Iron Overload in Myelodysplastic Syndromes: Diagnosis and Management

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Myelodysplastic syndrome (MDS) is composed of a diverse spectrum of hematopoietic stem cell malignancies characterized by ineffective blood cell production. Many MDS patients are dependent on red blood cell (RBC) transfusions for symptomatic management of refractory anemia. Iron overload ensues when the iron acquired from transfused RBCs exceeds body storage capacity, thereby raising the risk for end organ damage. This is of greatest concern in patients with lower-risk MDS whose expected survival is measured in years. Transfusion dependence is associated with shorter survival and an increased risk for progression to acute myeloid leukemia (AML) in transfusion-dependent patients. Application of recent advances in the treatment of MDS can reduce or eliminate the need for transfusions, thus minimizing the risk of iron overload. Case control studies, prospective surveys, and phase II studies indicate that iron chelation therapy reduces iron load as measured by changes in serum ferritin and may prolong overall survival. Iron chelation strategies include oral agents such as deferasirox (Exjade®, Novartis Pharmaceuticals Corp, East Hanover, NJ), deferiprone (Ferriprox®, Apotex Europe BV, Leiden, the Netherlands) and, for those patients who are intolerant of or for whom oral therapy is ineffective, parenteral administration of deferoxamine (Desferal®, Novartis). This review presents the data related to iron overload in MDS, including its prevalence, diagnosis, clinical impact, and management.

**Introduction**

Myelodysplastic syndrome (MDS) is composed of a group of hematologically and prognostically diverse hematopoietic stem cell malignancies characterized by ineffective blood cell production.1 MDS affects between 55,000 and 76,000 patients in the United States overall.1,2 Approximately two-thirds of patients have lower-risk disease as defined by the International Prognostic Scoring System (IPSS),3,4 which includes the categories of low-risk and intermediate-1 (Int-1)-risk disease. These categories tend to have an indolent clinical course and expectation for a prolonged survival. Overall, it is estimated that 39% of patients with lower- and Int-1-risk MDS will require regular red blood cell (RBC) transfusions for management of chronic anemia symptoms and thus are at risk for complications arising from iron overload.5 RBC transfusion dependence was only recently recognized to have prognostic implications for disease behavior separate from the effect of iron loading.6 In a retrospective analysis by investigators at the University of Pavia,6 RBC transfusion dependence was associated with a 36% reduction in survival for every 500 μg/L increase in serum ferritin above 1,000 μg/L. Similarly, baseline transfusion dependence and iron overload were independent prognostic
variables for overall survival and for time to progression to acute myeloid leukemia (AML), suggesting that transfusion dependence is a surrogate marker for the severity of maturation impairment of the MDS clone.

**Iron Overload**

While the average adult maintains 3 to 3.5 g of total body iron, iron storage capacity is estimated at 7 g. Each unit of packed RBCs contains approximately 200 to 250 mg of elemental iron. The only mechanism for the body to remove iron is by blood loss. With a transfusion frequency of 4 units of RBCs per month, the average patient will accumulate an extra 9.6 g of iron per year, which far exceeds iron storage capacity. With time, organ accumulation of nontransferrin-bound iron (NTBI) in MDS patients can result in oxidative cellular injury and clinical sequelae including cardiac and hepatic dysfunction, pancreatic endocrine insufficiency with glucose intolerance, arthropathy, impotence, and fatigue (Fig 1).

