Iron Chelation

8

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8.1 Introduction

"The dose makes the poison." This famous statement by Paracelsus is also true for iron. On the one hand, iron is essential for a variety of pivotal biological processes. On the other hand, iron can be toxic because it promotes oxidative stress. As it easily switches between its divalent (ferrous) and trivalent (ferric) form, iron can efficiently transfer single electrons and thus strongly catalyzes biochemical reactions like the Fenton reaction that generate reactive oxygen species. The latter attack macromolecules and organelles, thereby causing cellular damage that ultimately leads to tissue and organ dysfunction. This potential for toxicity is increased when too much iron is present.

8.2 What Are the Causes of Iron Overload in MDS?

Iron overload in MDS results from increased intestinal iron absorption and from chronic transfusion therapy. The process of iron overload starts

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before MDS patients become transfusion dependent because ineffective erythropoiesis suppresses hepcidin production in the liver, thereby causing unrestrained intestinal iron uptake [1].

Hepcidin normally inhibits iron uptake in the duodenum. In thalassemia major, hepcidin is suppressed by highly elevated serum levels of GDF15, secreted by maturing erythroblasts in the bone marrow [2]. In myelodysplastic syndromes, levels of GDF15 are much less elevated. Therefore, other signals from the bone marrow like TWSG1 ("twisted in gastrulation") seem to contribute to hepcidin suppression in MDS [3]. A promising candidate is erythroferrone (ERFE), a recently discovered hormone that mediates hepcidin suppression during stress erythropoiesis in mice after bleeding or hemolysis [4]. Whether erythroferrone also suppresses hepcidin in MDS patients with expanded, ineffective erythropoiesis has not yet been confirmed. ERFE mRNA is increased [5], but protein expression data are still lacking.

While increased intestinal iron absorption clearly contributes to iron overload, the most important cause of iron overload in MDS is chronic transfusion therapy. A patient who requires four RBC units per month, which is not unusual, will receive 100 units over 2 years, equivalent to at least 20 g of iron. The normal total body iron is 3–4 g.

Amelioration of anemia is important in patients with MDS. The probability of non-

leukemic death, particularly from cardiac complications, is dramatically increased in male MDS patients with a Hb <9 g/dL and female MDS patients with a hemoglobin <8 g/dL, indicating that MDS patients should be adequately transfused to maintain their hemoglobin levels at least above those critical thresholds [6]. However, while proper amelioration of anemia increases the quality of life and likelihood of survival, the concomitant development of transfusional iron overload may have an opposite effect.

8.3 What Are the Clinical Consequences of Iron Overload in MDS?

Iron overload, as measured by elevated serum ferritin (SF) levels, is associated with a decreased likelihood of survival in patients with lower-risk MDS. It has been shown that above a SF threshold of 1000 µg/L, iron overload has a dose-dependent impact on survival [6]. This looks like irrefutable evidence of a noxious effect, which must be abrogated by iron chelation. However, the data could also be interpreted in a different way: Higher serum ferritin levels may simply reflect greater transfusion need, which in turn reflects more severe bone marrow disease, the latter being the real cause of shorter survival. On the other hand, it was also shown that serum ferritin is an independent prognostic factor in MDS, even if transfusion burden is taken into account on multivariate analysis by including the number of transfusions per month as a covariate. Under these transfusion-adjusted conditions, there was still a 30% greater risk of death for every 500 µg/L increase in SF above the threshold of 1000 µg/L [7]. Similarly, the data from the European LeukemiaNet prospective MDS registry indicated that besides transfusion burden, which was the major prognostic factor, increasing levels of serum ferritin had independent impact on the overall survival of transfusion-dependent patients with lower-risk MDS [8].

Figure 8.1 illustrates that, on the one hand, transfusion dependency is clearly linked with shortened survival because it reflects severe bone
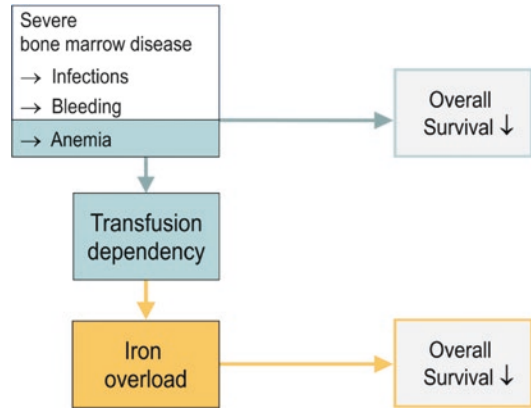

