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Iron overload in myelodysplastic syndromes

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Iron overload in myelodysplastic syndromes

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See page S16 or <http://ce.ashp.org> to locate the continuing-education learning objectives, self-assessment questions, and instructions covering the articles in this supplement.

Iron overload in myelodysplastic syndromes

Introduction

R. DONALD HARVEY AND CHRISTOPHER A. FAUSEL

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Myelodysplastic syndromes (MDS) include a variety of hematological disorders that are diagnosed in approximately 10,000 people each year in the United States.¹ Complications associated with MDS include cytopenias and eventual progression to acute myelogenous leukemia.^{2,3} The presence of chronic, symptomatic anemia in patients with MDS results in the regular use of red blood cell (RBC) transfusions as a supportive care measure, which can lead to a number of problems associated with transfusion dependence, including iron overload. The clinical consequences of iron overload in patients with MDS include organ damage and dysfunction, an increased frequency of stem cell transplant-related complications, and reduced survival rates.^{4,5} To address this particular clinical need, a number of MDS treatment guidelines and consensus statements have been published in recent years,

including specific management strategies for iron overload.

Since many patients with lower-risk MDS become candidates for iron chelation therapy (ICT), an overview of currently available chelators will be presented. Although prospective, randomized, controlled clinical trials are few, available information suggests that use of these agents can provide beneficial clinical outcomes in appropriately selected patients. In the latest set of guidelines for patients with MDS, the National Comprehensive Cancer Network has recommended that either deferoxamine or deferasirox be used for ICT when patients have received more than 20 RBC transfusions, particularly when transfusions continue for extended periods of time, as in patients with lower-risk disease.⁶ When devising management plans for transfusion-dependent patients with MDS, a balance between the potential for improved clinical outcomes, com-

parative economic burden, and incidence of toxicity associated with iron overload and treatment with ICT will need to be carefully considered.

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Myelodysplastic syndromes and the role of iron overload

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Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal lineage disorders that result in varying severity of cytopenias.^{1,2} This diverse group of disorders is characterized by bone marrow failure, dysplastic changes in hematopoietic cells, genomic instability, and a tendency to accumulate clonal undifferentiated blast cells. Data collected from the Surveillance, Epidemiology, and End Results Program from 2001–2003 indicate that >10,000 cases of MDS are diagnosed annually in the United States, with a median age at diagnosis of 76 years.³ The 3-year observed survival rate was only 35% for patients with MDS, with older patients (>60 years) and male patients having significantly reduced survival rates.³ Disease morbidities are primarily due to complications associated with cytopenias and evolution to acute myelogenous leukemia (AML). In particular, anemia (hemoglobin [Hb] <10 g/dL) is present in 80% of patients at diagnosis.^{2,4}

Use of a classification system for MDS is helpful for determining prognosis and for initiating treatment. Several different classification

Purpose. The epidemiology of myelodysplastic syndromes (MDS) and iron overload, recent clinical findings that highlight the importance of actively managing iron overload, and recommendations for initiating and maintaining iron chelation therapy (ICT) are summarized.

Summary. MDS are a variety of hematological disorders with differing time courses. Disease morbidities are primarily due to cytopenias and evolution to acute myeloid leukemia. Iron overload is a serious complication in patients with MDS due to the long-term use of red blood cell transfusions in patients with symptomatic anemia. Clinical consequences of iron overload include end-organ damage and dysfunction, an increased frequency of transplant-related complications, and reduced survival rates. To prevent these

complications, recommendations for initiating and maintaining ICT should be followed by clinicians caring for patients with MDS and iron overload.

Conclusion. As current therapeutic options for patients with MDS do not always reduce the transfusion burden, many patients will still need long-term transfusion therapy. Strategies for the management of iron overload in MDS should be considered early in the disease course and in appropriate patients in order to prevent negative clinical outcomes associated with excessive iron accumulation.

Index terms: Blood; Epidemiology; Heavy metal antagonists; Iron overload; Mortality; Myelodysplastic syndromes

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systems for MDS have been developed and used in clinical practice over the years, including the International Prognostic Scoring System (IPSS), French American British classification, and the World Health Organization (WHO) classification.⁵ IPSS has become widely accepted, as it incorporates a variety of different readily available clinical factors

including bone marrow blast percentage (i.e., <5%, 5–10%, 11–20%, 21–30%), cytogenetics (i.e., good = diploid, loss of Y chromosome, deletion of 5q and 20q chromosomes; poor = complex [three or more abnormalities], chromosome 7 abnormalities; intermediate = others), and cytopenias (i.e., hemoglobin <10 g/dL, neutrophils <1.8 × 10⁹/L, or

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platelets $<100 \times 10^9/L$), and provides a risk score that reliably predicts survival and risk of transformation to AML.^{6,7} Within this system, four risk groups have been identified based on the total IPSS score: low (risk score 0), intermediate-1 (risk score 0.5-1), intermediate-2 (risk score 1.5-2), and high (risk score >2).

Treatment strategies for patients with MDS are driven by analysis of risk using IPSS scores, as well as patient age and clinical performance status. Low-intensity pharmacological therapies such as biological modifiers or low-intensity chemotherapy are often recommended for patients with low-risk to intermediate-risk disease, while high-intensity therapies, including intensive induction chemotherapy or allogeneic hematopoietic stem cell transplantation (HSCT), are needed for high-risk patients, with the ultimate goal of improving hematopoiesis and quality of life.^{1,8} HSCT is the only known curative therapy for patients with MDS; however, according to the British consensus guidelines and the National Comprehensive Cancer Network (NCCN) clinical practice guidelines, this intensive therapy option is only recommended for use in a small subset of eligible patients.^{8,9} Some factors contributing to the increased success of allogeneic HSCT include younger age, short disease duration, bone marrow blast cells $<10\%$, good risk cytogenetics, few cytopenias, and the presence of a matched sibling donor.^{8,9} When allogeneic HSCT or intensive chemotherapy are not viable options, recommendations for most patients include ongoing supportive care measures and the possibility of incorporating newer therapies, such as immunomodulators (thalidomide, lenalidomide), hypomethylating agents (azacitidine, decitabine), or experimental therapies in the context of relevant clinical trials.^{8,10}