Although organ toxicities from iron have been well characterized in younger individuals with hereditary hemoglobinopathies such as β-thalassemia, the risks in older patients with MDS are less well defined. Although serum ferritin is an acute-phase reactant, serial monitoring remains a reasonable noninvasive measure of total iron body stores. Because of changes associated with inflammation, ferritin levels and iron saturation must be evaluated in the context of transferrin saturation and total iron-binding capacity to provide greater assurance of iron stores. Other direct measurements of iron load include liver biopsy with quantification of liver iron concentrations and magnetic resonance imaging (MRI; MRI T2*), both of which are not commonly used outside of clinical trials. Retrospective studies suggest that when serum ferritin levels exceed 1,000 μg/L, in the absence of inflammatory or other causes for ferritin elevation, transfusion burden often exceeds the body’s capacity to maintain iron bound to transferrin. Thus, a threshold level of serum ferritin of 1,000 μg/L can serve to distinguish mild from clinically significant iron overload. In one study, a median serum ferritin of 1,000 μg/L was reached after a mean interval of 10.8 months and 21 units of RBCs, above which survival incrementally decreased with further rise in serum ferritin. Patients with lower-risk World Health Organization (WHO) morphologic categories of refractory anemia or refractory anemia and with ringed sideroblasts (RA/RARS) who had ferritin levels above 1,000 μg/L experienced more cardiac complications and had a reduced overall survival (hazard ratio [HR] = 1.51; P < .001) in the Pavia study. However, in patients with refractory cytopenia with multilineage dysplasia with or without ringed sideroblasts and in patients with excess blasts for whom disease-related survival is more limited, ferritin level was not a significant prognostic factor in refractory cytopenia with multilineage dysplasia (RCMD) and RCMD with ringed sideroblasts (RCMD-RS) (HR = 1.34; P = .20), indicating that the risks from iron toxicities are greatest for individuals with the lowest disease-specific risk and corresponding longer survival.

**Impact of Iron Overload**

The actual prevalence of iron overload in MDS patients is not well described. National physician surveys estimate that between 50% and 80% of patients with MDS, both newly diagnosed and established, receive RBC transfusions and erythropoiesis-stimulating agents. More higher-risk MDS patients are dependant upon RBC transfusions than lower-risk patients (68% vs 22%), but low- and Int-1-risk MDS patients may survive 5 years or longer and with time may become RBC transfusion-dependant.

Sanz et al reported that transfusion dependence and iron overload are independent risk factors for overall survival and leukemic progression. In their review...
of 2,241 patients whose complete transfusional history was available, 835 were transfusion-dependent at the time of diagnosis, 526 became transfusion-dependant during follow-up, and 880 remained transfusion-independent. Median survival was significantly shorter in patients who were transfusion-dependent at diagnosis (19 months) compared with 60 months for those who later became transfusion-dependent and 96 months for those who remained transfusion-free \((P < .0001)\). Independent prognostic factors associated with overall survival in a multivariate analysis included iron overload \((HR = 52.4; P < .0001)\) and transfusion dependency \((HR = 8.8; P < .0001)\). Other factors that significantly influenced overall survival in univariate analysis included patient age and sex, hemoglobin level, absolute WBC, neutrophil and platelet counts, proportion of blasts in blood and marrow, percentage of dysplastic cells in the three different hematopoietic cell lines, cytogenetics according to IPSS cytogenetic risk subgroups, WHO and French-American-British (FAB) classifications, levels of ferritin, beta-2 microglobulin, erythropoietin, and lactate dehydrogenase (LDH) at diagnosis, and IPSS and WPSS risk categories.

Armand et al. retrospectively analyzed 922 MDS or AML patients receiving hematopoietic cell transplant (HSCT). Of the 590 with an elevated pretransplant ferritin level, the overall posttransplant survival was significantly inferior, with a corresponding HR of 2.6 for mortality for MDS patients with a median ferritin level \(\geq 2,515 \text{ng/mL} (P = .003)\). For patients with AML and ferritin levels greater than \(2,640 \text{ng/mL}\), the HR was 1.6 \((P = .031)\). The decrease in survival was attributed to increased treatment-related mortality and a trend to increased veno-occlusive disease.

