Introduction

The use of iron chelation in myelodysplastic syndrome (MDS) has generated much controversy recently. Interestingly, this debate has been sparked mainly by the availability of the oral iron chelator deferasirox, which is capable of achieving net negative iron balance in a variety of transfusion-dependent anemias including MDS with once-daily dosing. Before the development of the oral iron chelators, deferasirox and deferiprone, the only available iron chelator was deferoxamine, whose short half-life and need for parenteral administration made it impractical for chronic use in the MDS patient.

Proponents of iron chelation argue that iron overload would adversely impact the quality of life and survival of early-stage MDS patients who are likely to live long enough to experience effects of iron overload-induced tissue damage. They cite indirect evidence demonstrating increased cardiac mortality in transfusion-dependent patients as well as those with elevated serum ferritin and extrapolate these findings to suggest that iron overload contributes to increased morbidity and mortality in low-grade MDS. Opponents, on the other hand, point to the lack of direct evidence for deleterious effects of tissue iron overload in MDS and contend that management of iron overload with its side effects and cost detracts from the focus on disease-modifying therapy in MDS. They even liken the concern over iron overload to undue hysteria over other potentially toxic exposures.

In this article, I argue that unlike the case with hemoglobinopathies and other inherited anemias, the major benefit of iron chelation in MDS is not likely to come from reduction in cardiac and other end organ damage due to tissue iron overload, but from a potential favorable impact on 3 other outcomes, namely (1) reduction of infections, (2) improvement in survival after allogeneic hematopoietic stem cell transplantation (HSCT), and (3) delayed leukemic progression. The evidence in favor of this argument is discussed in the following sections.

Pathophysiology of iron overload in MDS

The principal cause of iron overload in MDS is the use of red cell transfusions for anemia. However, an underrecognized cause of iron overload in some patients with MDS is increased absorption of iron from the gut due to ineffective erythropoiesis. HFE mutations and polymorphisms in other regulators of iron metabolism may also influence susceptibility to iron overload. Hence, in certain patients with MDS, iron overload may not correlate well with the number of red cell units transfused and may occur early in the course of disease. The characteristics of such MDS patients who are particularly susceptible to iron overload remain to be defined.

Transfusional iron overload initially leads to accumulation of macrophage iron in tissues such as liver, spleen, and bone marrow. Iron export into plasma from iron-loaded macrophages as well as duodenal enterocytes occurs via the iron export protein ferroportin located on the membrane of these cells. Ferroportin expression in turn is negatively regulated by hepcidin, a key hormone that regulates iron metabolism by inducing the internalization and degradation of ferroportin.

In a study of 16 patients with MDS, urinary hepcidin excretion was undetectable or inappropriately low in most patients despite iron overload, similar to findings in thalassemia intermedia. Decreased hepcidin would mediate increased export of iron into plasma from iron-loaded macrophages as well as from duodenal enterocytes. The suppression of hepcidin is likely mediated by growth differentiation factor 15 (GDF-15)
or other erythroid regulators of iron absorption, the levels of which could be heterogeneous in MDS depending on the degree of ineffective erythropoiesis in a particular patient. Such heterogeneity is supported by the finding of marked variability of sera from MDS patients in their ability to suppress hepcidin expression in a hepatocyte cell line as well as the wide range of hepcidin levels measured in sera of MDS patients. MDS patients with suppressed hepcidin due to ineffective erythropoiesis may therefore be particularly susceptible to deleterious effects of iron overload irrespective of serum ferritin values. The availability of serum immunoassays for hepcidin should facilitate a more comprehensive evaluation of hepcidin levels in MDS and their correlation with tissue and plasma iron.

Role of labile plasma iron

Once the capacity of plasma transferrin to bind iron (released from the macrophage or duodenal enterocyte) is exceeded, non-transferrin-bound iron (NTBI) appears in the plasma. Labile plasma iron (LPI) refers to the toxic, cell-penetrating, redox-active component of NTBI that is directly chelatable. LPI can appear at transferrin saturations below 100% and lead to expansion of the cellular iron pool in susceptible organs. In a study of 176 patients with International Prognostic Scoring System low- and Int-1–grade MDS, 41% had elevated LPI levels.