Fig. 8.1 Relationship between bone marrow failure, iron overload, and prognosis in patients with MDS

marrow disease with all its possible complications like infections, bleeding, and adverse effects of chronic anemia. On the other hand, transfusion dependency causes iron overload, thereby creating a new medical problem that has its own negative impact on survival. The relative weight of these two risk factors may vary considerably between patients. A patient with pure sideroblastic anemia (RARS) is unlikely to die from infections or bleeding. Instead, transfusional iron overload may become a clinical problem. In contrast, a patient with RAEB-I or RAEB-II, despite similar transfusion dependency, may not have the time to develop clinical complications of iron overload because survival is limited by severe bone marrow failure.

Within that conceptual framework, cardiac dysfunction may play an important role, as a consequence of chronic anemia, age-related cardiac comorbidity, and iron overload. Cardiac iron overload in MDS is detectable by MRI after 75–100 units of RBC have been transfused. A British group evaluated 43 transfused MDS patients with T2* magnetic resonance scans and found that 81% had liver and 16.8% had cardiac iron overload [9]. This is in line with a study from France looking at a relatively large series of 75 regularly transfused MDS patients [10]. The investigators found cardiac iron overload, defined by T2* ≤20 ms, in 18.2% of the patients, who mostly belonged to the IPSS low- and intermediate-1-risk groups. Severe cardiac iron

overload with a T2* ≤10 ms was detected in 4% of the patients. There was a linear correlation between the T2* values and the number of RBC units transfused. Most of the patients were also studied by echocardiography. Severe cardiac dysfunction with a LVEF ≤35% was found in 3 of 11 patients (27%) with T2* ≤20 ms but only 1 of 46 patients with T2* >20 ms. The authors concluded that iron overload can be a significant aggravating factor in the pathophysiology of cardiac failure in MDS, in addition to chronic anemia and comorbidities.

Iron-related organ damage, including heart failure, may depend not only on tissue iron concentrations but also on the duration of chronic exposure to non-transferrin-bound iron and labile plasma iron, which generate oxidative stress. A patient with a serum ferritin of 2500 ng/mL may not only have more extensive iron accumulation but may also have had longer exposure to high levels of ROS than a patient with a SF level of 1500 ng/mL.

One should also be aware that cardiac function is more vulnerable to iron toxicity than liver function. It has been shown that clinically relevant cardiac dysfunction occurs at much lower tissue iron concentrations than clinically relevant liver dysfunction [11, 12].

Accordingly, the supportive care strategy for MDS patients must be twofold. On the one hand, ESAs and RBC transfusions should be used to avoid detrimental effects of chronic anemia. At the same time, iron chelation should be used to ensure that the benefits of transfusion therapy are not offset by harmful effects of iron overload.

Another potential problem, which may be underestimated, is iron-related endothelial dysfunction. This is not an entirely novel topic but one that has recently attracted renewed interest. There is some evidence that with increasing age, high circulating iron levels strongly enhance the severity of the atherosclerotic phenotype, indicating that systemic iron overload is a risk factor for atherosclerosis progression and development of cardiovascular disease [13]. According to the working hypothesis, iron can accumulate in macrophages from increased destruction of RBCs or from disturbed iron homeostasis under the influence of hepcidin. Accumulation of iron leads to increased production of ROS and decreased efflux of cholesterol from the macrophages. The resulting oxidative stress and LDL accumulation promote the formation of foam cells, inflammation, apoptosis, and eventually plaque destabilization.

Is there a beneficial role for iron chelation in that context? Fifteen years ago, it was shown that iron chelation improves endothelial function in patients with coronary artery disease [14]. Deferoxamine improved nitric oxide-mediated, endothelium-dependent vasodilation, suggesting that iron availability contributes to impaired nitric oxide action in atherosclerosis. A beneficial effect of iron chelation on arterial function has also been reported in patients with beta-thalassemia major. During 12 months of treatment, deferasirox significantly improved brachial artery flow-mediated dilation and significantly decreased the carotid arterial stiffness index. These findings were attributed to the ability of deferasirox to bind labile cell iron pools in the vascular wall, thereby diminishing reactive oxygen species formation and thus attenuating nitric oxide inactivation [15].

