



Review article

Myelodysplastic Syndromes and Iron Chelation Therapy

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Abstract. Over recent decades we have been fortunate to witness the advent of new technologies and of an expanded knowledge and application of chelation therapies to the benefit of patients with iron overload. However, extrapolation of learnings from thalassemia to the myelodysplastic syndromes (MDS) has resulted in a fragmented and uncoordinated clinical evidence base. We're therefore forced to change our understanding of MDS, looking with other eyes to observational studies that inform us about the relationship between iron and tissue damage in these subjects. The available evidence suggests that iron accumulation is prognostically significant in MDS, but levels of accumulation historically associated with organ damage (based on data generated in the thalassemias) are infrequent. Emerging experimental data have provided some insight into this paradox, as our understanding of iron-induced tissue damage has evolved from a process of progressive bulking of organs through high-volumes iron deposition, to one of 'toxic' damage inflicted through multiple cellular pathways. Damage from iron may, therefore, occur prior to reaching reference thresholds, and similarly, chelation may be of benefit before overt iron overload is seen. In this review, we revisit the scientific and clinical evidence for iron overload in MDS to better characterize the iron overload phenotype in these patients, which differs from the classical transfusional and non-transfusional iron overload syndrome. We hope this will provide a conceptual framework to better understand the complex associations between anemia, iron and clinical outcomes, to accelerate progress in this area.

Keywords: Myelodysplastic Syndromes; Iron Overload; Chelation Therapy; Cardiac Siderosis.

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Introduction. Recent retrospective studies suggest that MDS are more common than previously recognized; these diseases affect predominantly older individuals, with a median age at diagnosis of >70 years and with >10% of the patients¹ in

Europe and 6% in the United States being younger than 50 years of age.^{2,3}

After the development and introduction of oral iron chelators, the possibility to chelate iron overload in MDS patients became a practical

option. This review will discuss theoretical basis and rationale for iron chelation therapy in transfusion dependent patients affected by myelodysplastic syndrome.

For a rational approach to this problem, emphasis should be reserved for modern improvements in understanding iron metabolism and iron toxicity.

Iron Balance and Overload. Iron is essential for physiological health, playing an integral role in oxygen transport/storage, DNA synthesis, translation, cellular respiration, and a number of metabolic processes.⁴ Excessive iron, however, is injurious to cells, tissues, and organs.

The liver peptide hepcidin (for review see reference)⁵ regulates intestinal iron absorption and iron release from storage cells such as macrophages and hepatocytes. Hepcidin binds to ferroportin causing its internalization and degradation, thus exerting a general inhibitory effect on iron release within the body.^{3,6} The hepcidin-ferroportin pathway is emerging as a therapeutic target for iron modulation,⁷ and a number of animal models have shown how hepcidin mimetics have the capacity to reduce iron overload in response to hepcidin deficiency.⁸ Further, genetic deletion of the hepcidin inhibitor, *Tmprss6*, prevents iron overload in animal models of hemochromatosis and β -thalassemia.^{9,10}

Transferrin is a blood protein that acts both as a chelator and transporter for iron, taking it up into cells via the transferrin receptor 1 (TFR1). Increased iron absorption due to inadequate suppression of hepcidin (primary iron overload) that occurs as a consequence of HAMP regulatory network alterations (as seen in hereditary haemochromatosis) or ineffective erythropoiesis (as seen in non transfusion dependent thalassemia = NTDT), causes oversaturation of transferrin, generation of toxic non-transferrin bound iron (NTBI) and parenchymal iron accumulation. In transfusion-dependent patients (as seen in thalassemia major and myelodysplastic syndrome), iron accumulation occurs in the reticuloendothelial system (RES), in the spleen and liver as a consequence of parenteral input from blood transfusions (secondary iron overload).⁴ When the excess of iron overwhelms homeostatic mechanisms in RES cells, iron spills out into blood,¹¹ and transferrin becomes fully

saturated leading to NTBI and parenchymal iron overload.¹²

NTBI and its component labile plasma iron (LPI) are able to enter the cells via an unregulated automatic way and disturb the delicate intracellular balance between iron utilization, storage, and reactive oxygen species (ROS) formation, finally leading to organelle damage and cell death.¹³ As a consequence of this new acquisition, it follows that iron toxicity might develop long before the clear evidence of overload through the production of tissue reactive iron and consequent reactive oxygen species. Subsequently, iron overload constantly causes toxicity by continuing to produce tissue reactive iron and ROS. In this setting, the capacity to counteract these toxic effects might be relevant to the development of cellular damage.

