Myelodysplastic Syndromes: Iron Overload Consequences and Current Chelating Therapies

Peter L. Greenberg, MD, Stanford, California

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Abstract
Chronic red blood cell transfusion support in patients with myelodysplastic syndromes (MDS) is often necessary but may cause hemosiderosis and its consequences. The pathophysiologic effects of iron overload relate to increased non-transferrin bound iron generating toxic oxygen free radicals. Studies in patients with MDS and thalassemia major have shown adverse clinical effects of chronic iron overload on cardiac function in patients who underwent polytransfusion. Iron chelation therapy in patients with thalassemia who were effectively chelated has prevented or partially reversed some of these consequences. A small group of patients with MDS who had undergone effective subcutaneous desferrioxamine (DFO) chelation for 1 to 4 years showed substantial hematologic improvements, including transfusion independence. However, because chronic lengthy subcutaneous infusions of DFO in elderly patients have logistic difficulties, this chelation therapy is generally instituted late in the clinical course. Two oral iron chelators, deferiprone (L1) and deferasirox (ICL670), provide potentially useful treatment for iron overload. This article reviews data indicating that both agents are relatively well tolerated, were at least as effective as DFO for decreasing iron burdens in comparative thalassemia trials, and (for deferiprone) were associated with improved cardiac outcomes. These outcomes could potentially alter the tissue siderosis-associated morbidity of patients with MDS, particularly those with pre-existing cardiac disease. (JNCCN 2006;4:91–96)

Management of patients with myelodysplastic syndromes (MDS) requires general supportive care and therapies that specifically attempt to alter hematopoietic defects in the disease. Supportive care measures include transfusion and antibiotic treatment of the patient’s symptomatic cytopenias. In addition, because of the large number of red blood cell (RBC) transfusions often needed for the patients’ symptomatic anemia, and the ineffective erythropoiesis ongoing in MDS, tissue iron overload may frequently be a prominent clinical feature. This review focuses on the potential consequences of and therapeutic approaches to managing tissue iron overload in MDS. This management is now more relevant because, in addition to the currently available subcutaneous iron chelator desferrioxamine (DFO), two oral iron chelators now in clinical trials hold promise for diminishing the negative consequences of iron overload.

Most patients with MDS are anemic, often symptomatically so, and require RBC transfusions or specific cytokine therapy (e.g., with recombinant human erythropoetin) to improve hemoglobin levels. End-organ damage from consequent tissue siderosis in patients with MDS generally relates to cardiac, hepatic, or endocrine dysfunction. Because the patients are often elderly, pre-existing or coexisting disorders of these organs may exacerbate the effects of iron overload.

MDS is a heterogeneous disease in which individuals may have early or advanced stages of the illness. The risk for rapid evolution of acute myeloid leukemia (AML) or severe marrow failure predominates in the advanced stage, generally requiring active therapies to try to alter the natural history of the disease. However, for early-stage disease, chronic anemia and its consequent excessive RBC transfusion requirements often engender tissue iron overload, which may further contribute to the patient’s morbidity.
Pathogenetic Features

Several pathogenetic mechanisms contribute to increased apoptosis of hemopoietic stem cells and their progeny in MDS. These lesions are both endogenous (within the stem cell compartment) and exogenous (within the marrow stromal microenvironment). Oncoprotein abnormalities, telomere changes, genetic instability, deranged apoptotic signaling, gene mutations, and increased oxidant stress susceptibility that leads to mitochondrial dysfunction exist within MDS stem cells. Within the marrow stroma, inhibitory cytokines, increased toxic oxidants, decreased stimulatory cytokines, increased angiogenesis, and damaged microenvironmental adherence contribute to damaging the hematopoietic precursor cells.

Comparison of Biologic Features in Iron Overload States

Comparison of MDS and thalassemia major, two diseases with marked tissue siderosis, indicates that both have ineffective erythropoiesis, although in MDS it is prominent in early-stage disease when marked ineffective erythropoiesis, mitochondrial dysfunction, apoptosis, and oxidation damage related to non-transferrin bound iron (NTBI) occur. As the disease progresses, decreased apoptosis occurs, associated with an increased potential for expansion of the abnormal clone. However, stromal abnormalities also occur in MDS, such that increased levels of tumor necrosis factor and several other inhibitory cytokines that cause stem cell damage are elaborated in situ. These abnormalities (other than excessive NTBI) are not present in thalassemia.