### Pathology

Organ damage in iron overload arises from the deposition of either NTBI or insoluble iron complexes.\(^{15}\) Even prior to requiring RBC transfusions, MDS patients often have increased intestinal iron absorption to compensate for ineffective erythropoiesis.\(^{10}\) After only 20 units of RBCs have been transfused, 4 to 5 g of iron has accumulated in the body. With this amount of iron, serum ferritin levels increase to 1,000 \(\mu\text{g/L}\) or more and transferrin becomes saturated, leading to elevations in NTBI with further iron loading. NTBI enters organ cells causing oxidative damage to cellular DNA and apoptosis.\(^{10,16}\) This results in organ dysfunction and functional compromise, increased infection risk, and even malignancy.\(^{12}\)

Cardiac failure is one of the leading causes of non-leukemic death in MDS patients.\(^{5}\) Unbound iron accumulates in cardiac muscle and results in cardiomegaly and conduction problems. Cardiac dysfunction arises from hydroxyl radical formation in myocardial tissue, and increased peroxidation of membrane lipids slowly causes irreversible myocardial damage.\(^{5,16}\)

The liver is the second organ of concern and is the main repository of iron. Unbound iron accumulates when high iron plasma levels exceed the transferrin-binding capacity. This results in hypertransaminasemia, portal fibrosis, hepatomegaly, cirrhosis, and inflammation.\(^{17}\) In the pancreas and endocrine glands, unbound iron accumulation and secondary organ dysfunction lead to diabetes, hypothyroidism, and hypogonadism.\(^{17}\)

### Goals of Therapy

The overall goals of treatment for MDS patients with lower-risk disease are to alleviate cytopenias and related symptoms and to improve quality of life.\(^{18}\) Maintaining quality of life, reducing the need for RBC transfusions, preserving organ function, and extending overall survival are the key management goals in transfusion-dependent MDS patients.\(^{12}\)

### Treatment Strategies

While it is not the intent of this article to review the overall management of patients with MDS, it is clear that maintaining adequate hemoglobin levels by RBC transfusions and/or erythropoietin-stimulating agents or other active therapies is key to preserving quality of life. The venerated "best supportive care" approach is neither sufficient nor adequate treatment since recently developed drugs such as lenalidomide\(^{19,20}\) and the DNA methyltransferase inhibitors\(^{21,22}\) can reduce or even obviate RBC transfusion requirements, improve cytopenias, and prolong survival. The National Comprehensive Cancer Network (NCCN) continues to update guidelines for optimal staging and management of these diseases.\(^{1}\)

### Iron Toxicity: Chelation Agents

Chelation therapy is the cornerstone of supportive therapy to reduce iron accumulation and the potential for organ complications. Initiation of chelation treatment should be considered at a time sufficient to avoid myocardial iron loading and to prevent iron toxicity and dysfunction. NCCN guidelines recommend evaluation and chelation treatment when serum ferritin levels reach and/or surpass 2,500 \(\mu\text{g/L}\).\(^{1}\) Currently available chelating agents form a nonreversible complex with free iron. Only free iron, and not iron bound to transferrin, is chelated.\(^{23}\)

Three chelating agents are in use worldwide. Table 1 compares the two products available in the United States: deferoxamine (Desferal\(^{18}\), Novartis Pharmaceuticals Corp, East Hanover, NJ) and deferasirox (Exjade\(^{20}\), Novartis). A second oral agent, deferiprone, is available in Canada and Europe (Ferriprox\(^{26}\), Apotex Europe BV, Leiden, the Netherlands). Each agent has a different binding capacity. Approximately 100 parts of deferoxamine bind approximately 8.5 parts of iron.\(^{23}\) Deferiprone, a bidentate ligand, has a 3:1 iron-binding affinity,\(^{23}\) whereas deferasirox, a tridentate ligand, has a 2:1 iron-binding affinity.\(^{23}\) Doses of 10, 20, and 40 mg/kg per day of deferasirox yield a mean net iron excretion of 0.119, 0.329, and 0.445 mg Fe/kg body weight, respectively.\(^{25}\) Both deferoxamine and deferiprone are excreted mainly by the kidneys as unchanged drugs or as the iron
complex. Deferasirox and metabolites are excreted mainly in the feces (84%), with only 8% being excreted renally. Of the agents available in the United States, deferoxamine is administered parenterally, whereas deferasirox is the only oral chelating agent approved for chronic iron overload. This agent, by virtue of ease of administration, improves compliance and can minimize personnel, time, cost of equipment, and supplies necessary for parenteral drug administration.