As MDS is a disease characterized by ineffective erythropoiesis, in which patients may eventually become regularly transfused, both mechanisms are believed to be responsible for the generation of free iron reactive species and iron overload, although to varying degrees and at different stages of transfusion-dependence. The kinetics of iron release from RES cells has been partially studied in MDS, where there is a wide dispersion of hepcidin levels.⁶ **Figure 1** illustrates iron homeostasis in pathologic conditions and the sequence of events that leads to end-organ damage in response to iron overload.

Iron Overload in Myelodysplastic Syndromes.

Myelodysplastic syndromes represent a heterogeneous group of clonal stem cell disorders associated with worsening cytopenias. In general, these patients comprise frail and elderly individuals with multiple co-morbidities. Indeed, the prognosis for these patients has traditionally been so poor to negate consideration for novel therapeutic targets, as the underlying disease process has historically determined outcomes. Moreover, clinical researchers have reserved limited interest to what they call supportive care. However supportive care can, in several instances, substantially improves quality and duration of survival. Obviously for what concern iron chelation therapy intervention with daily subcutaneous chelating agents has not been an attractive option for these patients.

Moreover, novel disease-modifying agents and stem cell therapies have now extended the life

expectancy of these patients, allowing increased supportive care in the form of blood

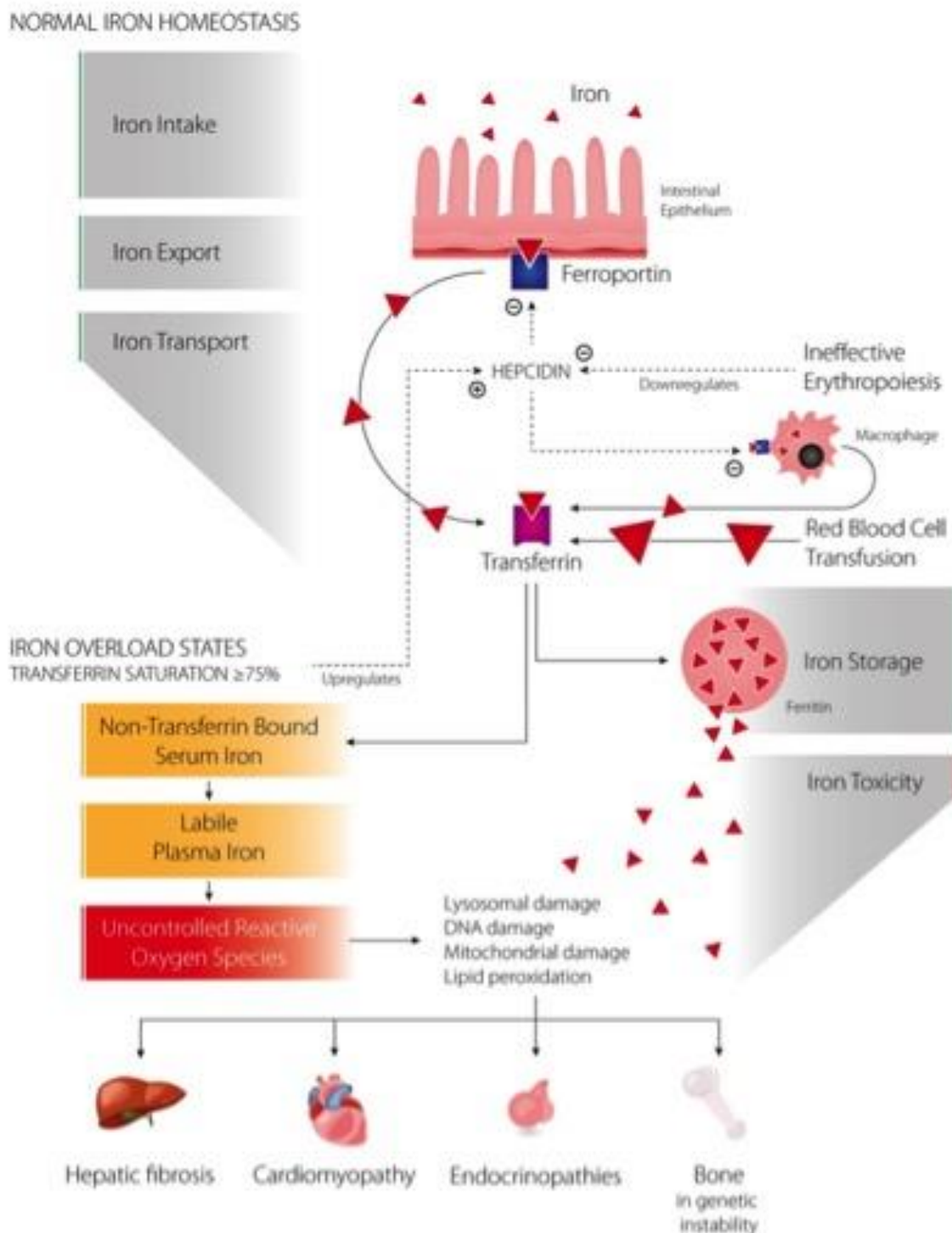


Figure 1: Schematic diagram illustrating iron homeostasis in pathologic conditions, and the sequence of events that leads to end organ damage in response to iron overload.

transfusions.^{14,15} In those patients with IPSS¹⁶ low to intermediate risk MDS and probably even in those successfully receiving disease modifying agents,¹⁷ life expectancy is sufficiently long for chronic transfusion therapy to generate iron free form and clinically relevant doses of iron.¹⁸ With the emergence of acceptable oral chelating agents,

examining the prognostic effect of iron toxicity in MDS is warranted.

Clinical Data. Leukemia-free survival and overall survival (OS) have been shown to be lower in transfusion-dependent patients with MDS (HR 1.91 and 1.84, respectively) and these two parameters progressively decrease with each

subsequent transfusion.¹⁹ Transfusion dependence has consequently been included in MDS risk calculations, with the introduction of the WPSS.²⁰ More recent longitudinal data on 2,994 MDS patients have provided further quantification of risk²¹ with those patients transfusion-dependent at baseline experiencing a mean survival of 19 months, compared with 60 months in individuals becoming transfusion-dependent during follow-up and 96 months in those remaining transfusion-independent. Multivariate analysis of a subgroup of these patients demonstrated high serum ferritin and transfusion dependence to add significant prognostic value to overall survival in IPSS and WPSS scores. Overall survival is reduced in MDS with increasing ferritin levels, with a hazard ratio of 1.42 for every 500 ng/mL increase in ferritin over 1,000 ng/mL.²²