As most patients with MDS experience hematopoietic failure, they

are generally treated from the time of diagnosis with supportive care to treat symptoms of and complications associated with anemia, neutropenia, and thrombocytopenia. The use of red blood cell (RBC) transfusions to treat symptomatic anemia and platelet transfusions for severe thrombocytopenia is generally recommended.^{8,9} Published information is limited regarding the use of prophylactic antibiotics for chronic neutropenia in patients with MDS, but this may provide benefit for selected patients.¹¹ Patients with MDS typically have chronic anemia, which then results in transfusion dependence and significant decreases in patient quality of life. Research has demonstrated that treatment with hematopoietic growth factors may help reduce the need for RBC transfusions in 20–25% of patients with MDS.^{11,12} Clinical studies with other therapies, such as antithymocyte globulin, azacitidine, decitabine, thalidomide, and lenalidomide, have also demonstrated decreases in transfusion requirements due to their ability to target impaired cellular differentiation in MDS.¹¹ However, if RBC transfusion dependence cannot be eliminated, iron overload may result and iron chelation therapy (ICT) is recommended. Generally, ICT should be initiated for patients undergoing long-term transfusions who have received 5 g of iron (25 units)⁹ or who have previously received ≥ 20 –30 units of RBCs.⁸

Transfusional iron overload

The balance of iron absorption, distribution, and storage in the body is important to maintain because both iron deficiency and iron overload can cause harm. Most adult men have 35–45 mg of iron per kg of body weight, of which the vast majority can be found in circulating erythrocytes. Iron is stored in association with ferritin within hepatocytes and reticuloendothelial macrophages, which can then be made available in

response to acute need (Figure 1).^{13,14} Iron absorption from dietary sources occurs mainly in the duodenum at a rate of 1–2 mg of iron each day.¹³ As the process of erythropoiesis requires around 25–30 mg of iron daily, recycling iron from aged erythrocytes via phagocytosis of reticuloendothelial macrophages is an important mechanism in maintaining iron homeostasis.^{13,14}

Iron stores need to be carefully monitored because the body has limited endogenous mechanisms to remove excess iron. In healthy adults, iron regulation occurs via sloughing of intestinal cells and blood loss in addition to modulating intestinal uptake.^{13,15} Because up to 90% of patients with MDS will receive RBC transfusions for treatment of anemia, this population is susceptible to problems associated with transfusion dependence and iron overload.¹⁶ Normally, iron redistribution is facilitated by binding to transferrin; however, during long-term transfusion use, plasma iron levels exceed the binding capacity of transferrin, which leads to accumulation of toxic iron amounts in tissue.¹⁵ Elevated iron from long-term transfusion use or disease-related increased dietary iron uptake can lead to persistent oxidative stress, progressive tissue damage, and eventual organ failure (e.g., liver, heart).^{15,16} Each RBC unit contains approximately 200–250 mg of elemental iron, so patients who receive two RBC units per month receive an excess of 5–6 g of iron per year (normal serum iron concentration = 60–150 $\mu\text{g/dL}$). At this rate, patients will become iron overloaded after approximately 20–30 transfusions.¹⁶ The occurrence of iron overload in patients with MDS is further complicated by the fact that as part of the disease, patients demonstrate ineffective hematopoiesis, which then stimulates increased absorption of iron from dietary sources.^{15,16}

The evolution of effective diagnostic methods to detect total body

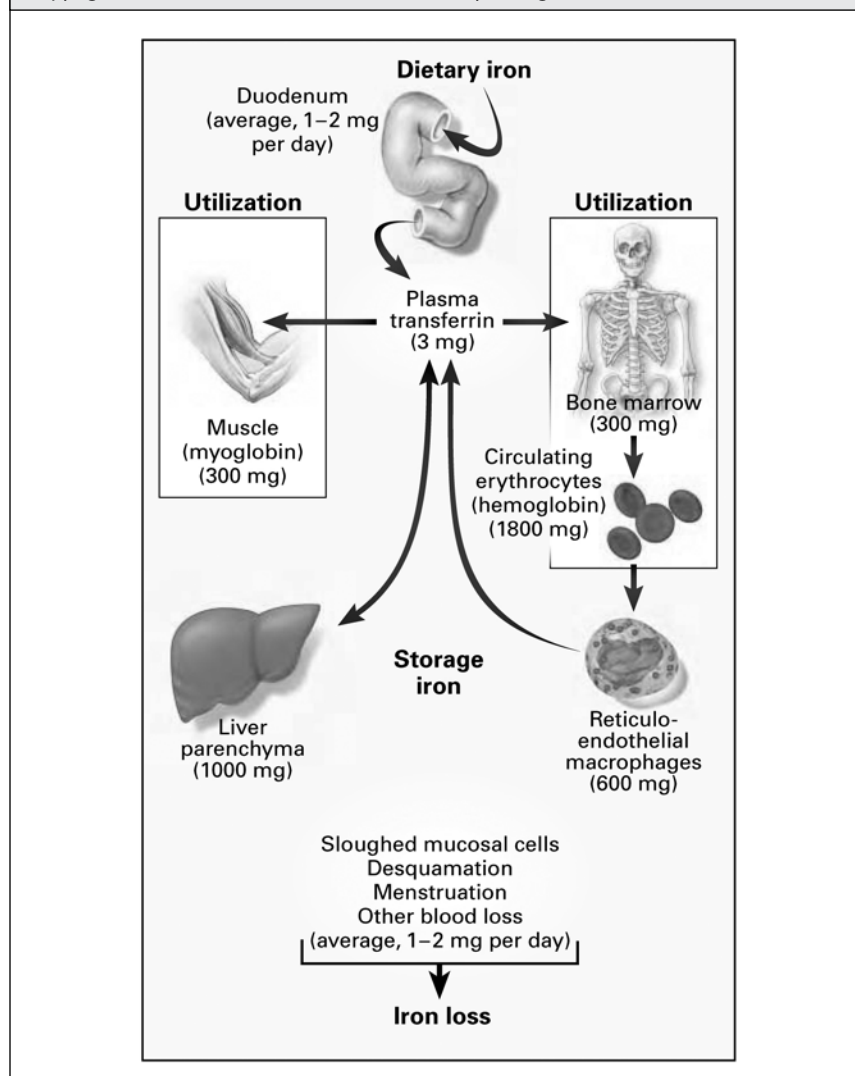
iron stores will aid in the management of iron overload. Several tools are currently available to evaluate iron overload in transfusion-dependent patients with MDS (Table 1).¹⁷ Measurement of serum ferritin is the most commonly used indirect measure of iron stores; however, serum ferritin levels are falsely elevated in the presence of infection, inflammation, or liver disease. Another laboratory evaluation that may correlate to total body iron stores is measurement of transferrin saturation.^{17,18} As hepatic iron concentration has been shown to reliably correspond to total body iron stores,¹⁹ a liver biopsy is the standard and most direct measure of liver iron concentration. However, because of the invasiveness of this technique, it often cannot be used for patients with MDS due to the potential for complications such as bleeding, infection, and hemobilia.¹⁶ Magnetic resonance imaging (MRI) with R2-star (R2*) or T2-star (T2*) parameters and superconductive quantum interference device (SQUID) are noninvasive but effective tools to measure liver and cardiac iron stores.^{16,17}

