NCCN Task Force: Transfusion and Iron Overload in Patients With Myelodysplastic Syndromes

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Key Words
Transfusion, iron chelation, iron overload, myelodysplastic syndromes, thalassemia, MRI, non–transferrin-bound iron

Abstract
The National Comprehensive Cancer Network (NCCN) convened a multidisciplinary task force to critically review the evidence for iron chelation and the rationale for treatment of transfusional iron overload in patients with myelodysplastic syndromes (MDS). The task force was charged with addressing issues related to tissue iron toxicity; the role of MRI in assessing iron overload; the rationale and role of treating transfusional iron overload in patients with MDS; and the impact of iron overload on bone marrow transplantation. This report summarizes the background data and ensuing discussion from the NCCN Task Force meeting on transfusional iron overload in MDS. (JNCCN 2009;7[Suppl 9]:S1–S16)

Background
The myelodysplastic syndromes (MDS) represent a heterogeneous group of bone marrow stem cell diseases largely characterized by ineffective hemopoiesis leading to cytopenias and, in many patients, progression to acute myeloid leukemia.

The prognosis of patients with MDS may be determined using the International Prognostic Scoring System (IPSS) that emerged from deliberations of the International Myelodysplastic Risk Analysis Workshop. Patients with MDS are stratified into 4 risk categories based on the IPSS score: low, intermediate-1, intermediate-2, and high. Physicians use the IPSS risk category to help determine therapeutic strategy.

Patients are diagnosed with MDS at a median age of 70 years; comorbid conditions often play a major role in determining optimal therapy. Although increasing the overall survival is usually the most important goal, improvement in hematologic parameters, suppression of leukemic transformation, and enhancing quality of life often represent key issues in evaluating a given therapy.

Novel therapies with potential to improve symptomatic cytopenias and change the natural history of the disease are being developed. The most typical clinical feature of MDS is anemia, which is present in approximately 90% of patients at diagnosis and varies in severity. Red blood cell (RBC) transfusions are currently a key component of supportive care, as highlighted by the NCCN Clinical Practice Guidelines in Oncology: Myelodysplastic Syndromes (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org). These guidelines also suggest platelet transfusions for patients with severe thrombocytopenia or thrombocytopenic bleeding.

Iron overload may be a complication of prolonged and frequent RBC transfusions. Iron participates in intracellular reactions that generate free radicals, inducing oxidative stress and apoptosis. In patients with β-thalassemia, it has been well documented that iron overload negatively impacts survival and quality of life. Effective iron chelation has been shown to improve overall survival and cardiac, endocrine, and gonadal function in patients with thalassemia. A major question relates to whether these results can be extrapolated to patients with MDS. Indirect evidence, obtained retrospectively, suggests transfusional iron overload could be a contributor to increased mortality and morbidity in early-stage MDS. Iron overload–related oxidative stress and mitochondrial dysfunction may account for these negative findings. Therefore, iron overload has deleterious intracellular physiologic consequences and could be clinically important, making the use of chela-
tion therapy worthy of consideration. However, the true clinical value of iron chelation in MDS remains unclear. This state of uncertainty is from the lack of prospective evidence documenting improvement in survival or increase in cardiac and other organ function, especially given the side effects and expense of chelation therapy.

The NCCN convened a multidisciplinary task force meeting to critically review the evidence for and against iron chelation in treating transfusional iron overload in patients with MDS. The task force, which consisted of 9 members with expertise in MDS within the fields of medical oncology, hematology, bone marrow transplantation, radiology, and interventional radiology, evaluated the issue of iron toxicity and chelation in patients with MDS. All members were from NCCN member institutions and were identified and invited solely by NCCN. The meeting was held on October 26, 2009, in Philadelphia, Pennsylvania. The members provided didactic presentations on topics such as the basic mechanisms of tissue iron toxicity in iron overload states, comparing MDS with thalassemia; the role of MRI in assessing iron overload; the evaluation of iron overload and chelation in MDS; and the impact of iron overload on bone marrow transplantation. The presentations were followed by extensive discussions. This report summarizes the background data and ensuing discussions from the meeting.

**Basic Mechanisms of Tissue Iron Toxicity in Iron Overload States: MDS Versus Thalassemia**

**Presented by Peter L. Greenberg, MD**

Total body iron balance depends on several processes: absorption of exogenous iron from dietary sources, recycling of endogenous iron from the hemoglobin of dead or damaged red blood cells, and loss of iron through physiologic means. Understanding the critical molecular mechanisms related to iron handling would be optimal for the development of therapeutic interventions. In most cases of iron overload, whether hereditary or from RBC transfusion, the export of iron from the cells overwhelms the ability of transferrin to bind iron (Fe3+) leading to free, non–transferrin-bound iron (NTBI). NTBI is higher in patients with low–risk than in those with high–risk MDS, and is associated with ineffective erythropoiesis. The redox-active component of NTBI, termed labile plasma iron (LPI), is the toxic compound and facilitates entry of iron into cells, causing a marked rise in labile cell iron (LCI). This in turn mediates tissue damage through superoxide generation, redox reactions, gene modulation, and direct interaction with ion channels. Intracellular iron concentrations control the production of ferritin, which sequesters iron (Fe3+) for later use, whereas unsequestered iron may be transported out of the cell through the export protein ferroportin. Ferroportin expression is negatively regulated by hepcidin.

