Consequences of Iron Overload in Myelodysplastic Syndromes

a report by
Peter L Greenberg, MD

Director, Stanford MDS Center

DOI: 10.17925/OHR.2006.00.02.72

Peter L Greenberg, MD, is Emeritus Professor of Medicine (Hematology Division) and the Director of the Stanford MDS Center at the Stanford University Cancer Center. Dr Greenberg's clinical and research interests focus on improving the understanding of the biology, prognosis and treatment of myeloid clonal hemopathies such as myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). Dr Greenberg coordinated the International MDS Risk Analysis Workshop. This collaboration generated the current International Prognostic Scoring System (IPSS) for MDS. In 1997, Dr Greenberg was awarded the JP McCarthy International Prize for outstanding research in MDS. He is currently Chairman of the National Comprehensive Cancer Network (NCCN) Panel on MDS Treatment Guidelines and is a member of the Leukemia Core Committee of the Eastern Cooperative Oncology Group (ECOG). His work with ECOG includes the role of Principal Investigator and co-Principal Investigator of several national clinical trials treating MDS and AML. He has authored or co-authored over 140 papers, edited a recent comprehensive book on MDS and is Board Certified in Hematology and Internal Medicine.

A rising incidence of myelodysplastic syndromes (MDS) associated with an aging population is placing an increasing disease burden on both patients and the health-care system. The disease itself is a heterogeneous clonal, hematopoietic stem cell disorder. It is characterized by ineffective and dysplastic hematopoiesis and MDS patients have widely variable cellular hematopoietic features, chromosomal abnormalities, clinical manifestations, and prognoses. The course of the disease may be indolent or aggressive, with progression to acute myeloid leukemia (AML) occurring in approximately one-third of adult MDS patients, and in the more advanced stages is associated with poor prognosis (median survival: 6–12 months).[1,2] The majority of adult MDS patients are asymptomatic or present with symptoms associated with anemia.[3,4] In the early stages of MDS, approximately 80% of adult MDS patients have anemia that is refractory to iron, folate, and vitamin B12 supplementation.[3,4] Anemia and its associated symptoms, particularly fatigue, are debilitating for MDS patients and adversely affects quality of life (QOL). Indeed, the burden associated with anemia, in terms of reduced QOL and economic cost, is much greater than generally appreciated.[5]

Management of patients with MDS who are not candidates for hematopoietic stem cell transplant (HSCT) requires general supportive care and therapies that specifically attempt to alter hematopoietic defects in the disease. These measures include transfusion and antibiotic treatment of the patient's symptomatic cytopenias.[6] Over 40% of MDS patients require red blood cell (RBC) transfusions at some stage of the disease. Moreover, a substantial proportion of MDS patients of all prognostic risk groups are RBC transfusion-dependent.[7] Importantly, because of the large number of RBC transfusions often needed for the patients' symptomatic anemia and the ineffective erythropoiesis on-going in MDS, tissue iron overload may frequently be a prominent clinical feature.[8] End-organ damage from consequent tissue siderosis in patients with MDS generally relates to cardiac, hepatic, or endocrine dysfunction.[9] Furthermore, because the patients are often elderly, pre-existing or co-existing disorders of these organs may exacerbate the effects of iron overload. This brief review focuses on the potential consequences of tissue iron overload in MDS and the management of the complication with iron chelation therapy.

Iron Overload—Screening and Monitoring

Serum ferritin levels are widely used to quantify iron overload, but are also limited because ferritin is an acute phase reactant that becomes elevated in various inflammatory situations and with hepatic damage. With this limitation in mind, the serum ferritin variations may be considered useful background for monitoring the individual patient. The latest US National Comprehensive Cancer Network's (NCCN's) guidelines recommend monitoring serum ferritin, especially in patients who have previously received 20–30 units of RBCs, with an aim to decrease ferritin levels to <1,000ng/ml.[10] The single most useful index of iron overload is the measure of hepatic iron or liver iron concentration (LIC). Liver biopsy provides a quantitatively accurate and specific test for LIC. However, due to the invasiveness of liver biopsy, LIC is not commonly used to screen for iron overload in MDS. The Superconducting Quantum Interference Device (SQUID) is an accurate non-invasive means to assess LIC, but due to the rarity of the device (four machines worldwide), this is a limited option for general assessment of tissue iron. Magnetic resonance imaging (MRI) techniques (termed T2*) have also been developed to quantify tissue iron levels. A good correlation between LIC determined through biopsy and through T2* MRI in a variety of iron overload states has been demonstrated.[11] Thus, T2* MRI will be very helpful in determining the effectiveness of iron chelation therapy in patients with MDS for whom liver biopsies pose a clinical risk (those with thrombocytopenia or thrombocytopathy).

Clinical Consequences of Iron Overload

With iron overload, when plasma iron exceeds transferrin's binding capacity, the increased non-transferrin bound iron (NTBI) combines with oxygen

to form hydroxyl radicals.[12] These toxic byproducts can cause lipid peroxidation and damage to cell membranes, protein, and DNA. Members of the Bcl2 family block this effect, however, in some clinical situations, such as MDS, the level of intracellular Bcl2 may be diminished. This can result in increased apoptosis of hematopoietic precursor cells and their hematopoietic progeny.