Clinical consequences of transfusion dependence in patients with MDS

A variety of clinical manifestations can occur in transfusion-dependent patients with MDS. Specifically, iron overload has been found to lead to end-organ damage and dysfunction, an increased frequency of transplant-related complications, and reduced survival rates. The frequency of these complications coupled with the fact that most MDS treatment options do not significantly reduce RBC transfusion requirements leads to the conclusion that therapeutic strategies to address transfusion-related iron overload in these patients are needed.

Organ damage associated with iron overload most commonly results in cardiac, hepatic, or endocrine

Figure 1. Distribution of iron in adults. Reprinted, with permission, from reference 13. Copyright © 1999 Massachusetts Medical Society. All rights reserved.



dysfunction. Heart failure as a consequence of iron overload is the primary cause of death in β -thalassemia patients.¹⁵ In the liver, fibrosis and cirrhosis are the primary complications of iron overload. Damage to the endocrine system can lead to hypogonadism, hypothyroidism, and diabetes.¹⁵ In a retrospective analysis, transfusion frequency was associated with increased risk of complications due to iron overload, including cardiomyopathy, heart failure, heart-rhythm disorders, diabetes, and liver disease.²⁰ In another retrospective

study, increased serum ferritin was found to be associated with fatal comorbidities, primarily cardiac and liver dysfunction.²¹

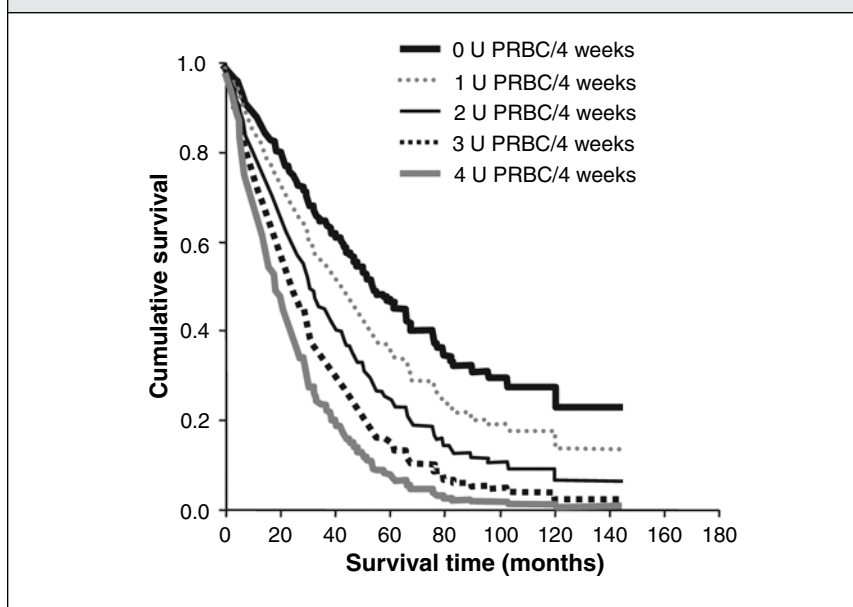
Although needed for most patients with MDS, RBC transfusions have been associated with a negative effect on survival, with a greater effect on low-risk patients. As patients become increasingly dependent on transfusions, prognoses become worse (Figure 2).¹⁸ In a study of 467 patients, development of iron overload significantly reduced survival with a hazard ratio (HR) of 1.36 for every

Table 1. Diagnostic Tools for the Evaluation of Iron Status in Patients with MDS Receiving Regular Blood Transfusions^{17,a}

Diagnostic tool	Current place in the evaluation of iron status in patients with MDS	Clinical significance
Serum ferritin	Simplest, noninvasive measure of iron stores	Level of serum ferritin parallels the concentration of iron stored in the body but inflammatory states and liver disease can disproportionately elevate the circulating protein.
Transferrin saturation	Practical screening test for locating the site of iron accumulation	Isolated reticuloendothelial iron overload is associated with normal transferrin saturation; parenchymal iron overload is associated with elevated transferrin saturation.
Serum hepcidin ^b	Only used as a research tool at present	Inappropriately low hepcidin levels in patients receiving regular transfusions may indicate a high risk of parenchymal iron overload.
T2* MRI technique to quantify LIC	Likely to become a routine, noninvasive method of assessing LIC	Patients with elevated LIC are at risk of developing myocardial iron overload.
T2* MRI technique to quantify myocardial iron concentration	Likely to become a routine, noninvasive method of assessing myocardial iron	A pathological value (<20 msec) indicates a high risk of developing cardiac disease.

^aMDS = myelodysplastic syndromes, MRI = magnetic resonance imaging, LIC = liver iron concentration.
^bA peptide produced in the liver that regulates iron absorption.

Figure 2. Overall survival of patients with myelodysplastic syndromes according to the intensity of their red blood cell (RBC) transfusion requirement, calculated as the number of packed RBC (PRBC) units (U) per four weeks. Reprinted, with permission, from reference 18.



500 ng/mL increase in serum ferritin above 1000 ng/mL ($p < 0.001$).²² In MDS patients classified using WHO subgroups of refractory anemia or refractory anemia with ringed sider-

oblasts (corresponds to patients with IPSS low-risk classification), a significant difference of iron overload on survival was still observed (HR = 1.51; $p < 0.001$) whereas it was not

significant in those with refractory cytopenia with multilineage dysplasia (RCMD) or RCMD with ringed sideroblasts (corresponds to patients with IPSS high-risk IPSS classification) (HR = 1.34; $p < 0.20$).²²

The incidence of iron overload also plays an important role in allogeneic HSCT outcomes. A retrospective series of 427 patients undergoing HSCT, of whom 129 had acute leukemia/MDS, evaluated the risk of sinusoidal obstruction syndrome (SOS; a syndrome following bone marrow transplant of hepatomegaly, right upper quadrant pain, jaundice, weight gain, and ascites) and the relationship to ferritin values before HSCT in a multivariate model.²³ SOS was diagnosed in 21% of patients (88/427) in the posttransplant period, and median ferritin values were higher in those patients who developed SOS (917.5 versus 531, $p = 0.002$). Additionally, patients with ferritin values >1000 ng/mL had lower five-year overall survival rates (42%) compared with patients with ferritin ≤1000 ng/mL (73%, $p < 0.001$; log-rank test).²³ In another

study, transfusion burden (as reflected by serum ferritin >2500 ng/mL) was correlated with a greater probability of severe acute graft-versus-host disease ($p = 0.03$).²⁴ Additionally, three-year survival was inferior in those patients with ferritin >2500 ng/mL (28%) compared to patients with lower ferritin values (50%, $p = 0.03$) measured before transplant.²⁴ These studies suggest a role for ICT before transplant to decrease the effects of iron overload that result from transfusion dependence.