The connection between iron and endothelial dysfunction illustrates that iron-related complications overlap with age-related clinical problems in elderly MDS patients (Fig. 8.2). Iron overload may simultaneously aggravate several common causes of death. However, even if that adds up to a strong cumulative effect, the impact of iron overload may easily hide behind the nor-
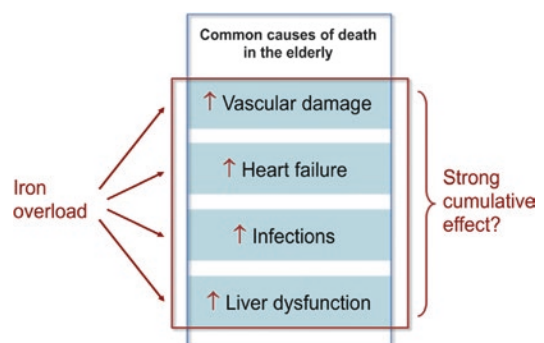

Fig. 8.2 Overlap between iron-related complications and common age-related medical problems

mal, common causes of death in the elderly. Accordingly, it is difficult to determine the extent to which iron overload contributes to morbidity and mortality in elderly MDS patients.

8.4   Does Iron Overload Affect the Bone Marrow in MDS?

The bone marrow seems to be one of the organs that suffer from iron overload. A vicious cycle is envisaged, starting with ineffective erythropoiesis that causes anemia and transfusion dependency, thereby leading to transfusional iron overload, which in turn aggravates the bone marrow failure. Figure 8.3 illustrates where iron overload may have an aggravating effect on MDS pathophysiology. Myelodysplastic syndromes arise from primitive hematopoietic stem cells that accumulate genomic damage from various insults. One of the damaging factors is oxidative stress, which can be promoted by iron overload. If an abnormal stem cell survives and is equipped with a proliferative advantage and some degree of genomic instability, a dominant clone as well

as subclones with multiple mutations can arise. The further development depends on the intrinsic qualities of the MDS clone and its interaction with the bone marrow microenvironment. Mutated clones may elicit an effective immune response and be eliminated or may elicit an ineffective immune response that may still create an inflammatory milieu. The latter may do more harm to normal hematopoietic cells than to the abnormal clone. Pathological clones may also condition the bone marrow stroma through epigenetic mechanisms, again favoring the growth of preleukemic hematopoietic cells. Abnormal selection pressure in the altered microenvironment will promote the outgrowth of maladapted clones, i.e., clones that are dysfunctional yet capable of taking advantage of the abnormal environment. Experimental evidence indicates that iron overload contributes to stromal dysfunction in MDS [16, 17]. Altogether, iron overload may exacerbate genomic instability and abnormal selection pressure, thereby hastening clonal evolution toward leukemia.

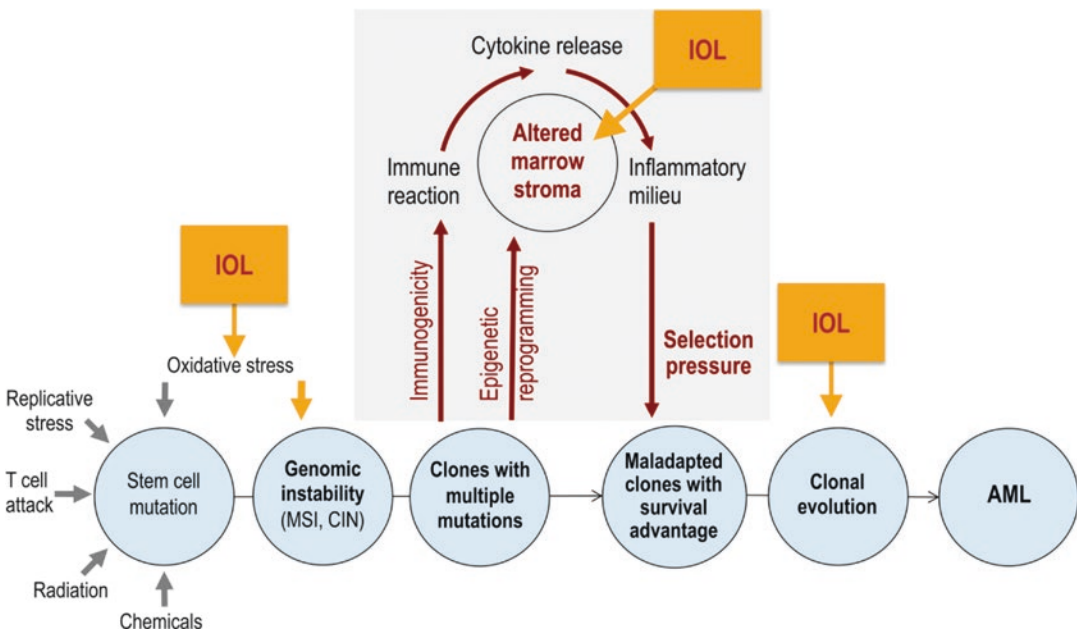The abovementioned concept is supported by experimental and clinical data. Iron overload is