Hepcidin, primarily made in hepatocytes, and which increases in response to high liver iron levels (iron overload) and inflammation, is one of the main iron regulatory hormones. Hepcidin binds ferroportin on enterocytes and macrophages and triggers its internalization and lysosomal degradation. Increased hepcidin levels block absorption and recycling of iron. Decreased levels of hepcidin occur in response to anemia, hypoxia, and enhanced erythropoiesis (which in MDS could be predominantly from ineffective erythropoiesis). Hepcidin deficiency allows greater export of iron from macrophages, thus lowering macrophage cytoplasmic iron and suppressing secretion of soluble ferritin. Additionally, it results in increased iron absorption, oversaturation of transferrin, and accumulation of NTBI, leading to predominantly parenchymal iron overload.

Therefore, low hepcidin expression may lead to iron overload. Because hepcidin normally acts to retain iron in the liver and spleen, the lack of hepcidin in the high–iron milieu could expose other organs, such as the heart, to iron loading. In contrast, in chronic inflammation and anemia, the excess of hepcidin decreases iron absorption and prevents iron recycling. Although the principal cause of iron overload in patients with MDS is RBC transfusions, increased absorption of iron from the gut and poor use of iron by RBC precursors from ineffective erythropoiesis may also contribute to this process.

The hemochromatosis gene mutation or aberrant expression of other regulators of iron metabolism may also cause iron overload through suboptimal levels of hepcidin. In a small study of patients with MDS, urinary hepcidin excretion was undetectable or inappropriately low in most patients despite iron overload, similar to findings in thalassemia intermedia and contrary to findings in thalassemia major. In thalassemia major,
iron overload is attributed mainly to blood transfusions required for treatment, but is also caused by increased iron absorption. In contrast, patients with thalassemia intermedia have a milder form of anemia and remain largely transfusion-independent. Nevertheless, patients with thalassemia intermedia also experience iron overload because of increased iron absorption from greatly expanded but ineffective erythropoiesis.17 Low levels of hepcidin seen in patients with MDS could be a result of ineffective erythropoiesis. Patients with thalassemia major frequently experience iron-induced heart disease and endocrinopathies.

Diagnosis of iron overload is largely based on serum ferritin assays, with the general standard being iron staining of liver biopsies, which is frequently impractical. However, because serum ferritin levels may be a poor predictor of impending cardiac iron overload, more sensitive indicators are needed. MRI is a noninvasive, albeit expensive, test that has been used with encouraging results in monitoring iron overload, and may be useful for gauging the effectiveness of chelation therapy in thalassemia. However, MRI seems to mainly detect inert iron in the form of ferritin, not NTBI, which is a key mediator of damage from iron overload (see The Role of MRI in Assessing Iron Overload; below).

Normally when the capacity of plasma transferrin to bind iron is overwhelmed, NTBI (also termed LPI) appears in the plasma. Elevated LPI and LCI seem to be important mediators of tissue damage.10,11 Therefore, mechanisms that may lead to cardiac iron deposition, especially as it relates to hepcidin level, ineffective erythropoiesis, and elevated NTBI/LPI, need further evaluation in larger studies. Prospective studies are needed to evaluate these issues and, most importantly, assess how they correlate with cardiac versus liver iron deposition and improvement in organ function or overall survival with chelation therapy. Other preliminary data suggest that chelation could theoretically improve outcomes of hematopoietic stem cell transplant (HSCT; see The Impact of Iron Overload on HSCT; page S-10).

The Role of MRI in Assessing Iron Overload

Presented by Cynthia K. Rigsby, MD

Liver biopsy and serum ferritin have been used to evaluate total body iron load. However, serum ferritin levels may also be elevated because of ineffective erythropoiesis or inflammatory conditions. Although liver iron content provides a good index of total body iron stores, an elevated liver iron level has no clear-cut predictive value for cardiac iron loading. The relationship among serum ferritin, cardiac iron, and liver iron content is complex.18-20 Liver biopsy, which can accurately measure body iron content, is risky in patients with MDS, who typically have neutropenia or thrombocytopenia, and because abnormal platelet function may be prevalent. Not only is cardiac biopsy highly invasive and expensive but also the right-ventricular biopsies usually performed may not yield an accurate representation of the iron content of the entire myocardium.

MRI is a noninvasive tool for prospectively studying the interplay between hepatic and extrahepatic iron stores.20,21 Superconducting quantum interference device (SQUID), available in only a few centers, is another noninvasive technique that provides a direct evaluation of liver iron deposits. MRI is now considered a primary standard for assessing iron overload in patients with thalassemia because it can detect cardiac and liver iron overload and can accurately measure left-ventricular dimensions and function. Iron causes magnetic field distortion, and the MRI approach involves measuring the proton relaxation rates $R_2^*$ ($R_2^* = 1/T_2^*$) or $R_2$-star ($R_2^* = 1/T_2^*$). Iron burden is indicated by increase in the MRI parameters $R_2$ and $R_2^*$ and a concomitant decrease in $T_2$ and $T_2^*$ in a predictable and reproducible manner.

$T_2^*$ values not only inversely correlate with iron burden but also have functional implications in that $T_2^*$ values less than 20 ms have a clear relationship with the potential for decreased ejection fractions.18 However, not all patients with low $T_2^*$ values are symptomatic or have evidence of cardiac dysfunction. Nonetheless, myocardial $T_2^*$ values less than 10 ms are considered severe and may be a reasonable indication for increased iron chelation in thalassemia. Unlike in thalassemia, however, no correlation was observed among increasing serum ferritin levels, hepatic iron overload, and myocardial $T_2^*$ in patients with MDS22,23 (except those with > 60 units of RBCs).