Studies in thalassemia major patients have provided much of data on the consequences of tissue iron overload. In patients with thalassemia receiving multiple transfusions, when the LIC reached approximately 10–15mg/g dry weight (approximately 40 transfusions), iron overload led to excessive toxicity in various organs.[13,14] Importantly, cardiac disease was diminished markedly for thalassemia patients who received effective chelation therapy that resulted in serum ferritin levels less than 2,500ng/ml for more than 33% of the time.[15]

In a study assessing the clinical sequelae of transfusional iron overload in 15 nonthalassemic adults who received multiple prior transfusions (mean 120 transfusions per patient), liver 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.[9]

In a retrospective analysis of transfusion data in 46 patients with generally low-risk MDS who underwent polytransfusions (>50 transfusions, with a mean of 79), 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, which suggests that cardiac abnormalities are the most frequent and serious clinical complications in patients with MDS. In addition, 26% suffered from hepatic impairment and 11% developed diabetes mellitus. These patients had shorter survivals than historic controls who had not undergone polytransfusions.[16] A recent study assessed prognostic factors in 467 patients with MDS who have iron overload. Data from the study showed decreased survival for RBC transfusion dependent low-risk patients compared with those patients not requiring transfusions.[17] This effect was noticeable mainly among the patients with refractory anemia who had longer survival and were therefore more prone to develop manifestations of long-term toxicity from iron overload. The study used a serum ferritin level of 1,000ng/ml as a threshold for distinguishing between mild and clinically relevant iron burden. In the study, patients receiving a median number of 21 units of RBCs passed this threshold.

Management of Iron Overload

Iron chelation therapy is the treatment of choice in the management of iron overload. As with the data on the clinical consequences of iron overload, most of the data on iron chelation are from studies in thalassemia major patients. Data for iron chelation in MDS are currently somewhat limited. The NCCN Myelodysplastic Syndromes Clinical Practice Guidelines panel recommends consideration of specific clinical factors for managing patients with MDS. For patients with clinically significant cytopenias, International Prognostic Scoring System (IPSS) score, performance status, and age are important determinants in the therapeutic algorithm. Patients with lower risk disease (low IPSS and intermediate-1 categories), hematologic improvement is generally suggested, whereas for the higher-risk patients (intermediate-2 and high IPSS categories), 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) 20–30 RBC transfusions, particularly those with evidence of cardiac or 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, for example, hematopoietic failure, potential progression to AML.[10]

The reference standard therapy for the treatment of iron overload was deferoxamine, a hexadentate iron chelator. It binds iron in a 1:1 ratio and forms a stable complex, which is excreted in bile or urine. There is extensive clinical experience with deferoxamine as an effective approach for iron chelation therapy. However, obstacles to using deferoxamine therapy exist. The predominant difficulties relate to deferoxamine's route of administration and dosing regimen. Generally it must be administered as a subcutaneous infusion for 8–12 hours, 5–7 nights per week, but patients and healthcare providers often find this approach burdensome. Moreover, the use of deferoxamine is hampered by poor patient compliance, potential drug toxicity, and the lack of proven efficacy of iron chelation for altering organ damage or survival in MDS.

To overcome the limitations of deferoxamine, oral iron-chelating agents were developed to address compliance issues and the deficiencies of deferoxamine therapy. Deferasirox was recently approved by the US Food and Drug Administration (FDA) as the first oral iron chelator for treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients two years of age and older. Deferasirox belongs to a new class of

tridentate chelators and has a half-life of 12–16 hours. It binds iron in a 2:1 ratio and it is primarily excreted in bile. It is administered orally, in tablet form, once daily. The pivotal efficacy study for the drug was conducted in regularly transfused patients with thalassemia major. The comparative multicenter, randomized trial compared the efficacy of deferasirox to that of deferoxamine.[18] The drugs showed comparable efficacy in stabilizing levels of ferritin using two different doses of deferasirox over one year. Patients were randomized to receive doses of deferasirox (n=296) or deferoxamine (n=290) that were dependent on their baseline LIC. The study showed that at higher doses, deferasirox was comparable with deferoxamine for decreased or stabilized LIC levels. Deferasirox once daily for one year at the 20mg/kg dose level (which corresponds to 40mg/kg of deferoxamine) led to maintenance of LIC, and the 30mg/kg dose level produced a statistically significant and clinically relevant reduction in LIC, effects that were mirrored by changes in serum ferritin. Lower doses of deferasirox did not induce and maintain a negative iron balance in these patients.

In a recent study evaluating the efficacy and tolerance of deferasirox in iron-overloaded patients with various causes of anemia (n=184), including 47 patients with MDS, deferasirox (20 and 30mg/kg/d) demonstrated good tolerance and effective, dose-dependent decreases or stabilization of body iron levels (LIC and serum ferritin levels).[19] In the multicenter phase II study, a total of 152 patients (83%) completed one year of treatment, and 147 (80%) had an end-of-study LIC measurement. Although deferasirox doses of 5 and 10mg/kg/d were insufficient to reduce body iron levels, a dose of 10mg/kg/day was able to decrease LIC and stabilize serum ferritin in patients with an iron intake rate of <0.3mg/kg/d. Deferasirox 10mg/kg/d also maintained iron balance in MDS patients who received a lower rate of iron intake. In contrast, doses of deferasirox of 20–30mg/kg were able to achieve effective iron chelation and removal for MDS patients receiving higher intake of iron (i.e. RBC transfusions).

Conclusion

Iron overload is a cumulative toxicity and is associated with significant morbidity and mortality. Effective iron chelation therapy has been shown to improve survival in patients with thalassemia major and further chelation studies are on-going in the MDS population and warrant extension. Efficacy assessment will need to include evaluation of hepatic and cardiac iron, plasma NTBI, end-organ function, hematologic function, and QOL. The latest NCCN guidelines have incorporated oral deferasirox as a new option in the management of iron overload. The MDS panel strongly recommends the consideration of deferasirox as an iron-chelating agent for lower risk MDS patients who have received greater than 20–30 RBC transfusions. ■

Editorial assistance supported by Novartis Pharmaceuticals, Inc.

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