The baseline cardiovascular risk in these individuals is significant: of 1,000 newly diagnosed patients with low and intermediate-1 risk in the European Leukemianet MDS (EUMDS) registry, 46% of patients had hypertension, 18% diabetes mellitus, 12% arrhythmia, and 12% thyroid disease.²³ Survival data were further confirmed by a recent update of the European registry.²⁴ Malcovati et al. reported that 51% of non-leukemic causes of death were due to cardiac failure in low-risk MDS, compared with 31% due to infection and 8% due to hepatic cirrhosis.²⁰ In a retrospective analysis of 840 MDS patients, 25% had cardiovascular comorbidities, and 63% of deaths were due to cardiac failure. Multivariate analyses showed that any cardiovascular comorbidity increased non-leukemic deaths significantly, with an HR of 3.7.²⁵ This risk is even more pronounced in patients who are transfused.²⁶ Indeed, the only study that do not report a correlation between transfusion burden and survival was the retrospective study from the Mayo Clinic, which examined a group of patients with RARS and limited follow up.²⁷ Hepatic dysfunction also correlates, although to a lesser degree, with both transfusion history and ferritin levels.²⁸

It is tempting to link the cardiovascular events in MDS with data on transfusion history and prognosis to speculate that iron loaded from transfusions leads to cardiac siderosis, which then triggers cardiovascular events.

A key confounding factor is, however, the presence of anemia per se. In addition, aging and

age-related disorders may have a clinical impact on iron overload in MDS. It is well established that chronic anemia is associated with adverse cardiac outcomes.²⁹ Anemia triggers a compensatory process of increased cardiac output to achieve sufficient oxygen delivery, which overtime results in maladaptive cardiac morphology. Malign remodeling has a higher metabolic demand, which is pro-ischemic and overtime leads to chamber dilatation and failure. Cardiac remodeling is prevalent in individuals with transfusion dependence and reduced mean haemoglobin levels.³⁰ Furthermore, in MDS, anemia has been shown to be associated with left ventricular hypertrophy, exacerbations of acute coronary syndromes, and coexistence of renal disease, which in turn may result in decreased erythropoietin (EPO) production and increasing severity of anemia.^{29,30} Moreover, transfusion therapy causes abrupt changes in cardiac preload, which leads to altered haemodynamic.