An MRI technique for measuring liver iron content was developed by St. Pierre et al.,24 who found that mean $R_2$ correlated strongly with biopsy-determined liver iron concentration, as demonstrated across a
Cardiac siderosis occurs in all transfusional anemias, but the relative clinical risk depends on the underlying disease state, transfusional load, and chelation history. Cardiac function remains normal until late in the course of cardiac iron deposition; therefore, systolic dysfunction is a late marker for iron overload. Cardiac failure resulting from transfusional iron overload remains a common cause of death in patients with thalassemia major. Development of cardiac failure may be unpredictable and rapid. Abnormal T2* may be a helpful adjunct in predicting impending heart failure. The cardiomyopathy in thalassemia may be reversible if intensive iron chelation treatment is instituted in time. Introduction of T2* MRI to identify cardiac siderosis and appropriate intensification of iron chelation treatment has been shown to significantly improve survival of patients with thalassemia major. After chelation begins, improvement in cardiac function is seen well before T2* MRI improvement (5.7–7.9 ms/y).

Iron bound to ferritin produces greater inhomogeneities in the magnetic field, leading to detectable changes in T2 and T2*. The free iron species have little or no effect on MRI measurements. Hence, MRI measures predominantly long-term storage depots of iron rather than the functionally active iron. This observation explains why some individuals may have massive cardiac iron deposition without cardiac symptoms or vice versa.

Cardiac Iron in MDS
A recent study identified congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD) as independent predictors of survival in a large cohort of patients with newly diagnosed MDS. Not surprisingly, anemia and infection, common in MDS, severely exacerbated CHF and COPD.

Data are limited concerning the role of cardiac iron overload in cardiac damage in patients with MDS. Cardiac iron deposits were observed at autopsy in patients with acute leukemia and those with chronic anemias who had a very large number of prior RBC transfusions (> 75). Retrospective evidence shows increased cardiac mortality among patients who had increased ferritin or transfusion dependence. However, whether this effect is mediated by transfusional iron overload or is from the severity of the transfusion-dependent anemia per se is unknown.

Recent studies using the MRI T2* technique have shown that cardiac iron accumulation, when detectable, is variable among patients, with no correlation among cardiac, serum ferritin, or hepatic iron. Di Tucci et al. used MRI T2* to study patients with MDS with chronic transfusion-dependent anemias and found that patients with hepatic iron overload, which was commonly detected on T2* MRI, showed no evidence of cardiac disease. Cardiac iron deposition was found only in a subset of patients with a heavy transfusion burden (approximately 60–100 RBC units). However, because MRI T2* does not detect NTBI/LPI, whether this parameter correlates with clinically important cardiac overload in MDS remains to be determined.

Determining a possible relationship between cardiac iron loading and cardiac function is more complex in patients with MDS than in those with thalassemia because of the potential coexistence additional risk factors for cardiac disease. Park et al. evaluated the correlation between the T2* value and left ventricular ejection fraction in patients with MDS. Patients who received an RBC transfusion of 200 to 400 mL/kg showed a progressive decrease of T2* values, without a reduction in ejection fraction, even though patients who received an RBC transfusion of 400 mL/kg or more showed progressive cardiac failure. Although the study failed to show a linear correlation between T2* value and left ventricular ejection fraction, the results indicate that the T2* value of MRI could detect cardiac iron deposition before apparent myocardial dysfunction. Larger clinical studies are necessary to determine the relationship between iron overload and cardiac dysfunction in adults with MDS.

The current NCCN guidelines recommend monitoring serum ferritin levels to help assess iron overload. Although ferritin measurements are less precise than cardiac or hepatic MRI or SQUID, ferritin measurements are currently the only practical way to assess iron stores in common clinical practice.
Prior Studies Evaluating Iron Overload and Chelation in MDS

Presented by Richard M. Stone, MD

Transfusion, Iron Overload, and Organ Dysfunction: Anemia has long been recognized as a potential risk factor for cardiac disease because it leads to increased cardiac demand and possibly high-output CHF. Most patients with MDS receive RBC transfusions at some point to treat symptomatic anemia. These patients have a significantly higher risk for cardiac-related events and death than nontransfused patients, indicating that secondary iron overload may be clinically problematic.35,36 The WHO prognostic scoring system (WPSS), which incorporates the WHO-based morphologic categories, has shown that the requirement for RBC transfusions is a negative prognostic factor for patients with MDS.37 Although most important in patients with lower-risk disease, the depth of anemia per se also has negative prognostic import for the intermediate IPSS categories.32

Limited evidence suggests that organ dysfunction can result from iron overload in patients with MDS. More than 25 years ago, Schafer et al.38 reported the clinical consequence of transfusional iron overload in 15 nonthalassemic adults older than 50 years who had anemia requiring transfusion. In most patients, the transfusion dependence was less than 4 years. Although no assessment of cardiac iron content was performed, liver biopsy indicated increased levels of iron in 10 of 15 patients. The authors also noted widespread cardiac, endocrine, and hepatic organ dysfunction that was attributed to transfusional iron overload. Another retrospective study showed iron overload and cardiac toxicity in heavily transfused MDS patients.39

