

Should Patients with Myelodysplastic Syndromes Undergo Iron Chelation Therapy? New Data Answering the Question

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Abstract

Although it is well established that transfusional iron overload leads to organ impairment and shortened survival among children with thalassemia and sickle cell anemia, the role of transfusional iron overload and its treatment among older individuals with the myelodysplastic syndromes (MDS) remains unclear. Recent reviews have noted that MDS patients requiring frequent red blood cell transfusions experience higher rates of cardiac, hepatic, endocrine, and other organ damage in patterns similar to pediatric transfusional hemochromatosis, with increased rates of transformation to leukemia and decreased survival. Through the use of prognostic scoring systems such as the International Prognostic Scoring System (IPSS) and the World Health Organization (WHO) classification-based prognostic scoring system (WPSS), MDS patients with projected survivals long enough to warrant concern about the toxicities of iron overload can be identified and iron chelation therapies can be considered. The results of two large prospective trials among transfusion-dependent MDS patients, US03 and EPIC, have demonstrated that the oral iron chelation agent deferasirox can successfully reduce iron content and has an acceptable safety profile in this elderly population. Furthermore, retrospective trials have suggested that iron chelation therapy may prolong survival in MDS, and prospective trials are being planned. This article will highlight some of these issues.

Keywords

Iron overload, red blood cell transfusion, myelodysplastic syndromes, iron chelation, deferasirox

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The myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis in one or more cell lines, leading to peripheral cytopenias with a tendency to develop into acute leukemia. Supportive care with red blood cell (RBC) transfusions is the mainstay of treatment, although newer 'low-intensity strategies' such as hypomethylating and immunomodulatory agents are changing treatment patterns. With repeated transfusions comes the risk of transfusional iron overload. However, should patients with MDS undergo iron chelation therapy (ICT)? New data are available that can help to answer this question.

Do Patients with Myelodysplastic Syndromes Suffer Organ Impairment from Iron Overload or Is this Identified Only in Children with Thalassemia or Sickle Cell Anemia?

Transfusion-related hemochromatosis has been identified in elderly MDS patients who are transfusion-dependent. A retrospective study of 46 MDS patients who had received >50 units of RBC transfusions noted evidence of cardiac disease in >40% of patients, arrhythmias in 10, and 14 deaths from intractable congestive heart failure. Evidence of hepatic enzyme abnormalities occurred in approximately 25% of patients, and

evidence of new endocrine effects was identified in approximately 10% of individuals.¹ An Italian series also identified a high rate of cardiac, diabetes/glucose intolerance, and hepatic enzyme abnormalities among 26 heavily transfused patients. Transfusion requirements >2 units per month were correlated with increased organ toxicity.² A retrospective study from Japan of 292 patients (52% MDS, 31% aplastic anemia) followed over a course of four years noted that >90% of the patients who had a ferritin level >1,000mcg/l had evidence of hepatic enzyme insufficiency (elevation in serum glutamic pyruvic transaminase/serum glutamic oxaloacetic transaminase [SGPT/SGOT]). Among the 75 deaths in this group of patients, the individuals who died from chronic liver failure or cardiac disease had received significantly more transfusions than those patients who died from other causes.³

Recent retrospective large database reviews have also demonstrated the negative impact of chronic transfusions on organ function among elderly patients with MDS. In a study of a US Medicare database, a cohort of 705 new cases of MDS was followed for three years. During the study period, 522 (74%) suffered a cardiac-related event, including 142 myocardial infarctions (MIs) (20%), 344 chronic heart failure (CHF) (49%), and 374 arrhythmias (53%). In comparison, of the approximately 1.7

million individuals in the Medicare database, 726,936 (42%) suffered cardiac disease during the three-year study, significantly fewer than in the MDS cohort ($p < 0.001$). MDS patients who received blood transfusions experienced a higher rate of cardiac events: 260 transfused MDS patients (80%) experienced a cardiac event compared with 262 MDS patients (69%) who did not receive transfusions ($p = 0.002$).⁴ Additional analysis from this cohort has noted that transfused MDS patients were more likely to develop other comorbidities: diabetes 45 versus 38% ($p = 0.09$), dyspnea 64 versus 39% ($p < 0.01$), hepatic events 2.2 versus 1.7% ($p = 0.68$), and infectious complications 81 versus 57% ($p < 0.01$). Transfused MDS patients were also more likely to transform to acute myeloid leukemia (AML) (19 versus 5%; $p < 0.01$) and had a significantly higher mortality rate at three years (63 versus 33%; $p < 0.01$). After adjusting for age, transfusion MDS patients were associated with an increased risk for death compared with their non-transfused MDS counterparts (hazard ratio [HR] 2.14; $p < 0.01$).⁵ A retrospective nested case-control study from a US health insurance claims database also found an increased risk for potential complications of iron overload among MDS patients receiving transfusions (odds ratio [OR] 2.90; $p = 0.0008$). Transfused MDS patients experienced more cardiomyopathy/heart failure (OR 1.62; $p = 0.2955$), conduction/rhythm disorders (OR 4.18; $p = 0.0005$), diabetes (OR 5.06; $p = 0.0025$), and liver disease (OR 3.31; $p = 0.0008$).⁶