Data from MRI studies of patients with MDS do not support a role for high-volume iron accumulation in the heart.³¹ Our study,³² conducted on 27 chronic transfusion dependent patients with acquired anemias revealed that only 3 patients with severe hepatic iron overload ($T2^* < 1.4$ ms) showed cardiac $T2^*$ value indicative of dangerous myocardial iron deposition as defined in young patients with thalassemia.³³ It should be noted that these studies are small, and the comparisons have been drawn against functional thresholds, established in thalassemia, but not validated in MDS. Similarly, thresholds for tissue toxicity and consequent fibrosis and cirrhosis have not been established in MDS cohorts. It is conceivable that iron may play a different role in these patients, and perhaps not cause damage through the traditional paradigm of transfusional siderosis. A more recent study reporting on a larger patient series³⁴ did detect iron overload using $T2^*$ values in 18.2% of regularly transfused MDS patients, with severe overload in 4% ($T2^* \leq 10$ ms). They reported reduced $T2^*$ values correlated with compromised left ventricular ejection fraction (LVEF) using echocardiography.

These data, taken together, suggest that, although iron infrequently accumulates to the degree seen with iron-related target organ damage in thalassemia, its mild overload is still associated with poor prognosis in patients with MDS. A mechanistic illustration of disordered calcium

handling and multiple ion channel disruption as a result of iron influx into the cardiac myocyte is

shown in **figure 2**.

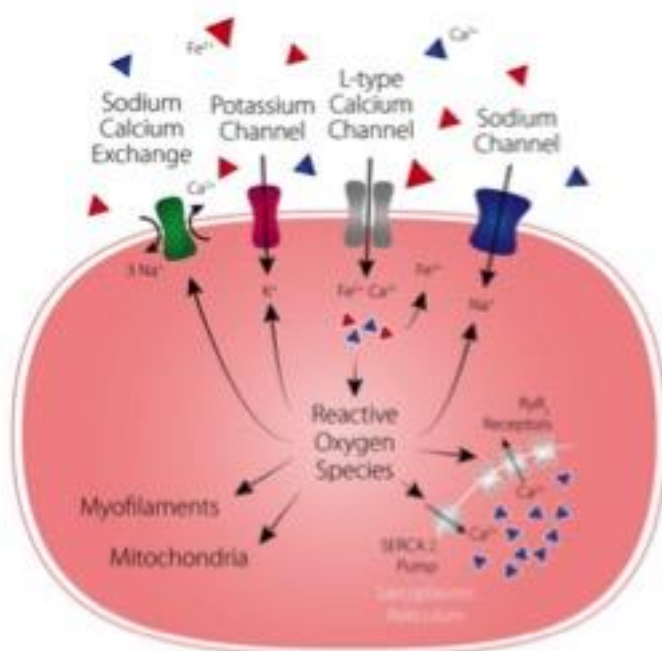


Figure 2: Mechanistic illustration of disordered calcium handling (and in turn excitation-contraction coupling) and multiple ion channel disruption as a result of iron influx into the cardiac myocyte, with generation of dangerous reactive oxygen species.

There are two possible explanation of this effect: 1) lower, not detectable, levels of iron accumulation can have dangerous clinical negative effect

2) circulating “reactive iron species - free iron forms” in myocyte cells can damage without clear evidence of overload.

MDS and other Diseases. MDS has been the last “iron overload” disease to be included in iron chelation therapy program. Several of the evidence on the clinical impact of iron toxicity and iron overload come from other diseases like thalassemia major and hereditary hemochromatosis. However, these other diseases are characterized by deep clinical differences (age, comorbidity, functionality of stem cell, anemia, non proliferative diseases, gastro intestinal iron absorption, life expectancy, etc.). Consequently MDS patient is a completely different clinical scenario whose characteristics in term of tissue and organ morbidity, quality of life, therapeutic options and finally survival is completely to be “de novo” designed. **Table 1** describes few of the various differences between MDS and the other iron overload disease.