No prospective data have compared different cohorts from the general population to confirm cardiac dysfunction as a significant problem in the natural history of MDS. In a retrospective analysis, Goldberg et al.40 compared the clinical sequelae in patients with newly diagnosed MDS followed up over 3 years with that in patients without MDS in the Medicare population. The patients with MDS in this study (n = 705) were older than the overall Medicare population, and consisted of more men (49% vs. 42%). The diagnosis of MDS was confirmed with bone marrow evaluation in 57% of patients (n = 400), and the MDS diagnostic code was applied by the treating physician based on clinical impression in the remaining 43%. During the 3-year follow-up, diabetes, hepatic problems, and infections were more common in patients with MDS receiving RBC transfusions than in those who were not and those in the overall Medicare population. Importantly, among patients with MDS, 522 (74%) experienced a cardiac-related event, compared with 42% in the non-MDS population. Furthermore, 80% of patients with MDS who received transfusions experienced a cardiac event, compared with 69% of patients who were not transfused, suggesting that either chronic anemia or transfusional iron overload contributed to cardiac dysfunction.

Prospective studies correlating iron overload with increased mortality in patients with MDS are lacking. In a large retrospective analysis of 467 patients with MDS, Malcovati et al.37 found that patients who were RBC transfusion–dependent had significantly decreased overall survival than those who were not. The hazard ratio for overall survival was 1.36 for every 500 ng/L increase in serum ferritin level greater than 1000 ng/L. In addition, cardiac deaths were more common in the transfusion–dependent group. The number of transfusions needed per month, adjusted for cytogenetics, had a negative impact on overall survival in all low-risk histologies.37

In contrast, a study by Chee et al.41 found that neither the serum ferritin nor the number of RBC transfusions predicted survival in 126 patients with refractory anemia with ringed sideroblasts. The results of the study confirmed previous observations that RBC requirement at diagnosis was an IPSS-independent adverse prognostic factor, thus suggesting that transfusion dependency is a marker of more advanced disease.6 However, although no evidence showed that serum ferritin or numbers of transfusions contributed to the 83 deaths, only 47 patients had available autopsy information.

Of interest are the recent preliminary data from Sanz et al.42 They sought to evaluate the independent prognostic value of transfusion dependency (as defined in WPSS) and iron overload (defined as serum ferritin level > 1000 ng/mL) in a large series of 2994 patients (median age, 74 years) with de novo MDS according to French-American-British (FAB) criteria (2107 with MDS according to WHO criteria). Median overall survival for patients who were transfusion–dependent at diagnosis, those transfused during the...
course of their disease, and those who were nontransfused was 19, 60, and 96 months, respectively.

Multivariate analyses in a set of 902 cases with complete data confirmed that serum ferritin and transfusion dependency were strongly and independently associated with overall survival. Furthermore, multivariate analyses showed that serum ferritin and transfusion dependency carried independent risks for AML transformation. This study confirms the negative impact of transfusion dependency on poorer outcomes.\textsuperscript{5,41} Large randomized prospective studies are needed to confirm that transfusional iron overload is independently associated with an increased risk for AML transformation and decreased overall survival, as opposed to being a marker of more aggressive disease. Prospective trials are also needed to evaluate whether chelation therapy to reduce iron overload will improve overall survival and reduce the risk for AML transformation in patients with MDS.

A retrospective analysis showed that an elevated pretransplantation serum ferritin level adversely affects the outcome of patients with MDS undergoing HSCT after conventional conditioning\textsuperscript{35} (see “The Impact of Iron Overload on HSCT”). In patients with high serum ferritin, lower overall and disease-free survival was attributable to a significant increase in treatment-related mortality with a trend toward an increased risk for veno-occlusive disease. A clinical trial is underway to prospectively examine the feasibility of chelation therapy in the pretransplant setting.

Taken together, the RBC transfusional need and markedly elevated serum ferritin levels correlate with worse outcome in patients with MDS, although the exact cause is not known. No prospective studies have shown that reducing either the number of transfusions or the serum ferritin level is associated with longer or better quality of life in patients with MDS. Whether the increased risk for cardiac disease and death in transfused patients is because of the depth of anemia itself or because of iron or related moieties such as NTBI/LPI is unknown, highlighting the urgent need for prospective studies to answer these questions.

**Iron Chelation in MDS:** Several studies have shown that chronic chelation therapy effectively reduces iron levels as measured by ferritin or LPI levels. Although strong prospective evidence shows that iron chelation improves overall survival and cardiac, endocrine, and gonadal function in patients with thalassemia,\textsuperscript{5} no prospective data are available for patients with MDS. Retrospective studies suggest that patients with MDS who undergo chelation live longer than those who do not;\textsuperscript{31,43} however, only small numbers of highly select patients were included. In one small study, Jensen et al.\textsuperscript{44} found that patients who underwent long-term treatment with deferoxamine had improved hematopoiesis, lower transfusional requirements, and better blood counts than before therapy.\textsuperscript{44} However, the impact of chelation per se on survival is difficult to determine given the inherent biases in these analyses.

Two iron-chelating agents are currently available in the United States: deferoxamine and deferasirox (see Table 1). A third iron-chelating agent, deferiprone, is approved in other countries, including Canada. Deferoxamine, the first iron-chelating agent approved by the FDA, is typically administered at doses of 20 to 60 mg/kg per day through subcutaneous infusion for 8 to 12 hours, 5 to 7 nights per week.\textsuperscript{45,46} Poor patient compliance attributable to its cumbersome administration schedule, and dermatologic and ocular side effects, limit its usefulness.