One of the goals of MDS treatment is to reduce transfusion requirements. In patients with low-risk MDS, the use of recombinant human erythropoietin has resulted in erythroid responses of around 20–25%, with the combination of granulocyte colony-stimulating factor and erythropoietin increasing erythroid response rates to around 50%.^{12,25} Many patients do not fully respond to growth factors, as 58 of 72 (80%) of transfusion dependent and 72 of 100 (72%) of all MDS patients with anemia, respectively, were nonresponders following treatment with erythropoietin.^{26,27} Treatment with darbepoetin alfa led to a 55% (29 of 53) failure rate in MDS patients with anemia.²⁸ Lenalidomide, azacytidine, or decitabine can produce transfusion independence in patients with MDS. When 148 patients with MDS and a chromosome 5q deletion were treated with lenalidomide, 62% responded to treatment and maintained transfusion independence for at least one year.²⁹ Treatment with decitabine resulted in progressively increasing transfusion independence with each cycle of treatment compared with no difference in patients receiving supportive care.³⁰ In patients with MDS treated with azacytidine, 65 out of 99 patients required transfusions at the beginning of the study and 30 of these patients did not significantly decrease their RBC transfusion requirements over the course of the study.³¹ Results

from these studies of hematopoietic growth factors, immunomodulating drugs, and hypomethylating agents in patients with MDS suggest that as the need for transfusions is not eliminated, patients will need to be monitored closely for iron overload and subsequent complications.

ICT treatment guidelines in patients with MDS

Due to the serious clinical consequences associated with iron overload in patients with MDS, a series of guidelines and consensus statements have been published on its management.^{8,9,32–34} Organizations who have compiled recommendations include the NCCN, the Italian Society of Hematology, the UK MDS Guidelines Group, the Nagasaki Group, and the MDS Foundation, whose recently published consensus statement is summarized in Table 2.

Generally, guidelines agree that RBC transfusions remain a critical component in the care of patients with MDS; therefore patients undergoing long-term transfusion support should be considered for ICT. However, the specific recommendations for initiation and ongoing management of iron overload vary by region and organization. In considering initiation of ICT, patients with low-risk MDS who will receive long-term RBC transfusions will be most likely to benefit from ICT.³⁵ Recommendations regarding the trigger to initiate ICT vary from a simple definition of transfusion dependency with serum ferritin 1000–2000 ng/mL³⁴ to a requirement of two RBC units/month for more than one year.³² Most organizations agree that patients should have serum ferritin concentrations above 1000 ng/mL although the NCCN guidelines suggest initiating ICT with serum ferritin levels above 2500 ng/mL.^{8,32,35}

According to the guidelines, ICT should be monitored by targeting appropriate serum ferritin levels for successful management of iron

overload during the course of continued transfusion support. Many of the guidelines recommend the use of deferoxamine for ICT based on available evidence.^{8,9,33} However, one set of guidelines noted that the advent of oral chelators may be useful to help overcome problems associated with the cost of infusion pumps and patient adherence concerns with the subcutaneous administration of deferoxamine.³⁴ Two of the guidelines were published before the European approval of deferasirox, so it was not included in their recommendations.^{9,33} NCCN recommends use of either deferoxamine or deferasirox and the MDS Foundation leaves the decision to the discretion of the treating physician.^{8,32} Regardless of which agent is used, it is important to actively monitor patients being treated with ICT. Most organizations recommend maintaining therapy as long as serum ferritin levels remain above 1000 ng/mL as a marker;³⁵ however, the NCCN guidelines note that screening methods using hepatic MRI evaluations or SQUID are more precise for measuring the effects of ICT on the reversal of iron overload.⁸

Conclusion

Due to the high prevalence of anemia in patients with MDS, supportive care with long-term RBC transfusion therapy is required, particularly in patients with low-risk disease and a longer life expectancy. Development of agents that help reduce transfusion dependency is an important focus and an ongoing area of research in MDS. However, many patients will still require long-term RBC transfusions, and as the endogenous mechanisms for removal of iron are limited, initiation of ICT will be necessary. Standard recommendations for initiation and maintenance of ICT should provide an optimal standard of care for transfusion-dependent patients with MDS.

Table 2.
Consensus Guidelines for the Management of Iron Overload in Patients with MDS by the MDS Foundation Working Group^{32,a}

Topic	Consensus Statement
Strategies for minimizing iron accumulation and cardiac risk	Hemoglobin transfusion threshold = 10 g/dL
Tools to assess and monitor body iron levels	Iron overload should be monitored by serum ferritin and TSAT. Liver imaging with T2 MRI and SQUID are not considered essential and should be further investigated.
Strategies for monitoring transfusion burden	No. individual patient transfusions aids a clinician in determining whether to initiate ICT. A standardized method of monitoring patient transfusion burden (e.g., personal RBC transfusion diary, blood bank transfusion tracking data, or automatic alerts sent after receiving 20 units of blood) will facilitate decision making.
When to assess and monitor body iron levels	Body iron stores should be assessed at diagnosis of MDS and at regular intervals thereafter. Transfusion-dependent patients require monitoring every 3–4 mo. ICT monitoring instructions including measurement of body iron stores, serum ferritin levels, and organ function, should be followed after initiation of ICT.
Criteria for the initiation of ICT for MDS	Serum ferritin reaches 1000 ng/mL or transfusions 2 units/mo continuing for at least 1 yr and a need to preserve organ function.
ICT for non-hemoglobinopathy transfusional iron overload patients	Consider for patients with idiopathic myelofibrosis who are allogeneic SCT candidates.
Patient selection	MDS patients most likely to benefit from ICT include: Transfusion dependent (2 units/mo × 1 yr) Ferritin levels >1000 ng/mL Low-risk MDS (Int-1, RA, RARS, 5q-) Life expectancy >1 yr without comorbidities that would limit prognosis Allogeneic SCT candidates Need to preserve organ function
Duration of ICT	ICT should continue as long as patient requires transfusions and iron overload remains clinically relevant.
Treatment in iron overload in MDS	MDS patients are likely to benefit from ICT. Variations such as availability of agents and reimbursement should be considered.