Clinical Experience

Several investigators have evaluated the benefit of chelation agents in MDS patients. In a retrospective, single-institution analysis, chelation therapy emerged as the only significant factor improving overall survival in IPSS low- or Int-1-risk patients ($P < .008$) in multivariate analysis ($P < .02$). Median survival was greater than 160 months in patients who received chelation therapy compared with 40 months in patients who did not receive chelation therapy ($P < .03$). Significantly more patients receiving chelation therapy survived 4 years compared with those who did not receive chelation therapy (80% vs 44%, $P < .05$).

Although supporting the benefit of chelation therapy, retrospective outcome analyses have inherent bias in treatment selection. Rose et al evaluated 170 MDS patients (all risk categories) who required transfusions for the first time in a prospective survey performed by the Groupe des Myélo dysplasies (GFM). The patients, who were referred for RBC transfusions at 18 GFM centers during a 1-month period in 2005, were followed for 2 years with assessment of RBC transfusions, use and type of iron chelation, and complications. Seventy-six patients (46%) received standard-dose chelation using deferoxamine by continuous (8-hour) subcutaneous (SC) infusion 40 mg/kg per day 3 to 5 days per week, deferiprone (30 to 75 mg/kg per day), deferiprone plus deferoxamine SC, or deferasirox (20 to 30 mg/kg per day) or low-dose chelation regimen of deferoxamine SC (2 to 3 g per week) or deferoxamine intravenously (50 to 100 mg/kg after initialization).

<table>
<thead>
<tr>
<th>Study</th>
<th># of Patients</th>
<th>Regimen</th>
<th>Transfusion Requirement</th>
<th>Serum Ferritin (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>List et al</td>
<td>176 low- and Int-1-risk MDS</td>
<td>Deferasirox 20 to 40 mg/kg per day</td>
<td>Baseline: 3,397 ± 233 μg/mL 3 mos: 3,057 ± 144 μg/mL 6 mos: 2,802 ± 128 μg/mL 9 mos: 2,635 ± 148 μg/mL 12 mos: 2,501 ± 139 μg/mL</td>
<td></td>
</tr>
<tr>
<td>Metzgeroth et al</td>
<td>12 MDS</td>
<td>Deferasirox 20 to 30 mg/kg/daily × 12 mos</td>
<td>Prior to study: 36 units During study: 23 units</td>
<td>Baseline: 1,575 μg/L 12 mos: 528 μg/L (per protocol: 413 μg/L)</td>
</tr>
<tr>
<td>Greenberg et al</td>
<td>24 lower-risk MDS</td>
<td>Deferasirox 20 mg/kg per day, adjusted to 10 or 30 mg/kg</td>
<td>Baseline: 3,848 μg/L 6 mos: 3,638 μg/L 12 mos: 2,685 μg/L</td>
<td></td>
</tr>
<tr>
<td>Gattermann et al</td>
<td>341 MDS</td>
<td>Deferasirox 10 to 30 mg/kg per day</td>
<td>Baseline: 116.4 mL/kg of blood in the previous year</td>
<td>Baseline: 2,730 μg/L 12 mos: 1,903.5 μg/L Reduction: –253 μg/L ($P &lt; .0019$)</td>
</tr>
<tr>
<td>Takatoku et al</td>
<td>292 (MDS, aplastic anemia, and other transfusion-dependent diseases)</td>
<td>Deferoxamine: - Intermittent (once/1.9 wk) - Concurrent with transfusion - Daily/continuous</td>
<td>61.5 units of RBCs during the previous year</td>
<td>Average change over study period: Intermittent: + 2,222.8 μg/L Concurrent: + 2,294.8 μg/L Daily: –1,152.2 μg/L</td>
</tr>
<tr>
<td>Cermák et al</td>
<td>5 MDS (RA or RARS subtype)</td>
<td>Deferiprone 4 to 6 g (70 to 80 mg/kg) × 26 mos Also, 150 IU/kg of rHuEPO 3 × per wk</td>
<td>Baseline: median 4 units/mo End of study: median 3 units/mo</td>
<td>Baseline: 2,086 μg/L End of study: 879 μg/L</td>
</tr>
</tbody>
</table>