Therapeutic Potential in MDS Patients. A number of medium-sized retrospective studies and single-armed prospective trials have tested the role of chelation therapy in MDS. These studies have shown that deferasirox is capable of lowering serum ferritin and liver iron concentration in MDS.³⁵⁻³⁹ The USO3⁴⁰ and EPIC⁴¹ trials, demonstrated sustained reductions in labile plasma iron (LPI). Post-hoc analyses from both studies^{40,42} showed improvements in erythroid, platelet, and neutrophil counts in subgroups of patients (in the range of 13-22%). In the US experience, median ferritin reductions were greater in patients with hematological improvements compared to patients without, but with no statistical differences detected in terms of LPI levels. There have also been some reports of transfusion independence in patients with MDS treated with iron chelation,⁴³⁻⁵⁰ and sub-analysis of 116 patients from the EPIC cohort reports hematological improvements with deferasirox treatment in patients with aplastic anemia.⁵¹ Our findings from the GIMEMA MDS0306 trial provide the first prospective evidence for positive hematological responses with deferasirox chelation therapy in MDS.⁵² Importantly, a subset of patients in this multicenter study also achieved transfusion-independence,

which may be related to iron-dependent or independent pathways.⁵² Iron depletion and

scavenging reactive oxygen species from the bone marrow and other organs involved

Table 1. Different pattern of iron overload in different diseases.

		TDT Suboptimal transfusion- chelation regimen	TDT standardized transfusion-chelation regimen (pre transfusion HB ≥ 9)	NTDT	HH	Lower risk MDS
Iron input	Transfusions	+ / ++	+++	- / +	-	++ / +++
	GI iron adsorption	+++	+	++	++	+(?)
Patient	Aging	-	-	- / +	++	+++
	Age related comorbidity	-	-	- / +	+ / ++	+++
	Anemia	+++	+	++	-	+++
Erythropoiesis	Ineffective	+++	+++	++	-	+ / ++
	Hyperplastic	+++	+	+++	-	+ / ++
		↓	↓	↓	↓	↓
Major causes of death		Anemia Cardiac disease	Cardiac disease Liver disease	Cardio-vascular disease Liver disease (?)	Liver disease	Cardiac disease infectious disease Liver disease. Acute leukemia

Legend: TDT: transfusion dependent Thalassemia, NTDT: non-transfusion dependent Thalassemia, HH: hereditary hemochromatosis.

in erythropoiesis is one potential mechanism.^{53,54}

Experimental data support the idea that removal of excess iron from the iron- and oxygen-dependent propyl hydroxylase in the renal oxygen sensing system may benefit erythropoietin production.^{55,56}

Iron accumulation is known to have a suppressive effect on erythroid production (in vitro), elevated ferritin levels are associated with suppression of erythroid progenitor cells in non transfusion dependent thalassemia (NTDT).⁵⁷ Hartmann et al. recently demonstrated that iron overload causes suppression of erythroid progenitor cells (BFU-E) in MDS and that patients with even slight elevations in serum ferritin have impaired proliferation capacity compared to those with normal ferritin levels. Interestingly, iron chelation can restore this deficit.⁵⁴

Iron Chelation and Survival. While chronic transfusion therapy is associated with reduced overall and leukemia-free survival, a clear confounder to any causative conclusions lie in the fact that transfusion-dependency represents more progressive bone marrow disease.

Iron overload does, however, remain prognostically important in multivariate analyses,^{20,21} suggesting a contributing role of iron on survival. More debate is on the role of iron overload in leukemia transformation.

Recent data from a prospective US registry of 600 lower-risk MDS patients with transfusional iron overload over 5 years⁵⁸ report improved median overall survival in those patients chelated for a minimum of 6 months, as compared with

non-chelated individuals – in both low-risk and intermediate-1 patients (median survival 98.7 vs. 53.6 months and 70 vs. 44.7 months, respectively). However, there were no statistically significant differences in the causes of deaths between groups, although there was a signal towards shorter AML-free survival in non-chelated patients. A matched-pair analysis of 188 patients with iron overload or a history of chronic iron transfusion in the Düsseldorf registry⁵⁹ showed no association between chelation therapy and the risk of leukemic transformation, although there was improved mean survival in chelated versus non-chelated patients (74 vs. 49 months, respectively). Inconsistencies in these data may reflect both limitations in registry data, such as selection bias (those patients with better overall performance status are chosen for treatment with chelation), as well as inherent challenges in MDS cohorts, including very high-dropout rates.⁵²