^aMDS = myelodysplastic syndromes, TSAT = transferrin saturation, SQUID = superconducting quantum interference device, ICT = iron chelation therapy, RBC = red blood cells, SCT = stem cell transplant, Int-1 = intermediate-1, RA = refractory anemia, RARS = refractory anemia with ringed sideroblasts, 5q- = chromosome 5q deletion.

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Iron chelation therapy in myelodysplastic syndromes

CHRISTOPHER A. FAUSEL

Myelodysplastic syndromes (MDS) are an incurable spectrum of hematologic malignancies characterized by progressive cytopenias and the emergence of a monoclonal myeloid blast population in the bone marrow that ultimately evolves to an acute myeloid leukemia presentation. The majority of patients with MDS will develop symptomatic anemia over the course of disease and 80–90% will be treated with long-term red blood cell (RBC) transfusions.^{1,2} Due to the lack of endogenous mechanisms for the removal of excess body iron, iron overload occurs, which then results in a variety of negative clinical outcomes including hepatic, pituitary, pancreatic and cardiac dysfunction, cardiac failure, and decreased survival.³

Rationale for iron chelation therapy for patients with myelodysplastic syndromes

Several general strategies exist for removal or prevention of accumulation of toxic levels of iron in the body. Phlebotomy can be used 1–2 times per week to remove up to one pint of blood, which contains approximately 200 mg of iron, in patients who do not have compromised

Purpose. To understand how to appropriately recognize and manage iron overload with iron chelation therapy (ICT) in patients with myelodysplastic syndromes (MDS), evaluation of the role of different agents available for management of iron overload, including efficacy, safety, and economic considerations for transfusion-dependent patients with MDS, is provided.

Summary. Patients with MDS have a high incidence of anemia, which often requires treatment. Supportive care measures such as red blood cell transfusions and erythroid colony stimulating factors are mainstays of therapy. Use of long-term transfusion therapy has limitations in patients with MDS due to the risk of developing iron overload. Strategies to manage iron overload include phlebotomy and ICT with agents such as deferoxamine and deferasirox. Data evalu-

ating pharmacologic therapy for treatment of iron overload in patients with MDS suggest timely intervention can mitigate the morbidity associated with this clinical syndrome.

Conclusion. Development of practical management strategies to implement and optimize ICT using deferoxamine and deferasirox will be important to provide optimal care for transfusion-dependent patients with MDS.

Index terms: Anemia; Blood; Colony stimulating factors; Deferasirox; Deferoxamine; Diagnosis; Economics; Epidemiology; Heavy metal antagonists; Iron overload; Myelodysplastic syndromes; Phlebotomy; Toxicity

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erythropoiesis.⁴ Use of therapies that reduce transfusion dependence can help prevent or delay problems associated with iron overload,⁵ but ultimately many patients with MDS will require iron chelation therapy (ICT). The definitive goal of ICT is to sustain safe iron concentrations in tissue. To achieve this endpoint, the dosing schedule of each iron chelator should take into account the need to maintain balance between

excess body iron and exposure to the iron chelating agent that may cause treatment-related toxicity.⁴

There are currently three iron chelating agents available for use in clinical practice: deferoxamine (Desferal), deferasirox (Exjade), and deferiprone (Ferriprox), although only the first two are approved for use in the United States (Table 1).⁶⁻⁹ Deferoxamine is indicated for the treatment of acute iron intoxication

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and of chronic iron overload due to transfusion-dependent anemias. Data have accumulated for over 30 years regarding the effectiveness of deferoxamine to prevent the clinical consequences of iron overload and promote long-term survival in transfusion-dependent patients.^{4,6} As an oral chelating agent, deferoxamine has been used extensively in clinical studies for patients with β -thalassemia and found to provide stable or decreased serum ferritin levels and tissue iron content compared with patients treated with deferasirox.^{2,4} However, the observation of relatively serious adverse events such as agranulocytosis, hepatic fibrosis, and arthropathy have delayed the approval of this agent for use in the United States.¹⁰ Deferasirox is another oral iron chelator that has been available for use in the United States since 2005. The extended half-life of this agent, which ranges 8–19 hours when unbound and 7–18 hours when found in a deferasirox–iron complex, allows for once-daily administration.^{11,12} Results from clinical studies with deferasirox indicate that it has beneficial effects on serum ferritin levels and liver iron concentration with a clinically manageable safety profile.^{11,12}

Until recently, there have been little clinical data available regard-

ing the use of ICT in patients with MDS. Current studies using ICT in transfusion-dependent patients with MDS are reviewed below.

Deferoxamine for ICT in patients with MDS

Early uncontrolled studies of treatment with deferoxamine in patients with MDS indicate that ICT with this agent provides clinical benefits such as reduction of transfusion dependence, lowering of the iron burden, and improvements in organ function. Long-term follow-up data were reported from a group of 11 patients with MDS who were receiving deferoxamine therapy for up to 60 months.¹³ Seven patients on deferoxamine had reduced RBC transfusion requirements, and five patients became transfusion independent. Following deferoxamine treatment, increases in platelet and/or neutrophil counts were observed in 82% of the patients, with five patients experiencing a trilineage hemotologic improvement where a simultaneous rise in hemoglobin, platelets, and neutrophils was observed.¹³ Results from a retrospective survey indicate that patients who received daily/continuous deferoxamine treatment demonstrated improvements in serum ferritin, serum alanine transaminase,

serum aspartate transaminase, and fasting blood sugar levels. However, improvements in these laboratory values were not observed in many of the patients reviewed in this study, as they only received deferoxamine intermittently or concurrently with transfusions, suggesting that regular administration of deferoxamine is likely needed to overcome sequelae associated with iron overload.¹⁴