**Table 1. — Studies With Chelation Therapy in Transfusion-Dependant Patients**

**Fig 2. — Iron chelation therapy and survival in MDS.** Standard chelation produced significantly better survival benefit than low-dose chelation. Multivariate analysis revealed that good level of chelation dramatically improved chance for prolonged survival ($HR = .215$, $P = .0002$). Higher IPSS risk was associated with decreased survival ($HR = 3.888$, $P = .0030$). Figure courtesy of Christian Rose, MD.
each RBC transfusion). The median survival for patients receiving chelation therapy was 115 months vs 51 months for nonchelated patients ($P < .0001$). In addition, median survival for patients receiving standard-dose chelation therapy was 120 months compared with 69 months for patients receiving low-dose chelation therapy (Fig 2, $P < .001$). Outcomes were consistent across all subgroups analyzed including IPSS low- and Int-1-risk, sex, and age, providing the first convincing evidence that chelation therapy improves overall survival in MDS patients. Moreover, chelation therapy significantly lowered serum ferritin levels over time in multicenter phase II clinical trials evaluating changes in iron loading in transfusion-dependant MDS patients (Table 1).$^{3,26-32}$ Others, however, have questioned the validity and clinical relevance of iron chelation.$^{33}$

In a phase II open-label, 3-year study, List et al.$^{28}$ evaluated safety and efficacy of deferasirox 20 to 40 mg/kg per day in 176 RBC transfusion-dependent, low- and Int-1-risk MDS patients (US-03). The mean serum ferritin level significantly decreased from baseline (3,397 ± 233 µg/mL) to month 12 (2,501 ± 139 µg/mL) (Fig 3). The labile plasma iron (LPI) concentration, a measure of the reactive species of NTBI, was reduced (3,397 ± 233 µmol/L) to nondetectable at 3 months in all patients from a mean at baseline of 0.4 µmol/L, with 41% of patients having an elevated level (greater than 0.5 µmol/L), to nondetectable at 3 months in all patients with sustained suppression to within the normal range ($P < .05$) in the rating of side effects of deferasirox (mean change 1.03), and burden of deferasirox treatment (mean change 0.88). There was no change in the perceived effectiveness of deferasirox over the course of the study. There was also an increase in adherence from 62.5% at baseline to 85.7% at the end of study.

NCCN guidelines recommend the use of deferasirox in the treatment of iron overload for low- and Int-1-risk MDS patients who are anticipated to receive, or have received, greater than 20 RBC transfusions and/or who will reach a serum ferritin level > 2,500 µg/L. The goal for these patients is to maintain a ferritin level < 1,000 µg/L, thereby preventing accumulation of NTBI and its adverse effects on cardiac, hepatic, and endocrine function.$^{1}$

### Dosing and Side Effects

Deferoxamine is administered by either intramuscular (IM) injection, slow intravenous (IV) or SC infusion, or deep SC depot injection 5 to 7 days a week.$^{23}$ A number of different dosing regimens can be used. The NCCN guidelines recommend 1 to 2 g as an SC infusion overnight, 5 to 7 nights per week.$^{1}$ However, the time, material, and manpower needed to maintain this sched-

**Table 2. — Characteristics of Patients Who Would Benefit From Chelation Therapy**

<table>
<thead>
<tr>
<th>Requirement of at least 2 units of RBCs per month for greater than 1 year</th>
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<tbody>
<tr>
<td>Serum ferritin &gt; 1,000 µg/L</td>
</tr>
<tr>
<td>Lower-risk MDS:</td>
</tr>
<tr>
<td>- Low-risk or Int-1-risk (IPSS)</td>
</tr>
<tr>
<td>- RA, RARS, andSq (WHO)</td>
</tr>
<tr>
<td>Life expectancy &gt; 1 year</td>
</tr>
<tr>
<td>No comorbidities that will attenuate their prognosis</td>
</tr>
<tr>
<td>Candidate for allograft</td>
</tr>
<tr>
<td>Need to preserve organ function</td>
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</tbody>
</table>

be considered for chelation therapy. The key features assists clinicians in deciding which MDS patients should myocardial stiffness. They may aid in assessing the stores and correlates with endothelial dysfunction and approximates the amount of parenchymal cardiac iron picture regarding organ consequences. MRI T2* has been used to provide further insight into the clinical (MRI T2*) in concert with indirect ferritin levels has been associated with deferasirox involve renal, hepatic, and cutaneous reactions as well as myelosuppression. Approximately one-third of patients treated with deferasirox experienced dose-dependent increases in serum creatinine. A study described on the package insert noted that among 296 patients receiving deferasirox, 113 had an increase in serum creatinine greater than 33% above baseline, and 25 required a dosing reduction.