### Table 1: Available Iron Chelation Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Route of Administration</th>
<th>Half-life (hr)</th>
<th>Schedule</th>
<th>Clearance</th>
<th>Toxicity</th>
<th>FDA approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deferoxamine</td>
<td>SQ, IV</td>
<td>0.5</td>
<td>8–24 hr x 5–7 d/wk</td>
<td>Renal and hepatic</td>
<td>Infusion site and allergic reactions, ocular, auditory</td>
<td>Yes</td>
</tr>
<tr>
<td>Deferiprone, L1</td>
<td>Oral</td>
<td>2–3</td>
<td>tid</td>
<td>Renal</td>
<td>Neutropenia, agranulocytosis, nausea/vomiting, arthropathy</td>
<td>No</td>
</tr>
<tr>
<td>Deferasirox, ICL670</td>
<td>Oral</td>
<td>12–16</td>
<td>1x/d</td>
<td>Hepatobiliary</td>
<td>Transient nausea, diarrhea, rash, renal toxicity</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Abbreviations: IV, intravenous; SQ, subcutaneous.
In November 2005, the FDA granted expedited approval for deferasirox, an oral iron-chelating agent with a long enough half-life to allow once-daily dosing. Patients with thalassemia taking deferasirox have reported increased patient satisfaction and improved quality of life (> 90% of those treated with deferasirox vs. < 20% of those treated with deferoxamine were satisfied with treatment).

Several studies have evaluated the safety and efficacy of deferasirox in patients with MDS. A recent study of 14 patients with lower-risk MDS who received deferasirox (500–1000 mg/d) for approximately 2 years showed that ferritin levels decreased during therapy in 13 patients, and in some of these patients, elevated liver enzymes at baseline decreased progressively. No substantial change in transferrin saturation or transfusion frequency was noted. Side effects were mild and tolerable in most patients; deferasirox treatment was stopped in one patient because of impaired kidney function.

The large multicenter EPIC trial included patients with various transfusion-dependent anemias, including MDS. It was designed to evaluate whether fixed starting doses of deferasirox based on transfusion history, with subsequent dose titration based on serum ferritin trends and safety markers, could provide clinically acceptable chelation as measured by changes in serum ferritin levels. All patients in the trial received an initial dose of 10 or 30 mg/kg per day of deferasirox, depending on their degree of transfusion dependence. Overall, median serum ferritin decreased from baseline by 264 ng/mL after 1 year (P < .0001), at an average actual received dose of deferasirox of 22.2 ± 5.9 mg/kg per day.

LPI, which is a toxic, directly chelatable form of NTBI (see section “Basic Mechanisms of Tissue Toxicity in Iron Overload States: MDS Versus Thalassemia”), seems to be a useful marker of tissue damage. Eliminating or reducing accumulation of LPI could potentially minimize iron-related morbidity and mortality. LPI may be a more specific marker of the biologic causes of tissue damage than serum ferritin.

The effect of deferasirox on LPI levels was evaluated in patients with transfusion-dependent anemias enrolled in the EPIC trial. Of these patients, 305 had MDS. Deferasirox starting dose was determined based on RBC transfusion frequency. Dose adjustments in steps of 5 to 10 mg/kg per day (in the range of 0–40 mg/kg per day) were based on serum ferritin trends and safety markers. Results from the 1-year study (Figure 1) confirm that deferasirox provides sustained reduction in toxic LPI levels across various transfusion-dependent anemias, including MDS. Gattermann et al., assessed the efficacy of deferasirox over 1 year in reducing body iron as indicated by changes in serum ferritin in patients with MDS enrolled in the EPIC trial. Median serum ferritin values at baseline, and at 3, 6, 9, and 12 months were

![Figure 1](Image)

**Figure 1** Effect of deferasirox on labile plasma iron (LPI) levels in heavily iron-overloaded patients with MDS and transfusion-dependent anemias. The dotted line represents the normal threshold for LPI (< 0.4 μmol/L). Data from Porter JB, Cappellini MD, El-Beshlawy A, et al. Effect of deferasirox (Exjade(R)) on labile plasma iron levels in heavily iron-overloaded patients with transfusion-dependent anemias enrolled in the large-scale, prospective 1-Year EPIC trial [abstract]. Blood 2008;112:Abstract 3881.
signed to evaluate the long-term efficacy and safety of deferasirox in patients with lower-risk MDS. The initial deferasirox dose was 20 mg/kg per day and was increased to 40 mg/kg per day based on tolerability and response. Serum ferritin was monitored monthly; LPI was assessed quarterly. The major inclusion criteria for patients in this study included low- or intermediate-1 IPSS-risk MDS; transfusional iron overload (serum ferritin, 1000 ng/mL, and RBC transfusions, > 20 units); serum creatinine less than 2 times ULN; minimal or no proteinuria; with or without prior chelation. Results after 12 months of chelation in 176 enrolled patients (mean age, 70 years) showed that the mean dose of deferasirox was 21 mg/kg per day and the mean transfusion rate was 3.4 units per month. The mean serum ferritin values at baseline and at 3, 6, 9, and 12 months were 3397 ± 233 (n = 176), 3057 ± 144 (n = 143), 2802 ± 128 (n = 126), 2635 ± 148 (n = 109), and 2501 ± 139 (n = 93), respectively (see Figure 2).