The cellular target is different in the two diseases; the hematopoietic stem cell and its progeny are the main targets in MDS, whereas the erythroid progeny is the target in thalassemia. Multiple genetic lesions occur in MDS, whereas the globin gene is the locus of thalassemia. The genetically targeted lesions provoke leukemic potential in MDS but not thalassemia. The risk for AML can progress from very low in early-stage MDS to very high in later stages, possibly contributed to by the genotoxic oxidative damage and stromal abnormalities. Thus, researchers should attempt to improve the negative consequences of iron overload in both clinical states.

Measurements of Tissue Iron

Liver biopsy iron is currently the standard measurement used for liver iron content (LIC) measures. Serum ferritin levels are useful in measuring iron overload, but are also limited because ferritin is an acute-phase reactant that becomes elevated in various inflammatory situations and with hepatic damage. The Superconducting Quantum Interference Device (SQUID) has been a useful and accurate non-invasive means to assess LIC. However, the rarity of the device (4 machines worldwide) make this a limited option for general assessment of tissue iron. Recently, special magnetic resonance imaging (MRI) techniques (termed \( T2^* \)) were developed to quantify tissue iron levels. Data from St. Pierre et al. in Australia showed good correlation between LIC determined through biopsy and through \( T2^* \) MRI in a variety of iron overload states. This method will be very helpful in determining the effectiveness of chelation in patients with MDS for whom liver biopsies pose a clinical risk (those with thrombocytopenia or thrombocytopathy).

Various methods evaluate in vitro NTBI, including directly chelatable, mobilizer-dependent chelatable, or labile plasma iron. A collaborative study between investigators in Israel and Thailand showed that effective doses of deferiprone (L1) caused a marked decrease in the oxidant redox compounds of iron in plasma.

Anemic MDS patients who have undergone polytransfusion have shown increased levels of plasma NTBI. NTBI increments were most prominent in individuals with relatively low-risk disease, associated with enhanced bone marrow apoptosis with increased markers of lipid peroxidation damage (e.g., serum malondialdehyde).

Clinical Effects of Iron Overload

This review focuses on the effects of intramedullary toxic oxidants extant in MDS. With iron overload, when plasma iron exceeds transferrin's binding capacity, the increased NTBI combines with oxygen to form hydroxyl radicals. These toxic elemental byproducts can engender lipid peroxidation and damage to cell membranes, protein, and DNA. Although members of the Bcl2 family block this effect, the level of intracellular Bcl2 may be diminished in some clinical situations (e.g., MDS), resulting in increased
apoptosis of hematopoietic precursor cells and their hematopoietic progeny.14,15

Most of the data on the consequences of tissue iron overload come from studies in patients with thalassemia major. Studies involving such patients who had received multiple transfusions indicate that thresholds for cardiac disease were reached when excess iron is present.16–19 When the LIC reached approximately 10 to 15 mg/g dry weight (approximately 40 transfusions), iron overload led to excessive toxicity in various organs. However, cardiac disease was markedly diminished for patients with thalassemia who received effective chelation therapy that resulted in serum ferritin levels less than 2,500 ng/mL for more than 33% of the time.20

In an initial study evaluating the effects of chelation therapy on iron overload in 15 adult patients with MDS who received multiple prior transfusions (mean, 110 transfusions per patient) biopsy showed increased serum ferritin levels and LIC. This increase was associated with organ damage, such as fibrosis and dysfunction of the liver, heart, and various endocrine organs.1

A larger study evaluated 239 patients with generally low-risk MDS, of whom 46 underwent polytransfusions (> 50 transfusions, with a mean of 79).4 Of these individuals, 40% had evidence of secondary hemochromatosis (with predominantly cardiac organ dysfunction). Secondary hemochromatosis was most prominent in patients with the refractory anemia with ringed sideroblasts (RARS) subtype of MDS. More than 40% of the patients had left ventricular dysfunction or cardiac arrhythmias, and 30% had congestive failure as a major cause of death. Hepatic dysfunction and diabetes were also present. In a retrospective analysis, these patients had shorter survivals than historic controls who had not undergone polytransfusions.