In addition to excessive export from macrophages and increased intestinal absorption, reduced erythropoiesis as well as use of myelosuppressive chemotherapy also contribute to elevated NTBI in MDS patients. In studies of patients undergoing allogeneic HSCT, NTBI and transferrin saturation peaked as early as day −4, and NTBI was elevated for up to 2 weeks after initiation of the conditioning regimen. A similar rise in NTBI has been shown with induction and consolidation therapy regimens for acute myeloid leukemia as well. Decreased use by the bone marrow as well as increased release of iron from bone marrow and other tissues have been postulated as possible mechanisms for elevation in NTBI after chemotherapy. This spike in NTBI/LPI after myeloablation may at least partly mediate the toxicity of iron overload in patients undergoing allogeneic HSCT and may have particular relevance for infection risk after HSCT or chemotherapy as discussed in “Iron overload and outcome of allogeneic HSCT.”

A phase 2 open-label trial of patients with low- or Int-1–risk MDS showed the ability of deferasirox at a dose of 20 mg/day to lower LPI below a threshold value of 0.5 μM by 3 months in patients who had elevated LPI at baseline. Essentially similar results were reproduced in another study of more than 300 patients with MDS, thereby proving the ability of once daily deferasirox to achieve sustained suppression of LPI levels in MDS patients. Laboratory studies have shown increased reactive oxygen species (ROS) and low reduced glutathione (consequent to excess free iron) in red cells and platelets of MDS patients. These abnormalities could be ameliorated by briefly incubating these cells with deferoxamine or deferiprone. Reduction in parameters of oxidative stress in peripheral blood cells after deferasirox treatment for 3 months has been demonstrated in MDS patients with iron overload.

Elevated LPI therefore is the most likely mediator of tissue damage, infectious risk, and increased transplantation-related mortality in MDS as discussed in detail in this article. Tissue iron and LPI should be correlated with survival in large studies to conclusively prove the adverse effect of iron overload in MDS. The pathophysiology of iron overload in MDS is depicted in Figure 1.

Iron overload and survival in MDS

Transfusion dependency is associated with shortened overall survival (OS) and leukemia-free survival (LFS) in MDS. The major question is whether this effect is mediated by transfusional iron overload itself or if need for red cell transfusion is simply a marker of disease severity. The contribution of anemia itself to cardiac dysfunction in a predominantly older patient population as well as lack of consideration in the International Prognostic Scoring System of the severity of anemia are confounding factors that make this evaluation difficult. Worsening of survival with increasing serum ferritin values has been seen in patients with refractory anemia, refractory anemia with ringed sideroblasts, and 5q− types of MDS, but not in patients with refractory cytopenia with multilineage dysplasia, suggesting that the longevity or other factors in patients with former subtypes make them susceptible to the adverse effects of iron overload.

However, it must be noted that all this evidence is indirect and large prospective studies that correlate accurate markers of iron overload like magnetic resonance imaging measurements of tissue iron and NTBI/LPI with survival are necessary to conclusively determine the impact of iron overload on survival in MDS.
Cardiac iron in MDS

The organ damage of most concern, given the advanced age and comorbidities in many MDS patients, is cardiac dysfunction resulting from myocardial iron deposition. Cardiac iron has been observed at autopsy in patients who have died of acute leukemia and other transfusion-dependent anemias and correlates with number of red cell transfusions. Indirect evidence attributing cardiac iron as a contributor to morbidity and mortality in MDS includes data from retrospective surveys or health insurance databases showing increased cardiac mortality among patients with increased ferritin or transfusion dependence.\(^3,^4\) Such data are confounded by the contribution of anemia itself to cardiac dysfunction as well as the fact that transfusion dependence is a feature of disease severity in MDS.

However, recent studies using the magnetic resonance imaging T2* technique have shown that cardiac iron accumulation is quite variable but infrequent among patients with MDS.\(^24^-^26\) Moreover, cardiac iron in MDS patients does not correlate with serum ferritin or hepatic iron,\(^25^-^28\) but shows correlation with chelatable iron pool as determined by urinary iron excretion, a surrogate for LPI.\(^27\) It remains to be determined whether LPI directly correlates with myocardial iron in MDS.

Mechanisms leading to cardiac iron deposition in particular patients with lower grades of MDS, especially as it relates to hepcidin level, ineffective erythropoiesis, and elevated LPI, need further evaluation in larger studies. Prospective studies correlating cardiac iron with cardiac function and survival as well as studies showing improvement in cardiac function with chelation will be necessary before averting or reversing cardiac dysfunction can be established as a primary goal of iron chelation in MDS.