In patients with elevated baseline LPI, sustained suppression of mean LPI to the normal range was achieved after 3 months of treatment (see Figure 4). Hematologic improvement by International Working Group (IWG) 2000 criteria was achieved in 8 patients (5%): erythroid response in 5 (major 3; minor 2), platelet response in 1 (major), neutrophil response in 1 (major), and combined platelet and neutrophil response in 1. Serious and other adverse events were mild-to-moderate (95%) in severity.

In total, 14.7% had 2 consecutive serum creatinine values more than 33% greater than baseline (in normal range), 10.6% had 2 values above upper limit of normal (ULN), and 85 (24.9%) had both 2 consecutive values greater than 33% and greater than ULN; no progressive increases occurred. Increase in alanine aminotransferase greater than 10 times ULN on 2 consecutive visits occurred in 1 patient (< 1%) who had normal levels at baseline.

US03 was a phase II, open-label, 3-year trial designed to evaluate the long-term efficacy and safety of deferasirox in patients with lower-risk MDS. The initial deferasirox dose was 20 mg/kg per day and was increased to 40 mg/kg per day based on tolerability and response. Serum ferritin was monitored monthly; LPI was assessed quarterly. The major inclusion criteria for patients in this study included low- or intermediate-1 IPSS-risk MDS; transfusional iron overload (serum ferritin, 1000 ng/mL, and RBC transfusions, > 20 units); serum creatinine less than 2 times ULN; minimal or no proteinuria; with or without prior chelation. Results after 12 months of chelation in 176 enrolled patients (mean age, 70 years) showed that the mean dose of deferasirox was 21 mg/kg per day and the mean transfusion rate was 3.4 units per month. The mean serum ferritin values at baseline and at 3, 6, 9, and 12 months were 3397 ± 233 (n = 176), 3057 ± 144 (n = 143), 2802 ± 128 (n = 126), 2635 ± 148 (n = 109), and 2501 ± 139 (n = 93), respectively (see Figure 2).

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verse events seen in this study were similar to those observed in prior studies with deferasirox; 17 deaths (10%) occurred, all believed to be unrelated to deferasirox. The 2-year extension phase of this study will assess the long-term safety and efficacy of deferasirox and the clinical impact on organ function.

LPI and LCI play an important role in generating reactive oxygen species with resultant cellular, tissue, and organ damage (see section “Basic Mechanism of Tissue Toxicity in Iron Overloaded States: MDS Versus Thalassemia”). Preliminary data suggest that treatment with deferasirox reduces not only the toxic iron species but also several other parameters of oxidative stress in iron overloaded patients with MDS. Among 15 iron-overloaded patients with lower-risk MDS (5 men and 10 women; mean age, 66 years), 12 received 20 mg/kg per day of deferasirox and 3 received a lower dose of 4 to 6 mg/kg per day (because of side effects, mainly gastrointestinal, increased creatinine, and rash) for an average of 95 days (range, 63–163 days). The mean number of transfusions was 65 RBC units and the mean ferritin level before treatment was 3008 ng/mL (±1797 ng/mL). Results showed a statistically significant decrease in reactive oxygen species (28%), lipid peroxidation (138%), and the cellular labile iron pool (23%) of RBC, with a concomitant increase in levels of the antioxidant reduced glutathione (123%).

Figure 3 Serum ferritin of transfusion-dependent patients with MDS at baseline and after treatment of deferasirox. (A) Mean serum ferritin level at baseline and at every 3 months for 1 year. (B) Change in serum ferritin levels compared with baseline at quarterly intervals. Data from (A) and adapted from (B) List AF, Baer MR, Steensma D, et al. Iron chelation with deferasirox (Exjade(R)) improves iron burden in patients with myelodysplastic syndromes (MDS) [abstract]. Blood 2008;112:Abstract 634. Copyright © 2008 by American Society of Hematology (ASH). Reproduced with permission of American Society of Hematology (ASH); permission conveyed through Copyright Clearance Center, Inc.
patients the mean initial LPI levels of 0.39 units decreased to 0.12 units. Additional larger randomized studies assessing the correlation of these changes to the long-term morbidity, mortality, and quality of life of patients with MDS are warranted.

A multicenter, randomized, double-blind, placebo-controlled trial of deferasirox in patients with MDS is planned. The primary end point of the trial will be event-free survival (death or nonfatal cardiac or hepatic event). Secondary end points include overall survival, organ function, and safety. The results from this trial are likely to provide clinically useful answers about the true value of iron chelation in patients with MDS who have transfusion dependence and iron overload. Therefore, the task force panel members highly recommend that eligible patients participate in this trial.

The Impact of Iron Overload on HSCT

Presented by H. Joachim Deeg, MD

Allogeneic HSCT is currently the only treatment with curative potential for patients with MDS. This treatment can be associated with considerable morbidity and mortality; many elderly patients are not eligible for “standard” allogeneic transplantation, and careful patient selection is key to treatment success. More than 90% of MDS patients are likely to receive RBC transfusions at some point in their clinical course for treatment of symptomatic anemia. Consequently, most patients have a history of transfusions at HSCT. Transfusion requirement has been found to affect the outcome of patients with MDS and is considered an independent indicator of disease severity. Transfusion dependence also seems to be associated with reduced probability of survival after transplantation.