Recent meta-analyses further support this statement: of 8 studies, comparing chelation versus not chelation in MDS, 7 showed a significant statistical benefit on survival, while the other one showed a not statistically significant advantage for chelation.⁶⁰ However, it should be underlined that evidence of these study is limited being or retrospective or match paired or prospective but not a randomized study. Existing data, taken collectively, indicate a role for iron chelation therapy in MDS, and this is reflected by its inclusion in a number of societies and national guidelines.^{17,61,62} We are currently coordinating the phase II randomized TELESTO trial (URL: <http://clinicalTrials.gov/ct2/show/NCT00940602>), which has completed the recruitment of patients with low and intermediate-1 risk MDS to receive either deferasirox monotherapy or placebo. The trial will include a composite primary endpoint of death and non-fatal cardiac and hepatic events in lower risk MDS patients (with secondary outcomes including metabolic effects and disease progression). This will hopefully provide definitive evidence for the efficacy of iron chelation therapy in MDS. When considering the heterogeneity of MDS, the complexity of the patient cohort, with an elderly population and multiple comorbidities, a “blanket” approach to treatment is unlikely to be the best by utilizing chelating agents. A more sophisticated approach will require a better understanding of

pathophysiology and toxicity of iron in specific subgroups of MDS.

Perspectives. Removal of iron is a slow and progressive process. Compliance with chelation therapy is often challenging in elderly patients with multiple comorbidities and polypharmacy, as demonstrated by the high drop-out rate in all existing MDS chelation studies.^{36,40} Against this background, and when considering that reparative mechanisms are likely compromised or even absent in this frail cohort, “debulking” of iron from organs is unlikely to be the relevant mechanism. Given that the reduced overall survival in MDS occurs prior to a transfusion history expected to cause cardiac siderosis, it seems likely that alternative mechanisms of tissue damage are taking place. Recent studies have seen a transition in our understanding of transfusional iron overload, from a disease of “bulking” of organs through progressive accumulation, to one of “toxic” damage. Indeed, increased LPI and NTBI levels may cause injury in the absence of evidence of iron loading on MRI, although this is yet to be determined in clinical studies. Importantly, these toxic iron species are chelatable targets as also evidenced in studies using deferasirox in MDS patients.⁴⁰ Any protective benefits conferred by chelators in MDS may, therefore, occur through mechanisms at least partially independent of “debulking” of iron stores in the liver and heart. Instead, a more accurate picture may be one of “detoxifying” against deleterious derivatives of iron, such as reductions in LPI and NTBI levels. The dynamic regulation of iron loading between the heart and liver (relative delay in heart iron loading and unloading) is yet to be determined but it may be that initial exposure to NTBI even in iron-free hearts is sufficient to establish cardiovascular disease in these elderly patients.

Conclusions. In patients with thalassemia, iron-induced tissue damage occurs through high-volume deposition of iron in target organs, with progressive bulking and eventual mechanical failure. In MDS the prognostic consequences of iron appear to occur prior to perceived thresholds of significant iron burden. Advances in our understanding of the mechanisms of iron-induced tissue damage have shown direct toxic cellular damage through multiple molecular pathways. In

frail elderly cohorts with MDS, on a background of poor physiological reserve and anemia, iron may provide the final insult through toxic ROS, endothelial injury, and erythroid suppression, causing tissue death and triggering a cycle of progressive anemia and organ damage. Toxic thresholds in this setting may, therefore, be dramatically lower than those used to assess cardiac siderosis in thalassemia, as iron is working through fundamentally different pathways to confer organ damage. Worryingly, current MDS protocols have adopted a paradigm identical to iron in thalassemia, which involves waiting for iron levels to reach levels representative of target organ injury in disorders of secondary iron overload. These reference thresholds are invalid in MDS, and during this observation period clinically relevant injury may be occurring at the cellular level, and the window of opportunity to halt organ damage may be lost.

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Ultimately, if the basis in which we treat patients and design trials is incorrect, advancing the management and therapeutic framework will be severely hindered. As the iron overload phenotype in MDS remains uncharacterized, we urgently require further experimental studies in models of MDS, in tandem with dedicated clinical trials, to build a legitimate evidence base for iron toxicity and the role of chelation therapy in MDS.

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All Authors and has approved the final submitted version of the manuscript.

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