Further studies regarding the effects of treatment with deferoxamine in transfusion-dependent patients with MDS found significant improvements in survival. In a retrospective review of 178 patients with MDS, 18 patients received subcutaneous deferoxamine for a median of 15 months.¹⁵ Treatment with deferoxamine was initiated when ferritin levels were greater than 1000 ng/mL, greater than 20 units of RBCs transfused, or following clinical suspicion of iron overload. A multivariate analysis showed overall survival was significantly related to the International Prognostic Scoring System (IPSS) risk score ($p < 0.008$) and the presence of iron chelation therapy ($p < 0.02$). Patients with MDS in the category of low or intermediate-1 IPSS had a significantly improved overall survival when treated with ICT compared with those who did not receive ICT; however, neither group reached

Table 1.
Available Treatment Options for Iron Chelation Therapy^{6-9,a}

Parameter	Deferoxamine	Deferasirox	Deferiprone ^b
Dosage	i.m. 0.5–1 mg/day; give 2 g i.v. with, but separate from, each RBC unit s.c.: 20–40 mg/kg/day	20–40 mg/kg/day p.o.	75 mg/kg/day p.o.
Half-life (hr)	6	8–16	2–3
Route(s) of iron excretion	Urine, stool	Urine, stool	Urine
Toxicities	Ocular, auditory, bone	Renal, hepatic, cutaneous, myelosuppression, GI bleeding	GI, hepatic, myelosuppression
Monitoring	Annual eye and audiometry examinations	Monthly urinalysis, SCr, LFTs; annual eye and auditory examinations	Weekly CBC

^aRBC = red blood cell, GI = gastrointestinal, SCr = serum creatinine, LFTs = liver function tests, CBC = complete blood count.

^bCurrently unavailable in the United States.

median overall survival (by 160 months with ICT) versus 40 months without ICT ($p < 0.03$).¹⁵ In a prospective study, 170 patients who were referred for RBC transfusions were evaluated for overall survival for a two-year period and 46% of patients received ICT therapy: deferoxamine continuous s.c. (8 hours, 40 mg/kg/day, 3–5 day/week [$n = 41$]), deferiprone alone (30–75 mg/kg/day [$n = 5$]), deferiprone p.o. + deferoxamine s.c. ($n = 5$), deferasirox p.o. (20–30 mg/kg/day [$n = 6$]), and deferoxamine s.c. bolus (2–3 g/week [$n = 12$]) or deferoxamine i.v. (50–100 mg/kg/day once after each RBC transfusion [$n = 7$]).¹⁶ Median overall survival was 115 months for patients on ICT and 50 months in patients without any ICT ($p < 0.0001$).

Deferasirox for ICT in patients with MDS

Deferasirox is an oral, once-daily iron chelator approved for use in patients with long-term transfusion dependency resulting in a state of iron overload.^{11,12} A Phase II, prospective, multicenter study was conducted to measure the safety and efficacy of treatment with deferasirox in patients with MDS ($n = 47$), β -thalassemia ($n = 85$) or Diamond-Blackfan anemia ($n = 52$).¹⁷ For inclusion in the study, patients were required to have had ≥ 8 transfusions per year or a liver iron concentration (LIC) of ≥ 2 mg Fe/g dry weight (wet-to-dry conversion factor of 3.33), with a life expectancy greater than one year. Deferasirox was initiated at 20 or 30 mg/kg/day in patients with baseline LIC ≥ 7 mg Fe/g dry weight and produced statistically significant decreases in LIC ($p < 0.001$). Treatment with deferasirox was determined to be successful (defined as maintenance or reduction of LIC based on the patients' baseline LIC in 78% of patients with MDS). The greatest changes in LIC (-9.4 mg Fe/g dry weight) were observed in patients with MDS who were treated

with 30 mg/kg/day of deferasirox. This finding was correlated with changes in serum ferritin concentration, suggesting that this value is an effective measure for monitoring deferasirox treatment.¹⁷ The most common drug-related adverse events observed in this study were transient gastrointestinal events, including abdominal pain, nausea, vomiting, diarrhea or constipation, and skin rash. Elevated serum creatinine levels were observed in 73 patients (39.7%) but they were controlled with dosage reductions or treatment interruption. Until the effects of deferasirox on the kidney are better understood, it is recommended that this agent should be used cautiously in patients with renal impairment, and all patients should be carefully monitored for kidney function.¹⁷

In another Phase II study, 12 patients with MDS, who had 20 or greater transfusions and ferritin levels above 500 ng/mL, were enrolled to demonstrate the tolerability and efficacy of deferasirox.¹⁸ Treatment with deferasirox was initiated at 20 mg/kg/day in all patients and then the dosage was escalated 5 mg/kg every 3 months to the maximum dose of 30 mg/kg/day if serum ferritin levels decreased less than 10%. After one year, the median serum ferritin levels dropped from 1575 ng/mL (range: 665–6900 ng/mL) to 413 ng/mL (range: 105–3052 ng/mL) in the seven patients who received deferasirox for the 12-month study period. Additionally, the median LIC declined significantly ($p < 0.02$). Three of the seven patients who completed the study discontinued therapy at some point due to adverse events, including incidence of pneumonia, skin rash, and a case of persistent osteomyelitis. Other observed adverse events included transient gastrointestinal symptoms ($4/12$), tachycardia ($1/12$), and various liver and renal function abnormalities.

The Evaluation of Patients' Iron Chelation (EPIC) trial was an open-

label, single-arm prospective study of 1744 patients with transfusion-dependent anemias, including 341 transfusion-dependent patients with MDS who were observed for one year. The patients with MDS also met the following criteria for study inclusion: serum ferritin levels of greater than 1000 ng/mL, serum ferritin levels less than 1000 ng/mL with at least 20 lifetime transfusions, or 100 mL/kg blood with R2 magnetic resonance imaging (MRI)-confirmed LIC of greater than 2 mg Fe/g dry weight.¹⁹ These patients were treated with an initial dosage of deferasirox at 10–30 mg/kg/day with dose adjustments of 5 to 10 mg/kg/day made every three months based on serum ferritin levels. The primary endpoint of this trial was serum ferritin change at 12 months compared with baseline, with a secondary endpoint of the tolerability of therapy. At one year, a significant reduction in median serum ferritin levels from baseline was observed (by last-observation-carried-forward method: -253.0 ng/mL, $p = 0.0019$); however, 48% of patients discontinued therapy before the one-year study duration due to a variety of reasons including adverse events (mostly mild to moderate), consent withdrawal, unsatisfactory treatment effect, lost to follow-up, and death (not treatment-related). Common investigator-assessed adverse events included diarrhea (110 patients, 32%), nausea (45 patients, 13%), vomiting (26 patients, 8%), abdominal pain (25 patients, 7%), rash (23 patients, 7%), and constipation (21 patients, 6%).