In transfusion-dependent patients with thalassemia undergoing allogeneic HSCT, iron-related tissue damage is an important adverse prognostic factor. Iron overload may also be a factor that influences the timing of HSCT or impacts on transplant outcome in patients with MDS. Available data, such as those presented by Armand et al. (Figure 5), suggest that iron overload, as measured with serum ferritin levels, is associated with poor outcome after transplantation.

These results were confirmed in several additional retrospective transplantation studies. Platzbecker et al. showed that elevated ferritin levels had a negative impact on survival because of increased nonrelapse mortality and possibly more severe acute graft-versus-host disease (GVHD). The investigators also analyzed the effects of transfusion dependence...
on various MDS risk groups. The analysis suggested that transfusion independence, particularly among patients with intermediate-risk cytogenetics, is associated with better outcomes. Overall survival was inferior in patients with serum ferritin levels greater than 1000 ng/L (see Figure 6, in basic agreement with the findings of Armand et al.\textsuperscript{35}).

Kataoka et al.\textsuperscript{59} retrospectively evaluated 264 patients (including those with MDS) undergoing allogeneic HCT for hematologic malignancies from 1996 through 2006, and used pretransplantation serum ferritin levels as a surrogate marker of iron overload. At 5 years, patients with ferritin levels of 599 ng/mL or higher had significantly lower overall survival (33% vs. 64%) and higher nonrelapse mortality (35% vs. 14%) rates than those with lower ferritin levels.

In another recent retrospective study, Alessandrino et al.\textsuperscript{60} reevaluated the prognostic significance of pretransplantation transfusion history and secondary iron overload in a cohort of patients with MDS who underwent allogeneic HSCT between 1997 and 2007. They observed an inverse relationship between transfusion burden and probability of survival after transplantation. The posttransplantation outcome was comparable in patients who received 20 (or fewer) RBC units and those who were transfusion-independent. In multivariate analysis, transfusion dependence was found to be a risk factor for acute GVHD. In patients who underwent transplantation after conventional conditioning regimens, pretransplantation serum ferritin levels were inversely related to overall survival and correlated with nonrelapse

Figure 5  Outcome of patients with MDS stratified by pretransplantation ferritin level. Patients are stratified using the fourth quartile (ferritin 2515 ng/mL) versus the lower 3 quartiles. (A) Overall survival. (B) Disease-free survival. (C) Cumulative incidence of treatment-related mortality. (D) Cumulative incidence of relapse. From Armand P, Kim HT, Cutler CS, et al. Prognostic impact of elevated pretransplantation serum ferritin in patients undergoing myeloablative stem cell transplantation. Blood 2007;109:4586-4588. Copyright ©2007 American Society of Hematology. Copyright restrictions may apply.
mortality. The impact of transfusion dependence was restricted to patients with MDS undergoing conventional (high-dose) conditioning, an approach that is known to confer a higher risk for transplant-related toxicity, whereas no significant effect was noticed in patients undergoing a reduced-intensity conditioning regimen before transplantation.

Thus, several retrospective studies have confirmed the prognostic significance of transfusion history and pretransplantation serum ferritin levels in patients who undergo allogeneic HSCT.

Other adverse consequences of iron overload in the HSCT setting may include increased risk for infections, which could lead to nonrelapse mortality. However, the relationship between iron and posttransplant toxicity and mortality, related to GVHD and infections, is not clearly understood.

An association between iron overload and invasive fungal infections has been shown in several small studies. Altes et al. determined the frequency and severity of iron overload in a group of 59 patients who died after conventional-intensity autologous (n = 24) or allogeneic (n = 35) HSCT. Of these patients, 36 had myeloid malignancies, including MDS; 17 lymphoma; 4 myeloma; and 2 aplastic anemia. Of 32 patients with hepatic iron content less than 150 μmol/g dry weight, 4 (12%) showed invasive aspergillosis at autopsy, compared with 10 of 27 (37%) who had hepatic iron content of 150 μmol/g or greater. This study suggests a relationship between severe iron overload and invasive aspergillosis. However, this study is limited by its small size and potential confounding variables.

Strasser et al. determined the iron content in marrow and liver in 10 consecutive allogeneic HSCT recipients, aged 10 to 59 years, who died 0.5 to 8.7 (median 2.2) years after transplantation. Patients had received 47.6 ± 25.9 RBC units from disease diagnosis to death, including 30.2 ± 17.4 units of red cells during the peri- and posttransplantation period. The median hepatic iron content was 4307 mg/g dry weight (range, 1832–13,120; normal, 530–900), and the median biochemically determined marrow iron was 1999 mg/g dry weight (range, 932–3942). A strong correlation was seen between morphometric marrow iron content and biochemical hepatic iron index. Again, data from these patients could be biased because only autopsy samples were evaluated.