Does Chronic Transfusional Support and/or Iron Overload in Patients with Myelodysplastic Syndromes Lead to Shortened Survival?

A review of 467 MDS patients treated at the University of Pavia in Italy between 1992 and 2002 validated the ability of the World Health Organization (WHO) classification system to stratify patients for prognosis. In this analysis, it was also noted that transfusion-dependent patients had a significantly shorter survival than those not requiring transfusions ($p < 0.001$).⁷ Recognition of the important negative impact of chronic transfusions in patients with MDS has led to the development of a new prognostic system, the WHO classification-based prognostic scoring system (WPSS), which incorporates transfusion dependency along with karyotype and WHO subgroup to classify patients into five prognostic groups.⁸

A recent study presented at the American Society of Hematology (ASH) 2008 meetings also sought to evaluate the independent prognostic value of transfusion dependency (as defined in WPSS) and iron overload (defined as serum ferritin level $> 1,000$ ng/ml) in a series of 2,994 patients (median age 74 years) with *de novo* MDS according to French–American–British (FAB) criteria. Multivariate analyses in a set of 902 cases with complete data confirmed that development of iron overload (first variable selected to enter the model, HR 52.4; $p < 0.0001$) and transfusion dependency (second to enter, HR 8.8; $p < 0.0001$) were strongly associated with overall survival and added significant independent prognostic information to that afforded by the International Prognostic Scoring System (IPSS) and WPSS scores or by other characteristics with universally recognized prognostic value. Furthermore, multivariate analyses of AML transformation risk showed that iron overload (first to enter, HR 6.6; $p < 0.0001$) and transfusion dependency (second to enter, HR 3.5; $p = 0.003$) also had an independent impact on that end-point.⁹

Another important question is: if we can identify patients with good-risk MDS (via the IPSS or WPSS prognostic models) who live long enough to suffer consequences of transfusion-iron overload, at what level of iron (ferritin) should we consider chelation therapy? The National Comprehensive Cancer Network guidelines currently recommend consideration of ICT after 20–30 units of RBCs or with a serum ferritin level that exceeds 2,500mcg/l. The goal of therapy is to reduce ferritin levels to below 1,000mcg/l. This ferritin level stems from older data, primarily obtained from children with thalassemia, who developed organ damage from chronic transfusions.¹⁰ More recently, however, the group from Pavia has suggested that we may wish to consider chelation therapy earlier, when the ferritin level approaches 1,000mcg/l. For every 500mcg/l increase in serum ferritin above the threshold of 1,000mcg/l, there was a 36% increase in the risk for death.⁷ Similarly, the group from MD Anderson Cancer Center demonstrated a divergence in the survival curves at a ferritin level of 1,000mcg/l, with a 2.7-fold risk for death and a 30% decrease in survival.^{11,12} As noted above, a Japanese retrospective review noted that among patients whose ferritin values were available, 97% died with ferritin levels above 1,000mcg/l.³ The MDS Foundation, a large international patient advocacy group, supports the use of ICT at a ferritin value of 1,000mcg/l.¹³ A recent Canadian consensus statement recommended consideration of iron chelation for MDS patients with good prognosis (low IPSS or intermediate 1), life expectancy exceeding one year, and a ferritin value $> 1,000$ mcg/l.¹⁴ Similarly, guidelines are being developed worldwide that incorporate good prognosis and ferritin levels.^{15–17} Thus, it appears that we are able to identify lower-risk MDS patients who may survive long enough to suffer the consequences of iron overload and also to identify a level of iron in which toxicity begins.

Will Iron Chelation Therapy Reduce the Iron Burden Among Patients with Myelodysplastic Syndromes?