Prior Studies of Chelation Therapy in Myelodysplastic Syndromes

The data for iron chelation in MDS are currently limited. Provocative and encouraging data come from a Danish study in 1996 involving 11 patients with multiple prior transfusions (mean of 90), increased serum ferritins, high liver iron by MRI, and evidence of marrow dysfunction (i.e., thrombocytopenia, neutropenia).21 These individuals received subcutaneous DFO chelation for a median of approximately 2 years. A substantial proportion of these individuals showed improvement in hematologic parameters after effective chelation, with an increase in hemoglobin levels, neutrophil counts, or platelet counts. Of the 11 patients, 7 had erythroid responses with a dramatic decrease in RBC transfusion requirements. All 4 patients with initially less than 20,000 platelets/mm³ who received chelation therapy showed improved levels, and the 6 who were neutropenic also showed improved neutrophil counts. Neither the marrow iron nor the French-American-British (FAB) morphologic grouping changed after this therapy. This finding is consistent with improvement in hematopoiesis after effective iron chelation associated with alleviated toxic marrow damage.

These investigators also evaluated the cardiac effects of iron chelation in patients with MDS.22 These individuals underwent polytransfusions, had high serum ferritin, liver, and cardiac iron levels, and showed a decrease in cardiac iron after subcutaneous DFO chelation, associated with a decrease in chelatable NTBI.

A collaborative international group evaluated the therapeutic effects of the oral iron chelator deferiprone in a small group of patients with thalassemia intermedia.23 Some of these patients showed decreases in iron content associated with increments in hemoglobin and decreased need for RBC transfusion. These data also suggested that improving the marrow microenvironment by iron chelation may improve hematopoiesis. However, this apparently beneficial effect of iron chelation therapy on hematopoiesis requires extension and confirmation.

Categorization of Myelodysplastic Syndromes Risk Status

Prognostic risk factors have been defined for clinical outcomes (e.g., survival, AML evolution) to categorize disease stage in MDS. The International Prognostic Scoring System (IPSS) indicates that at least 3 factors are critical for this evaluation: proportion of marrow blasts; cytogenetic risk category; and number of cytopenias.24 Patient age also plays a major role in assessing survival. The categories low and intermediate-1 are associated with relatively lower-risk disease, whereas intermediate-2 and high categories are relatively higher-risk. Since development of the IPSS, studies have indicated that the immunophenotype of the marrow myeloblasts, degree of marrow cell
apoptosis, marrow neovascularity, and the intramedullary expression of various cytokines and molecular abnormalities play important roles in the pathogenesis and prognosis of MDS.

**Therapeutic Approaches for Iron Chelation in Myelodysplastic Syndromes**

The NCCN’s Myelodysplastic Syndromes Clinical Practice Guidelines panel has recommended consideration of specific clinical factors for managing patients with MDS. For patients with clinically significant cytopenias, IPSS score, performance status, and age are important determinants in the therapeutic algorithm. For patients in the IPSS low and intermediate-1 categories (with lower-risk disease), hematologic improvement is generally suggested, whereas for those in the intermediate-2 and high categories (the higher-risk patients), therapy is aimed at altering the natural history of the disease.

The panel recommends iron chelation for relatively low-risk polytransfused patients who have received (or are anticipated to receive) 20 to 40 units or more of red cells (≥ 5 to 10 g of iron), particularly those with evidence of organ (e.g., cardiac, endocrine, hepatic) dysfunction. Iron chelation is less likely to be useful for individuals with higher-risk disease because clinical issues other than tissue siderosis are generally more prominent (e.g., treatment needed for hematopoietic failure, potential progression to AML).

However, obstacles to using DFO therapy exist, even for those recommended to receive the drug. The predominant difficulty is that the drug generally must be administered as a subcutaneous infusion for 8 to 12 hours, 5 to 7 nights per week. This timing is required because of the short half-life of the drug (0.5 h), but patients and health care providers often find this approach burdensome. Other impediments to using DFO include: poor compliance; lack of patient preference; potential drug toxicity; and the lack of proven efficacy of iron chelation for altering organ damage or survival in MDS.