Fig. 8.3 Possible role for iron overload (IOL) in the pathophysiology of myelodysplastic syndromes

known to increase oxidative stress, thereby contributing to mutagenesis. Increased oxidative stress is indeed detectable in MDS and aggravated by iron overload [18–25]. It causes oxidative DNA damage that is also made worse by iron overload [26]. The consequences of increased oxidative stress are particularly detrimental in erythroid progenitors. It has been demonstrated that iron overload impairs the proliferation of erythroid progenitor cells in patients with MDS, even at moderately elevated ferritin values, whereas the number of granulopoietic colonies is largely unaffected [27]. The negative impact was reversible through iron chelation therapy.

Why should erythropoiesis be particularly vulnerable to the toxic effects of iron overload? Researchers in Israel, using flow cytometry techniques, found that both the TfR-deficient mature RBC and their TfR-containing precursors at all stages of maturation can take up non-Tf iron that accumulates as redox-active labile iron and generates reactive oxygen species [28]. This transferrin-independent pathway is operative in pathological iron overload situations in the presence of non-Tf iron in the serum. Unfortunately, the incoming non-Tf iron does not participate in heme synthesis and Hb production but induces ROS generation that results in cytotoxicity and a decrease in the erythroid cell yield. The effect of iron overload and chelation on erythroid differentiation has also been investigated [29]. Iron overload significantly suppressed the formation of BFU-E and their differentiation to mature erythroblasts; these effects were canceled by iron chelation with deferoxamine (DFO). Moreover, excessive iron burden promoted apoptosis in immature erythroblasts by elevating intracellular reactive oxygen species (ROS).

Iron overload also causes stromal dysfunction, as shown in a mouse model [16]. BM transplantation from normal donors to IO recipients resulted in delayed hematopoietic reconstitution, indicating that excess iron has an unfavorable impact on the hematopoietic microenvironment. MSC showed markedly reduced expression of surface molecules known to be involved in stem cell homing.

Also in mice, IOL impaired the proliferation of mouse BM mesenchymal cells, and free iron catalyzed in vitro oxidative damage to mesenchymal cells, thereby attenuating hematopoiesis [17].

When the effects of iron overload on genomic instability in MDS were investigated, the results supported the assumption that iron overload might be causally related to genetic instability [30]. The data also suggested that SF levels not only above 1000, but also between upper limit of normal value but below 1000, adversely affect genetic stability. Therefore, iron chelation might be relevant for patients with MDS at lower SF levels than previously thought.

The fact that hereditary hemochromatosis and thalassemia major are not associated with an increased incidence of MDS and AML suggests that iron overload by itself does not transform normal hematopoietic stem cells into preleukemic stem cells. However, hematopoietic stem cells that have already acquired genomic instability from other causes and are also subject to continuous proliferative stress seem to be vulnerable to the additional genotoxic stress from iron overload.

Apparently, the abovementioned vicious cycle between iron overload and bone marrow failure can be interrupted by iron chelation therapy. A number of case reports, small patient series, and larger studies found that the iron chelator deferasirox can improve hematopoiesis in MDS. Table 8.1 shows the largest studies conducted so far. Erythroid response rates range between 11 and 22%.

Using strict criteria for erythroid response, a prospective Italian multicenter study found that during 12 months of treatment with DFX, the RBC transfusion requirement declined significantly from a median of 3 per month to a median of 1 per month [34]. The cumulative incidence of transfusion independence (the latter defined as more than 3 months without transfusions and a hemoglobin maintained above 9 g/dL) increased from 2.6% at 6 months to 12.3% at 9 months and 15.5% at 12 months.