The use of prolonged subcutaneous deferoxamine was not widespread among patients with MDS.¹⁸ However, the development of a convenient once-daily oral iron chelator, deferasirox (Exjade®, Novartis Oncology), which has been better accepted by patients, has resulted in a re-evaluation of the role of ICT in this patient population.^{19–21}

In the deferasirox licensing trial (Study 108), 47 patients with transfusion-dependent myelodysplasia (median age 66 years) were enrolled. Net iron balance was achieved with 10mg/kg/day and negative iron balance was reached with 20–30mg/kg/day, despite ongoing transfusion requirements. Overall, liver iron content (LIC) changes were dependent on the deferasirox dose ($p < 0.001$) and transfusional iron intake ($p < 0.01$). Changes in serum ferritin and LIC were correlated, thus supporting the potential use of serum ferritin for monitoring deferasirox therapy. Deferasirox had a safety profile compatible with long-term use; the most common adverse events were gastrointestinal disturbances, skin rash, and non-progressive serum creatinine increases.²²

Given the limited experience with deferasirox in the licensing trials among elderly MDS patients, several large multinational studies have been launched. An ongoing trial in the US (US 03) has enrolled 176 patients with low- or intermediate-risk MDS who had baseline ferritin values $> 1,000$ mcg/l and/or had received > 20 units of RBCs. The mean

transfusion rate during the first 12 months of this trial was 3.4 RBC units per month. With a mean daily dose of deferasirox of 21mg/kg/day, the median decrease in serum ferritin at 12 months was 896mcg/l. In patients with elevated baseline labile plasma iron, sustained suppression to the normal range was achieved after three months of treatment.²³

Preliminary data have recently been reported from the largest iron chelation trial to date. The EPIC study is a one-year open-label, single-arm, multicenter trial that targeted patients with transfusion-dependent MDS and iron overload (serum ferritin 1,000ng/ml, >20 transfusions, 100ml/kg of blood, or an R2 magnetic resonance imaging [MRI]-confirmed LIC >2mgFe/g dry weight). Three hundred and forty-one MDS patients (mean age 67.9 years) with a median baseline serum ferritin 2,730ng/ml were enrolled. Mean transfusion duration was 3.6 years. Almost half (48.4%) had not received previous chelation therapy. With a mean dose of 19mg/kg/day of deferasirox over the one-year study, at 12 months there was a significant reduction in median ferritin of 253ng/ml from baseline ($p=0.0019$), and among those completing the year of treatment the median ferritin decreased by 826ng/ml.²⁴

Smaller studies have begun to explore reduction in iron content from specific organs. Among 29 heavily transfused patients with MDS (mean serum ferritin 4,788ng/ml) using deferasirox 20mg/kg/day despite ongoing transfusions of 3.7 units per month, serum ferritin values decreased to 69% of baseline levels over one year. In 24 of the subjects who underwent R2 MRI, a decrease in the level of LIC to 64% of baseline was achieved.²⁵ Of nine MDS patients in a second trial who completed one year of treatment with deferasirox (mean dose 20.1mg/kg/day), the mean serum ferritin values decreased by 1,730 μ g/l ($p=0.30$) and a mean decrease of LIC of 6.93mgFe/g ($p=0.203$) was achieved. The mean labile plasma iron decreased by 0.76 μ mol/l ($p=0.023$) over the year.²⁶ A third trial of 12 patients noted a one-year decline of LIC measured by MRI of 8.5mgFe/g ($p=0.02$), accompanied by a reduction of bone marrow siderosis.²⁷

A reduction in reactive oxygen species and in parameters of oxidative stress has also been demonstrated with deferasirox therapy. Whether this will change the leukemia evolution potential remains unknown.^{28,29}

Does Iron Chelation Therapy Improve Survival in Myelodysplastic Syndromes?

To date, two retrospective studies have addressed the matter of survival with ICT in MDS. Among 178 transfusion-dependent MDS patients treated at St Paul's Hospital in Vancouver from 1981 to 2006, 18 patients received ICT for a median of 22 months. The reasons for offering chelation therapy included elevated ferritin levels ($n=13$), evidence of iron overload ($n=3$), and transfusion history ($n=2$). ICT was associated with significantly longer overall survival among patients with low IPSS or intermediate-1 MDS; median overall survival was not reached at 226 months with chelation versus 40 months among those not receiving chelation ($p<0.003$). Significantly more patients receiving ICT survived to four years (64 versus 43%; $p<0.003$). Leukemia-free survival (LFS) was also improved with ICT. In a subgroup analysis comparing chelated patients with 18 non-chelated matched patients, the median LFS was

not reached at 225 months versus 40 months, and the four-year LFS was 64 and 49%, respectively ($p=0.01$). Receiving ICT remained significant in a multivariate analysis.³⁰