Economic considerations for ICT

In the overall management of patients with MDS, economic considerations, in addition to efficacy and safety, require careful consideration. One study evaluated the costs of treatment as recommended by the National Comprehensive Cancer Network (NCCN) for lower-risk patients with MDS, and estimated

that the average annual cost for anemia-altering therapy is \$63,577 per patient. When following the NCCN-recommended treatment guidelines, about 35% of patients with IPSS-based low- or intermediate-1-risk MDS will most likely require ICT. As a result, estimated annual costs of treatment per patient with deferasirox or deferoxamine would be \$46,008 and \$21,048, respectively.²⁰

In a study examining the clinical effectiveness, economic burden, and quality of life associated with deferoxamine treatment in patients with iron overload in the United Kingdom, ICT with deferoxamine resulted in various suboptimal health and economic outcomes.²¹ Adherence to treatment with deferoxamine was low, with patients missing doses or otherwise not taking the drug as prescribed, leading to an association of ICT-related adverse events and nonadherence. Also, clinically meaningful decreases were noted in health-related quality of life scores between deferoxamine-treated patients and normal population scores. The total annual cost of deferoxamine treatment (estimated mean weighted) per patient was approximately £19,000

per year, in which the most significant portions of the costs were associated with equipment needed for deferoxamine administration, the medication itself, and home health-care costs.²¹

The cost effectiveness of ICT with deferoxamine compared with deferasirox in β -thalassemia patients was analyzed from a United States health-care system's perspective.²² Some basic assumptions were made from published literature for the purpose of the study, including the estimation of a 16% increase in adherence to deferasirox, an annual mortality rate of 16% due to cardiac disease, and the use of wholesale acquisition costs for deferoxamine (\$35.77/g) and deferasirox (\$89.49/g), reflecting market values from the year 2006. Using a Markov model, it was estimated that patients gained an additional 4.5 quality-adjusted life years (QALYs) with an additional lifetime cost of \$126,018 per patient (Table 2). This results in a cost-effectiveness ratio of \$28,255 per QALY gained, which falls below the \$50,000-100,000 range of what is generally considered a reasonable investment for healthcare in the United States.²²

Practical considerations for implementation of ICT

Generally, the decision to initiate ICT is based on identification of iron overload while considering the anticipated prognosis and life expectancy of the individual patient. Patients with MDS who will benefit most from ICT have been identified as those with relatively low-risk disease (IPSS categories of low-risk or intermediate-1) who have received at least 20–40 RBC units over the course of their disease.^{2,23} Patients with serum ferritin levels above 1000 ng/mL coupled with the long-term need for RBC transfusions meet the criteria for ICT as detailed in most of the guidelines and consensus statements recommended by leading organizations regarding principles of MDS management.²⁴ NCCN has recommended in its 2010 MDS management guidelines that ICT with either deferoxamine or deferasirox be considered for patients who have received greater than 20 RBC transfusions, when ongoing transfusions are anticipated. Stronger consideration is given for low, intermediate-1, or potential stem cell transplant candidates for ICT.²⁵

Table 2.

Estimation of Total Lifetime Costs and Quality-Adjusted Life Years (QALYs) Gained with Deferasirox Versus Dferoxamine: Results from Base-Case Analyses^a

Outcome Measure	Deferasirox	Deferoxamine	Difference
Cardiac-disease-free life-years	29.3	24.0	5.4
Life-years			
Not discounted	34.4	29.6	4.8
Discounted	21.0	19.3	1.8
QALYs			
Not discounted	28.6	20.1	8.5
Discounted	17.6	13.2	4.5
Costs (\$US, 2006 values)			
Chelation therapy			
Drug	536,692	222,869	313,823
Administration	0	179,331	-179,331
Total	536,692	402,200	134,492
Iron overload-related cardiac disease	34,464	42,939	-8,474
Total	571,156	445,139	126,018

^aReprinted, with permission, from reference 22.

For most patients, standard dosing recommendations for initiation of ICT should be used, as given in Table 1. Deferoxamine should be administered subcutaneously over 8–12 hours for 5–7 days per week with a starting dose of 20–40 mg/kg/day.^{2,6} Additionally, treatment with deferoxamine could be administered via 24-hour continuous infusion, a strategy that is applicable for patients with consistently high levels of iron overload or those who develop cardiac or other serious complications.⁴ This method of drug delivery is arduous for many patients, which can result in poor adherence.² Development of oral chelating agents, such as deferasirox, was hoped to eliminate these compliance issues. Initiation of ICT with deferasirox is recommended at a dose of 20–40 mg/kg as calculated to the nearest whole tablet (available as 125-, 250-, or 500-mg tablets).^{8,10} Every 3–6 months, the dose should be adjusted by 5–10 mg/kg/day if inadequate responses are achieved according to serum ferritin levels.¹⁰

Following initiation and implementation of ICT, iron levels of patients should be monitored carefully, guided by maintaining target serum ferritin levels (<1,000 ng/mL) and observing the number of transfusions received. When serum ferritin levels fall below 500 ng/mL during the course of treatment, or if the patient is no longer receiving RBC transfusions, ICT should be temporarily discontinued but monitoring of iron levels should continue.²³

Treatment with iron chelating agents has been found to result in some instances of adverse events, some of which may need to be addressed with dose interruptions or adjustments. Due to the progressive nature of MDS, at times it is difficult to distinguish between drug- and disease-related toxicities. For example, some reports of cytopenias with deferasirox use have been reported in patients with MDS; however, these are mostly attributed to the progres-

sion of MDS.²³ Adverse events that have been observed in association with deferoxamine include localized injection-site reactions, ocular and auditory disturbances, growth retardation, respiratory distress syndrome, and some instances of renal impairment.^{4,6} Common adverse events associated with deferasirox treatment include gastrointestinal intolerance, increased serum creatinine levels, myelosuppression, liver function abnormalities, skin rashes, and auditory and ocular disturbances.^{8,10} If any of these or other adverse reactions are observed, therapy may be held or a dose reduction may be considered. For adult patients that have an increase in serum creatinine of 33% over baseline with no other obvious cause, the manufacturer recommends reducing the dose by 10 mg/kg.⁸

The Food and Drug Administration (FDA) has recently published an Early Communication on their website about toxicity monitoring with deferasirox.²⁶ All patients that are prescribed deferasirox have toxicities reported to a company-sponsored global database that the FDA reviews. The FDA's initial report suggests that known serious toxicities with deferasirox, such as renal failure, gastrointestinal hemorrhage, and death, have occurred at a higher frequency in patients with MDS relative to other patient populations exposed to the drug. The FDA has stated that it is difficult to draw conclusions about causality of deferasirox with these events due to similar events being reported in patients with MDS that are not undergoing active treatment. Patients who are older than 60 years, with multiple medical comorbidities, poor-risk MDS, and the need for frequent blood transfusions are confounding the agency's ability to assess likelihood of toxicity associated with the drug. The FDA continues to work with the manufacturer of deferasirox to determine the relationship between the adverse events in the data-

base with drug exposure and whether there is a need to modify the labeling of the drug.