The US Food and Drug Administration (FDA) recently released an early communication concerning the safety of deferasirox. New data suggest that MDS patients may be at an increased risk for renal insufficiency, gastrointestinal hemorrhage, and death compared with non-MDS patients. Confounding factors in the analysis include advanced age, seriousness of the disease state, comorbidities, and the need for blood transfusions. There has not been a comparison to patients with similar characteristics not receiving deferasirox or younger patients with other chronic anemias.

**Monitoring**

Patients with as few as 20 to 30 RBC transfusions may develop iron overload, with serum ferritin levels exceeding 1,000 μg/L. Therefore, once a patient has received 20 to 30 RBC transfusions or is receiving at least 2 units per month, the serum ferritin and transferrin saturation should be monitored to identify iron overload. In clinical trials, cardiac T2 MRI imaging (MRI T2*) in concert with indirect ferritin levels has been used to provide further insight into the clinical picture regarding organ consequences. MRI T2* approximates the amount of parenchymal cardiac iron stores and correlates with endothelial dysfunction and myocardial stiffness. They may aid in assessing the degree of cardiac and liver damage.

**Putting Transfusion Dependency and Iron Overload Guidelines Into Practice**

The MDS Foundation Working Group on Transfusional Iron Overload published a consensus statement that assists clinicians in deciding which MDS patients should be considered for chelation therapy. The key features are summarized in Table 2. In general, chelation therapy may delay organ complications and possibly extend survival in lower-risk MDS patients when initiated after the serum ferritin level exceeds 1,000 μg/L.

The characteristics of the two chelating agents available in the United States are summarized in Table 3. Deferasirox, the only oral agent, is generally preferred because of ease of administration, tolerance, compliance, and maintenance of quality of life; however, close observation and laboratory monitoring is necessary, given the recent FDA warning. Chelation therapy is generally continued as long as the patient is receiving RBC transfusions and the ferritin level exceeds 1,000 μg/L, provided that the drug is well tolerated.

**Conclusions**

Patients with lower-risk MDS have a survival expectancy often measured in years. However, a significant number of these patients will develop RBC transfusion dependence, which raises the potential for iron overload. Body iron stores generally become saturated after 20 or more units of RBCs, with an incremental negative impact on mortality and quality of life. Iron chelation therapy reduces serum ferritin levels over time in MDS patients, and a prospective survey suggests that this may also translate into improved survival. A phase III placebo-controlled trial is underway to test the long-term benefit of deferasirox in transfusion-dependent patients with MDS. This study and longer follow-up of phase II chelation trials will provide needed insights into the impact of chelation therapy on organ function and survival. Clinical guidelines point to the need for surveillance of MDS patients who are receiving transfusions for evidence of iron overload, proper patient selection for iron reduction, and close monitoring of patients once treatment to reduce excess iron has been initiated.

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**References**


<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Mode of Administration</th>
<th>Usual Dosage Regimen</th>
<th>Dominant Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deferoxamine</td>
<td>Parenteral: SC, IV, IM</td>
<td>1 to 2 g SC infusion overnight, 5 to 7 nights per wk</td>
<td>Dizziness, vision impairment, hearing impairment</td>
</tr>
<tr>
<td>Deferasirox</td>
<td>Oral</td>
<td>20 mg/kg taken on an empty stomach, 30 minutes before food</td>
<td>Diarrhea, vomiting, nausea, abdominal pain, skin reactions, elevated serum creatinine</td>
</tr>
</tbody>
</table>

Table 3. — Comparison of the Two Chelating Agents Available for Use in the United States