An analysis by the Groupe Francophone Des Myelodysplasies evaluated 165 patients with transfusion-dependent myelodysplasia (median age 77 years). Approximately one-third of the patients had low-risk WHO MDS subtypes, approximately one-quarter had refractory anemia with excess of blasts (RAEB) subtypes, and approximately 16% were unclassified. The IPSS identified approximately 27% of the patients as being at low risk, 32% intermediate risk group I, and was not available for 29% of the patients. Forty-six percent of the patients ($n=76$) received ICT for more than six months. A variety of chelation schedules were utilized, including deferoxamine, deferiprone, and deferasirox.

The median duration of chelation therapy was approximately 35 months. The median interval from MDS diagnosis to start of chelation therapy was approximately 30 months. The chelation therapy group had a significantly lower mean age (70 versus 76 years) and had a greater proportion of low-risk patients (49 versus 27%). However, the mean RBC units transfused were significantly higher in the group who were receiving chelation therapy (104 versus 57 units; $p<0.001$). The median overall survival was significantly improved with chelation therapy (115 versus 51 months; $p<0.0001$). After adjustment for other prognostic parameters (sex, age, IPSS, transfusion requirement), the survival difference remained significant.

When stratified by IPSS, patients in the low-risk category had not reached their median survival with chelation therapy, but median survival was 69 months for those who did not receive chelation ($p=0.002$). For patients with low- and intermediate-risk group I IPSS, the median survival was 115 versus 50 months ($p=0.003$). In the multivariate analysis, the use of appropriate good chelation strategies was found to be a favorable prognostic factor for overall survival.

Similarly, patients with lower IPSS, patients who were receiving fewer than three units of blood per month, and patients <77 years of age all fared better.³¹ These retrospective studies, with appropriate caution for selection bias, suggest that ICT may favorably influence survival in MDS, similar to the well-known beneficial survival effects of ICT among children with thalassemias.

Is Deferasirox Chelation Therapy Safe for an Elderly Patient with Myelodysplasia?

In the US 03 trial of deferasirox chelation therapy in 173 patients with low- or intermediate-risk MDS, 3% discontinued because of serious adverse events and 10% discontinued because of suspected adverse events. Of 147 patients with normal baseline serum creatinine, 26 (18%) increased the upper limit of normal (ULN) (maximum 3mg/dl). New onset of thrombocytopenia and neutropenia was reported in nine of 172 (5%) and 22 of 168 (13%), respectively; none were suspected to be related to ICT.²³

In the EPIC trial, of the 341 MDS patients, 166 (49%) discontinued therapy. Reasons for withdrawal included 13% for drug-related

adverse events and 2% for unsatisfactory therapeutic effect. The most common investigator-assessed drug-related adverse events were diarrhea (32%), nausea (13%), vomiting (8%), abdominal pain (8%), upper abdominal pain (7%), rash (7%), and constipation (6%). Only 25 patients discontinued the study drug for drug-related gastrointestinal events.

In total, 14.7% had two consecutive serum creatinine values >33% above baseline (in normal range), 10.6% had two values above ULN, and 24.9% had two consecutive values both >33% and >ULN; 19 patients had dose decreases, there were 10 dose interruptions due to abnormal creatinine, and there were no progressive increases. One patient (<1%) with normal baseline alanine aminotransferase had an increase that exceeded >10xULN on two consecutive visits.²⁴

Overall, these two large, multicenter trials have confirmed the safety of deferasirox, yielding results consistent with the licensing trials that enrolled primarily young patients with congenital bone marrow failure syndromes; however, these results continue to emphasize the need for adequate monitoring and maintenance of adequate hydration.

Gastrointestinal complaints may be more frequent in this elderly MDS population compared with children, with diarrhea and nausea being the most common adverse events responsible for treatment discontinuation.²¹ Ongoing food interaction trials with deferasirox are

evaluating safety and tolerability questions to increase medication compliance and retention.

Conclusions

In the last decade, the management of patients with MDS has advanced dramatically, with the development of prognostic scoring systems and low-intensity therapies that are improving outcomes. However, as transfusional support remains the mainstay of treatment, an awareness of the potential toxicities and concerns surrounding transfusion-related iron overload is needed. As discussed in this article, recent data suggest that oral ICT with deferasirox can be effective and well-tolerated in this group of elderly individuals. Therefore, it is now imperative for the hematologist caring for patients with MDS to re-examine the role of iron chelation in this population. ■



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