Pharmacists can play a pivotal role in advocating for appropriate management strategies to minimize the effects of complications associated with ICT. For example, strategies to control local, mild reactions to deferoxamine administration can be initiated, such as varying the site of injection, lowering drug strength, adding hydrocortisone (5–10 mg) to the infusion, and making appropriate needle choices.⁴ Techniques for monitoring and encouraging adherence could include providing a patient-specific calendar with dosing information and information on follow-up laboratory tests, monitoring used vials, or logging of infusion times with pumps.⁴ Enhanced adherence and patient satisfaction may help delineate the role of deferasirox in patients with MDS.¹² Despite the lack of large, Phase III trials with either deferoxamine or deferasirox in the MDS population, these agents provide viable options for ICT compared with phlebotomy.

Conclusion

Use of long-term transfusion therapy for patients with MDS has limitations because of the risk of developing iron overload. Optimal treatment strategies with pharmacologic therapies such as deferoxamine and deferasirox can lessen the negative consequences of iron overload in transfusion-dependent patients with MDS.

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Iron overload in myelodysplastic syndromes

Article 204-999-10-002-H01P

Knowledge-based activity

Qualifies for 1.5 hours (0.15 CEU) of continuing-education credit

Learning objectives

After studying these articles, the reader should be able to

1. Describe the epidemiology of myelodysplastic syndromes (MDS) and iron overload.
2. Summarize recent clinical findings that highlight the importance of treating iron overload.
3. Discuss the risk factors for iron overload in MDS.
4. Identify MDS patients who would benefit the most from iron chelation therapy (ICT).
5. Discuss monitoring parameters and adverse effects associated with ICT.
6. Appropriately manage iron overload with ICT in patients with MDS.

Self-assessment questions

For each question, there is only one best answer.

1. The risk of iron overload in MDS increases after _____ units of red blood cells have been transfused.
 - a. 5–10
 - b. 20–30
 - c. 40–50
 - d. > 50
2. Development of iron overload in patients with MDS is related to the following conditions *except*
 - a. Transfusion of 20–30 units of red blood cells.
 - b. Occurrence of ineffective hematopoiesis.
 - c. Increased uptake of dietary iron.
 - d. Sloughing of intestinal cells.
3. On average, the iron content of a unit of red blood cells is
 - a. 35–45 mg.
 - b. 500–600 mg.
 - c. 200–250 mg.
 - d. 20–30 mg.
4. A liver biopsy is the standard and most direct measure of liver iron concentration, and should be used to determine iron levels in all patients with MDS.
 - a. True
 - b. False
5. Reasonable parameters for initiation of ICT include all of the following *except*
 - a. Serum ferritin > 1000 ng/mL.
 - b. Two or more transfusions per month continuing for greater than one year.
 - c. Need to preserve organ function.
 - d. Prolonged use of erythropoietic stimulating agents for greater than one year.
6. Which of the following agents is commercially available in the United States as an oral option for ICT?
 - a. Deferoxamine
 - b. Deferasirox
 - c. Deferiprone
 - d. Aminocaproic acid
7. In patients with MDS, ICT compared with no ICT has yielded which of the following results when evaluated in retrospective patient cohorts?
 - a. No difference in overall survival between groups
 - b. An overall survival difference favoring no chelation
 - c. An overall survival difference favoring ICT
 - d. An increase in number of red blood cell transfusions required during ICT
8. Adverse effects associated with deferiprone include all of the following *except*
 - a. Agranulocytosis.
 - b. Injection-site reactions.
 - c. Hepatic fibrosis.
 - d. Arthropathy.
9. Results from clinical studies in patients with MDS, treated with deferasirox, have demonstrated:
 - a. Significant improvements in survival.
 - b. Increased need for red blood cell transfusions.
 - c. Significant decreases in liver iron concentration.
10. Potential benefits associated with the use of deferasirox for ICT in transfusion-dependent patients with MDS include all of the following *except*
 - a. Oral administration.
 - b. An extended half-life.
 - c. Lower whole-sale cost.
 - d. Improved patient satisfaction and quality of life measures.
11. ICT should be temporarily discontinued if serum ferritin levels drop below 500 ng/mL during the course of treatment.
 - a. True
 - b. False

AJHP Continuing Education

Supplement: **Iron overload in myelodysplastic syndromes**

ACPE #: 204-999-10-002-H01P

CE Credit: 1.5 hours (0.15 CEU)

Expiration Date: April 1, 2013

The CE Process

The continuing-education (CE) test for this supplement can be taken online at the *ASHP Learning Center*. All tests are free to both members and nonmembers. As you take the test, you may stop and return to it at any time before submitting your final answers. If you score 70% or better on the test, you may immediately print your *CE Statement of Credit* for your records. If you do not score at least 70%, you are permitted to retake the test. ASHP keeps a record of the credits you have earned from this and other CE activities.

Instructions

- Access this test by going to <http://ce.ashp.org>.
- Log in using your email address and password. If you need help logging in, send an email to educserv@ashp.org. If you have forgotten your password, click on the *Forgot Your Password* link to receive an email with your password or a link to create a new one.
- When you log in, the *My Account* page will appear. Click on *Take CE Test* for available tests, listed by topic or by your profession.

- You can filter by topic or press ctrl + F to search for a specific test.
- Click the checkbox for the test you want to take, and then scroll down and click on *Register* at the end of the list.
- The test you have selected will appear along with instructions for completing it.
- Follow the prompt at the end of the test to complete the evaluation and print your *CE Statement of Credit*.
 - *Note: You will not be able to print your CE statement unless you complete the test evaluation.*
- To print your CE statement, click on the “*Print CE Statement*” button.
 - *Note: you must select the activity from the dropdown box that reads “no activity” (default) before your CE statement will appear on the screen.*

Questions?

Call the ASHP Processing Center:

866-279-0681 (toll free)

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