Iron and infection risk

There is ample evidence in various disease states for the adverse impact of iron overload on the risk for bacterial and fungal infections.\(^28\) However, infection risk remains the least studied aspect of iron overload in MDS. A study done 4 decades ago showed that patients with acute leukemia had markedly decreased or absent unbound iron-binding capacity (a surrogate marker of elevated NTBI and LPI), and sera from such patients supported profuse growth of *Candida albicans* compared with normal sera.\(^29\) Reduced total iron-binding capacity has been implicated in fungal infection risk in granulocytic patients with acute leukemia.\(^30\) The ability of NTBI to support growth of *Staphylococcus epidermidis* has been demonstrated in patients undergoing allogeneic HSCT.\(^31\)

Iron overload increases risk of bacterial and fungal bloodstream infections after allogeneic HSCT as discussed in “Iron overload and outcome of allogeneic HSCT.” The same may apply to neutropenic patients with MDS as well, many of whom would be expected to have elevated LPI. The combination of severe neutropenia, neutrophil dysfunction, and high LPI in higher grades of MDS is particularly conducive to the development of bacterial and fungal infections. This risk can be expected to rise with the use of myelosuppressive agents that further increase NTBI.\(^32^-^35\)

The use of deferoxamine for the purpose of lowering infection risk is complicated by the fact that the iron-bound deferoxamine can act as a siderophore, thereby promoting growth of pathogenic fungi such as *Mucor*.\(^35\) This is not the case with the newer oral chelators deferiprone and deferasirox that appear to have fungicidal effects in vitro and in animal models.\(^34\)

Iron chelators, especially deferasirox with its long half-life, are capable of lowering LPI around the clock and may lower infection risk in MDS even before tissue iron stores are lowered. The benefit of iron chelation on infection risk should therefore be evaluated in future trials of iron chelation for MDS that include patients with higher grades of MDS and severe neutropenia. It is quite possible that reducing risk of infections may emerge as the single most beneficial effect of iron chelation therapy in MDS.

Iron overload and outcome of allogeneic HSCT

Allogeneic HSCT remains the only known curative treatment for MDS. With the increasing pool of available unrelated donors as well as improved prevention and management of transplantation complications, it can be expected that allogeneic HSCT will be an option for an increasing number of patients with MDS.

Iron overload as measured by pretransplantation serum ferritin is common in patients undergoing allogeneic HSCT for MDS.\(^35^-^36\) Pre-HSCT serum ferritin has been shown in multiple studies to adversely impact overall survival as well as other outcomes of HSCT.\(^35^-^39\) This survival impact was more significant in patients with myelodysplasia/acute leukemia compared with patients who underwent transplantation for other indications.\(^35^,^37\) This adverse survival impact has been shown for reduced-intensity HSCT as well, suggesting that lowering conditioning intensity alone may not obviate the risk in iron-overloaded patients.\(^39\) The adverse impact on survival and other outcomes was seen when serum ferritin was looked at as a continuous or dichotomous variable.\(^35\) In a study of patients undergoing allogeneic HSCT for MDS, OS was inferior in patients with serum ferritin more than 1000 μg/L but was not related to transfusion dependence, suggesting that use of red cell transfusions may not be the only factor contributing to elevated serum ferritin.\(^39\) Other adverse consequences of iron overload in the HSCT setting include increased risk of complications such as bloodstream infections and sinusoidal obstruction syndrome.\(^35^,^37^,^40\) Other small studies have shown association of iron overload with invasive fungal infections after allogeneic HSCT.\(^41^-^43\) Interestingly, most of this increase in transplantation-related mortality appears to occur as early as within the first 3 months after HSCT.\(^35^,^37\) This early mortality may be mediated by LPI, which has been shown to rise immediately after initiation of conditioning, most likely due to ablation of the erythron, and remain elevated at least until engraftment.\(^16^,^17\) Measures to suppress LPI during this critical period could have a favorable impact, irrespective of the degree of tissue iron overload. The optimal strategy for this goal remains to be defined since both deferoxamine and deferasirox have disadvantages for use in the immediate peritransplantation period, the former due to increased infection risk and the latter due to gastrointestinal and renal side effects. In a clinical trial of patients undergoing allogeneic HSCT, administration of plasma apotransferrin was able to lower NTBI and restore the inhibitory effect of patient sera on the growth of *S epidermidis* in vitro.\(^31\)

Patients with MDS are often referred to HSCT centers late in the course of disease when a transplantation needs to be performed expeditiously, leaving little time for effective chelation. Currently, there is compelling evidence to support prevention and aggressive management of iron overload to reduce transplantation-related
mortality in MDS patients who are potential candidates for allogeneic HSCT.