The liver is a target organ of GVHD. In one small report, 6 patients (age range, 29–63 years) suspected of having hepatic GVHD were found to have severe iron overload with serum ferritin concentrations of 2398 to 11159 ng/mL (4 patients also had liver biopsies showing high hepatic iron concentrations). Liver function improved with erythropoietin-assisted phlebotomy, resulting in nor-

Figure 6 Pretransplant ferritin levels and hematopoietic stem cell transplant comorbidity index (HCT-CI). Reprinted from Platzbecker U, Bornhauser M, Germing U, et al. Red blood cell transfusion dependence and outcome after allogeneic peripheral blood stem cell transplantation in patients with de novo myelodysplastic syndrome (MDS). Biol Blood Marrow Transplant 2008;14:1217–1225, Copyright © 2009, with permission from The American Society for Blood and Marrow Transplantation.
malization of liver function at a median of 7 months and serum ferritin at a median of 11 months. Immunosuppressive therapy (for presumed GVHD) was successfully tapered in all 4 patients who completed the phlebotomy program. This observation suggests that iron overload may have presented with features that were confused with GVHD but were, in fact, the cause of post–HSCT liver dysfunction. At a median follow-up of 50 months (range, 18–76 months) from transplantation and 25 months (range, 5–36 months) from ferritin normalization, all 4 patients still required maintenance phlebotomy.

In summary, iron overload related to prior transfusion burden is common among patients with MDS who undergo HSCT. The WPSS, which includes transfusion dependence as a prognostic variable, may offer a better prognostic assessment of transplant outcome than the IPSS alone. Data indicate that transfusion-dependent patients with MDS have a reduced survival probability after conventional conditioning for HSCT. The increased risk for nonrelapse mortality is believed to be related to organ dysfunction secondary to iron overload (for which serum ferritin levels serve as a surrogate marker).

Transfusions are also associated with increased rates of fungal infections and GVHD, possibly linked to increased serum ferritin levels. These factors support the study of iron chelators in the setting of clinical trials in patients with low- and intermediate-1–risk MDS who have had excessive RBC transfusions in the months or years pre-HSCT. Given that all studies have been retrospective, prospective studies are needed to arrive at a definitive answer.

Management Strategies for Iron Overload in MDS

Panel Discussion

MDS presents significant health issues among older patients with substantial economic implications. Organ dysfunction is common in patients with transfusion dependency, although the cause is often unknown. Indirect evidence suggests that chronic anemia along with transfusional iron overload may lead to cardiac dysfunction. Therefore, strategies to improve anemia and maintain normal iron balance are desirable in patients with MDS receiving blood transfusions. The issue of chelation therapy in MDS remains highly controversial; although this approach can lead to a more negative iron balance, the clinical benefit has not been established. Therefore, the panel members strongly support prospective, randomized, placebo-controlled trials designed to evaluate the clinical benefit of iron chelation for treating lower-risk MDS.

Based on the available evidence, patients with lower-risk MDS may receive many RBC transfusions over an extended duration and are particularly at risk for developing transfusional iron overload, although the clinical consequences of this remain undefined. The NCCN guidelines and published consensus statements concur that patients with low-/intermediate-1–risk MDS receiving a high number (> 20–30) of RBC transfusions are most likely to benefit from iron chelation.

Although serum ferritin levels are currently accepted as a surrogate marker for iron overload, serum ferritin may be elevated in acute or chronic inflammation, despite normal iron stores, and therefore levels should be interpreted with caution. MRI T2* may be used to measure tissue iron levels, when detectable, in cardiac and liver tissue.

No prospective studies in MDS have validated a threshold for serum ferritin levels that should be used to initiate chelation therapy, if used at all. The threshold suggested in the literature for initiating chelation ranges from 1000 to 2500 ng/mL. Extrapolating from the thalassemia studies, the NCCN task force members recommend considering chelation therapy in patients with low- or intermediate-1–risk MDS who have undergone or are anticipated to undergo more than 20 units of RBC transfusions, for whom ongoing RBC transfusions are anticipated, and who have serum ferritin levels greater than 2500 ng/mL, aiming to decrease the levels to less than 1000 ng/mL. This is particularly important for those with preexisting cardiac disease.

The currently available oral iron chelators deferipone (outside of the United States) and deferasirox, and the parenterally administered drug deferoxamine are potentially useful for treating iron overload states. These drugs can be given to patients with MDS, with careful consideration of the respective potential toxicities.

Conclusions

This task force review discusses several critical is-
susues involving iron overload in patients with MDS. The biologic mechanisms and consequences of iron overload in these patients who are frequently heavily transfused are described, with an emphasis on how NTBI and organ iron deposition contribute to the potential toxicity of tissue iron excess. Discussion of the potential usefulness of T2* MRI, an important noninvasive method for evaluating organs that are potentially damaged by iron overload, highlighted the value of assessing this parameter for the liver and heart. However, the implications of this technology in determining clinical outcomes of patients need further evaluation; one reason is that the MRI measures iron deposition but not NTBI.

Evidence-based data were reviewed and reported from several retrospective studies showing parameters of iron overload in polytransfused patients with MDS. These patients seemed to be at risk for shortened survival and cardiac dysfunction. However, the number of transfusions associated with these findings is likely greater than that for patients with thalassemia. The current clinical guidelines and their limitations were reviewed.

A critical issue requiring direct evaluation is whether iron chelation alters the natural history of patients with MDS who are frequently transfusion-dependent. Although retrospective data have indicated the ability of iron chelation to decrease serologic and MRI parameters of iron overload in MDS, no prospective data on these patients indicate the clinical efficacy of iron chelation (e.g., improved survival, preservation of cardiac function) in contrast with clear data being available in patients with thalassemia major. Retrospective data indicate that patients with iron overload pre-HSCT are at risk for increased morbidity and mortality. Prospective controlled studies are clearly warranted to assess the clinical value of iron chelation in modifying these negative outcomes and to better define patients who should receive this therapy.

References
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