities, the global impact of iron overload in MDS treatment includes cost of transfusions and associated healthcare use. A study of the Medicare claims database of patients from the first quarter of 2003 evaluated 512 patients aged 65 years and older with newly diagnosed MDS, 40% of whom were TD with three years of follow-up (Goldberg, Chen, Corral, Guo, & Laouri, 2010).

TABLE 5. Current Iron Chelation Therapies in Patients With Iron Overload Secondary to Receiving Blood Transfusions				
Parameter	Deferoxamine	Deferasirox	Deferiprone	Phlebotomy
Dosage	0.5–1 mg per day IM 20–40 mg/kg per day SC	20–40 mg/kg per day orally	75 mg/kg per day orally	Venipuncture
Half-life (hours)	6	8–16	2–3	N/A
Schedule	Administered in 8–24 hours, 5–7 days per week	Once daily	Three times daily	Once or twice weekly
Routes of iron excretion	Urine, stool	Urine, stool	Urine	N/A
Toxicities and adverse effects	Ocular, auditory, localized site injection reaction, allergic reaction, growth and skeletal abnormalities	Renal, hepatic, rash, myelosuppression, gastrointestinal disturbances	Gastrointestinal and hepatic disturbances, myelosuppression	Noninvasive
Screening	Annual eye and audiometry examinations	Monthly urinalysis, serum creatinine check, liver function; annual eye and auditory examinations	Weekly complete blood count	Not required
Pharmaceutical company	Novartis	Novartis	Apotex	N/A
Annual costs (\$) <sup>a</sup>				N/A
Total	11,478–23,859	29,563	8,849	
Monitoring <sup>b</sup>	–	229	2,150	
Administration	2,213–14,594 <sup>c</sup>	0	0	
Drug	9,265	29,338	6,700	
Web site	www.desferal.com	www.exjade.com	www.ferriprox.com	N/A
<sup>a</sup> Assuming mean patient weight of 50 kg				
<sup>b</sup> Monitoring costs in excess of normal testing are required with deferoxamine treatment (e.g., auditory)				
<sup>c</sup> Cost of 100% pump use versus 100% balloon infuser use for administration				
IM—intramuscular; N/A—not applicable; SC—subcutaneous				
Note. Based on information from McLeod et al., 2009; Novartis Pharmaceuticals, 2007, 2011; U.S. Food and Drug Administration, 2011.				

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## Implications for Practice

- ▶ Patients with myelodysplastic syndromes (MDS) and transfusion dependence with life expectancy of more than one year are most at risk for the secondary effects of transfusion-related iron overload.
- ▶ Baseline and periodic follow-up assessments are critical for identification of patients at risk for iron overload, early identification of iron-related toxicity, and selecting patients who may benefit from iron chelation therapy.
- ▶ Iron chelation therapy may provide benefit for selected transfusion-dependent patients with MDS, including improvement in quality of life.

Medicare costs in patients with TD (\$88,824 per patient) were three times higher compared with nontransfused patients (\$29,519 per patient) ( $p < 0.001$ ). Patients with MDS and TD had higher rates of dyspnea, cardiac disease, diabetes, hepatic disease, and infection than nontransfused patients with MDS, as well as greater numbers of hospitalization and office visits. Although the data demonstrate that healthcare costs are significantly greater in patients with TD compared with transfusion-independent patients, the impact of ICT on those costs is unknown because the population examined had infrequent use of ICT. Transfusion administration costs accounted for only 19% of total Medicare costs in patients with TD, implying that the majority of the increased cost in these patients was from either comorbidities or complications related to iron overload (Goldberg et al., 2010). When further controlled for baseline characteristics, multivariate analysis revealed that the primary independent cost drivers for patients with MDS was TD and clinical complications (e.g., cardiac issues, dyspnea, sepsis, pneumonia).

Given the high costs associated with both TD MDS and ICT, a comparative cost analysis of transfusion versus chelation agents should be considered. Transfusion costs include blood products, personnel, and clinic time, as well as diagnostic monitoring to determine transfusion frequency and iron levels. Table 5 estimates the ICT costs for the various agents but does not include the costs normally associated with iron level monitoring (e.g., auditory monitoring, iron monitoring). Although the costs of continued transfusions plus ICT are greater than those for transfusions alone, studies have demonstrated that TD has a negative effect on survival in patients with low-risk MDS (Cermak et al., 2009; Goldberg et al., 2010; Malcovati et al., 2005). Iron overload is likely to be a factor in this issue based on the correlation of decreased overall survival with increased ferritin levels (Garcia-Manero et al., 2008; Malcovati, Della Porta, & Cazzola, 2006). Therefore, costs and potential toxicities associated with ICT must be weighed against the very real risk of early death. In the future, more prospective studies will be needed to better clarify the cost-benefit ratio of ICT for patients with low-risk MDS.

## Future Management of Iron Overload

Symptomatic anemia occurs at some point during the disease for the majority of patients with MDS, and 80%–90% will re-

ceive long-term RBC transfusions (Jabbour, Kantarjian, Koller, & Taher, 2008). Studies have shown that patients with TD with high iron levels are at risk for shorter overall survival and a higher incidence of secondary organ damage. Given the older age of many patients with MDS and the increased comorbidity incidence in older adults, the MDS population is at particular risk for the deleterious effects of chronic anemia and TRIO. Safe and effective iron overload treatment in patients with MDS requires an understanding of the disease process, physiology of iron homeostasis, and the impact of iron deposits to various organs. Continued refinement of consensus guidelines for indications for ICT requires ongoing patient enrollment in prospective clinical trials. Familiarity with the currently available iron overload treatment options, consideration of the cost-benefit ratio, as well as individual patient characteristics, potential side effects, and regimen adherence, will improve patient outcomes.

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