**LFS and effect on hematopoiesis**

ROS can induce genomic instability in hematopoietic progenitors. Excessive LPI can lead to increased generation of ROS in MDS progenitors, thereby augmenting their genomic instability. Moreover, iron is a key component of enzymes that are critical for oncogenesis. Hence, it is not entirely surprising that iron chelation would have a favorable impact on LFS, possibly by quenching LPI and thereby inhibiting generation of ROS. Long-acting iron chelators such as deferasirox that are capable of binding LPI around the clock can be expected to be more effective in this regard. Studies published only in abstract form have addressed the impact of iron overload and chelation on OS and LFS in MDS. In a large multicenter study evaluating the impact of iron overload and transfusion dependence on survival of patients with all grades of MDS, iron overload defined as serum ferritin more than 1000 ng/mL was strongly associated not only with OS, but also with LFS in multivariate analysis. An evaluation of 165 MDS patients from 18 centers in France showed a significantly improved OS among patients who received iron chelation compared with nonchelated patients. LFS was not reported in this study. In another study of 18 low- or Int-I–risk MDS patients who were treated with subcutaneous deferoxamine, median LFS was not reached at 226 months compared with a matched control group who had a median LFS of 40 months. These results suggest that LFS should be a key outcome measure in future trials of iron chelation in MDS.

Iron chelation appears to have favorable effects on hematopoiesis in certain patients with MDS. Hematologic improvement by International Working Group 2000 (IWG2000) criteria was observed in 5% of patients in a phase 2 trial of deferasirox for low- and Int-I–grade MDS patients. This effect could be mediated by the effect of deferasirox on suppressing LPI and ROS, thereby inhibiting apoptosis or another independent effect of deferasirox, mediated for instance by its effect on nuclear factor κB. In a laboratory analysis of colony-forming assays from peripheral blood of MDS patients of all grades, patients with elevated serum ferritin had fewer burst-forming unit erythroid colonies but no difference in number of granulocyte-macrophage colony-forming units compared with non–iron-overloaded patients. The effect of iron chelation on colony growth was not tested and hence it cannot be determined whether the difference was due to more advanced disease in iron-overloaded patients. Additional studies are needed to identify characteristics of MDS patients whose hematopoiesis improves with iron chelation.

**Conclusions**

In my opinion, prevailing arguments for and against iron chelation therapy have taken an overly simplistic view of the consequence of iron overload in MDS. Given the heterogeneity of MDS, it is possible that derangements in iron metabolism are equally heterogeneous among patients. Iron overload in MDS has unique pathophysiologic features that make it distinct from hemoglobinopathies and other transfusion-dependent anemias. This warrants assessment of a different set of end points besides end organ damage in future trials of iron chelation. Our knowledge of the regulation of iron metabolism is rapidly expanding and we need to incorporate this understanding into the design of future studies.

Improvement in organ function although relevant and important is unlikely to be the most tangible measure of the benefit of iron chelation in MDS. An undue focus on end organ damage with its attendant necessity for long life expectancy has generally excluded Int-2- and higher–grade MDS patients from trials of iron chelation. It is possible that, contrary to current thinking, this may be precisely the group of patients in whom iron chelation would have a favorable survival impact. There is an urgent need for well-designed randomized trials to evaluate survival benefit of iron chelation therapy in MDS. Decrease in infections, improved outcome of allogeneic HSCT, and delayed leukemic transformation may be the more practical outcomes to evaluate in such trials that should include patients with more advanced grades of MDS.

**Authorship**

**Contribution:** V.P. wrote the paper.

**Conflict-of-interest disclosure:** V.P. is a member of the Speakers Bureau for Novartis and has served as a consultant for Novartis, the manufacturer of deferasirox.

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Objectives of iron chelation therapy in myelodysplastic syndromes: more than meets the eye?

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