To assess the point of current practice patterns, a questionnaire was submitted to members of the Myelodysplastic Syndromes Clinical Practice Guidelines panel inquiring about their individual institution’s iron chelation practice for patients with MDS. Their responses indicated, in the relatively low-risk patients (IPSS low and intermediate-1), approximately 65% patients had symptomatic anemia and 50% had symptomatic anemia and were receiving chronic transfusion therapy. However, only 15% were receiving chelation therapy. When asked the proportion of patients who should undergo chelation, the panel suggested approximately 60% to 70% of patients. In contrast, the number of patients who had symptomatic anemia was still high for those with IPSS intermediate-2 (high-risk) MDS. However, the percentage of patients receiving chelation was low (approximately 15%), and, not unexpectedly, fewer panel members (approximately 40%) believed the patients should undergo chelation. These data supported the belief that major impediments (discussed previously) exist against the use of DFO therapy for chelation in iron-overloaded patients with MDS.

**Oral Iron Chelating Agents: Therapeutic Results**

Several clinical trials have been performed with 2 oral iron chelators: deferiprone (L1) and deferasirox (ICL670). Deferiprone is administered orally 3 times daily, has a half-life of 2 to 3 hours, and is renally excreted. Deferiprone has had extensive use in thalassemia trials. Data from 5 trials with more than 20 patients per trial treated for at least 1 year with a standard dose of 75 mg/kg/d or more indicated decreased or stable values for serum ferritin (417 patients), liver iron (156 patients), and cardiac iron (151 patients). Phase III trials (comprising approximately 300 patients) comparing this drug with DFO also showed increased or equal efficacy of the two drugs at decreasing tissue iron. Eleven deferiprone trials in thalassemia (including those mentioned previously) that comprised more than 1,000 patients indicate the relatively lower incidence of adverse events, including transient gastrointestinal symptoms, arthropathy, or increased hepatic enzyme abnormalities in 7% to 11%. However, some patients experienced important adverse effects of the drug, including agranulocytosis (1%) and neutropenia (5%), that required careful monitoring of leukocyte counts.

Deferasirox has a somewhat longer half-life of 12 to 16 hours, is administered once a day, and is excreted by hepatobiliary means. This drug has undergone trials in thalassemia demonstrating its good safety and tolerability profile. A phase III trial compared its efficacy to that of DFO in patients with thalassemia.
major. The drugs showed comparable efficacy in stabilizing levels of ferritin using 2 different doses of deferasirox over 1 year. The studies also showed that, at least at higher doses (20 and 40 mg/kg/d), deferasirox was also comparable with DFO for decreased or stabilized LIC levels. In these trials, mild transient nausea, diarrhea, and rash were the main, though uncommon, adverse effects of this drug.

Recent studies have evaluated the efficacy and tolerance of deferasirox in iron-overloaded patients with various causes of anemia (N = 184), including those with MDS (n = 47). These results show that good tolerance and effective, dose-dependent decreases or stabilization of body iron levels (LIC and serum ferritin levels) occurred with 20 and 30 mg/kg/d deferasirox in this broad group of patients. Researchers noted these effects over a 1-year treatment period for all levels of iron intake (i.e., RBC transfusions) and also at 10 mg/kg/d for patients with relatively low iron intake levels.

**Effects of Oral Iron Chelation on Cardiac Disease**

Deferiprone has been compared with DFO for effects on cardiac disease. A retrospective study by Piga et al. evaluated young patients with thalassemia who were RBC transfusion-dependent and treated for more than 4 years (median of 6 years). A small proportion of patients in both study arms had pre-existing cardiac disease, but a much higher proportion developed cardiac disease when receiving DFO compared with deferiprone. More deaths occurred in patients who received DFO compared with deferiprone. Cardiac disease-free survival was improved more for those receiving deferiprone than those receiving DFO. Thus, this study showed deferiprone to be at least as effective as DFO in diminishing cardiac toxicity in these iron-overloaded patients.

**Future Directions**

These studies indicate that body iron stores in patients with various anemias may be managed effectively with use of the oral iron chelators deferiprone and deferasirox. Further studies with these drugs are ongoing and warrant extension. These agents are being used singly or in combination with subcutaneous DFO to evaluate their safety and clinical efficacy profiles. Efficacy assessment will need to include evaluation of hepatic and cardiac iron, plasma NTBI, end-organ function, hematologic function, and quality of life. Use of noninvasive measurements of tissue iron stores (i.e., with T2* cardiac and hepatic MRI) to assess clinical efficacy of these agents will be a valuable and practical method. Researchers must determine whether improved clinical outcomes (e.g., less cardiac toxicity, improved hematologic parameters and survival) will occur in patients with MDS receiving effective iron chelation.

**References**