Table 8.1 Clinical trials showing erythropoietic improvement during iron chelation therapy in patients with lower-risk MDS [31–34]

Study	Risk IPSS	RBC response	Neutrophil response	PLT response
List et al. (2012) [31]	Low/Int-1	15% (n = 173)	15% (n = 52)	22% (n = 77)
Gattermann et al. (2012) [32]	Low/Int-1	21.5% (n = 247)	22% (n = 50)	13% (n = 100)
Nolte et al. (2013) [33]	Low/Int-1	11% (n = 50)	NR	NR
Angelucci et al. (2014) [34]	Low/Int-1	Transfusion independence in 15.5% (n = 152)	NR	NR

This is not a novel phenomenon. About 20 years ago, Jensen et al. [35] achieved a remarkable effect of iron chelation on hemopoiesis in MDS patients with transfusional iron overload when they followed 11 MDS patients for up to 60 months during and after treatment with deferoxamine. They observed a greater than 50% reduction in transfusion requirement in 7 of 11 patients, and 5 patients even became transfusion independent. All patients in whom iron chelation was highly effective showed improvement of erythropoietic output. As this was achieved with deferoxamine (rather than deferasirox), hematological responses do not seem to be restricted to a particular iron chelator. It is probably more important to keep patients well chelated over a long time. Long-term suppression of oxidative stress may improve conditions in the bone marrow microenvironment and may slow down the pace of genetic evolution.

8.5 Is There a Survival Benefit from Chelation Therapy?

Numerous studies suggest that iron chelation improves survival in transfusion-dependent MDS (Table 8.2). However, the main problem with these studies is that patient populations were usually well characterized regarding disease-related risk factors, but not characterized and stratified according to overall performance status. This introduces a possible bias because patients with a better overall performance status may have been more likely to receive iron chelation, thus shifting survival curves in favor of this treatment.

This problem has been addressed by a recent study from the Canadian MDS Registry, which appears to be the only MDS registry that carefully documents performance status and comorbidities. The investigators examined the outcomes of 70 patients with low/Int-1-risk MDS who received ICT in comparison with 149 who did not [45]. There was no significant difference in the frailty and comorbidity scores between the iron-chelated group and the non-iron-chelated group. On multivariate analysis, ICT retained significance for overall survival, with a hazard ratio of 1.8 and p value of 0.0152. However, despite showing no significant bias in terms of general fitness, MDS patients receiving iron chelation were significantly younger and had a more favorable distribution among MDS risk groups. Therefore, this study only partly alleviates the concerns regarding selection bias.

Age and risk group distribution were not problematic in a matched pair analysis performed in the Düsseldorf MDS Registry [38]. Here, cohorts were carefully matched for age, gender, MDS type, and MDS risk groups. Again, there was a significant survival advantage for the patients receiving iron chelation therapy. The disadvantage of this study was that the matching did not include performance score and comorbidities caused by a lack of data. Assuming that hematologists in Germany acted similar to their Canadian colleagues and did not restrict iron chelation to fitter patients, this potential bias may be negligible, and the Düsseldorf data may reflect the true survival advantage of iron chelation therapy.

Probably, the best data available so far are those from the European LeukemiaNet MDS (EUMDS) Registry [46]. Overall survival of 192 chelated patients was shown to be significantly better when compared with a large control group of 573 non-chelated patients, even after adjustment for all relevant prognostic factors,

Table 8.2 Clinical studies showing that iron chelation improves survival in patients with lower-risk MDS [36–44]

Study	N	Design	Survival	Non-chelated patients	Chelated patients	p value
Leitch (2008) [36]	36	Retrospective	Median OS	40 months	Mot reached	0.003
			4-year survival ıale	43%	64%	0.003
Rose (2010) [37]	97	Prospective follow-up	Median OS from diagnosis	53 months	124 months	<0.0003
			Median OS with adequate vs. weak chelation	NA	124 vs. 55 months	<0.001
Neukirchen (2012a) [38]	IBS	Matched pair analysis	Median OS	49 months	75 months	0.002
Neukirchen (2012b) [39]	417	Retrospective, registry	Median time to death in TD patients	30 months	67 months	NR
Komrokji (2011) [40]	97	Retrospective	Median OS	34 months	59 months	0.013
Zeidan (2012) [41]	4226	Retrospective, registry	Median survival	47 weeks	110 weeks	0.003
			HR for 27–52 weeks on DFX	1	0.77	NR
			HR for ≥53 weeks on DFX	1	0.34	NR
Langemeijer et al. (2016) [78]	1000	Prospective, registry	Adjusted HR	1	0.51 (0.19–1.32}	MS
Delforge (2014) [42]	127	Retrospective	Median OS in low/Int-1	3.1 years	10.2 years	<0.001
Lyons et al. (2014) [43]	600	Prospective, registry	Median OS from diagnosis	47.8 months	All 88.0 months ICT >6 months 100.0 months	<0.0001
Remacha (2015) [44]	263	Retrospective	Median OS	105 months	133 months	<0.001

i.e., age, sex, comorbidity, performance status, and number of RBC units transfused prior to the start of chelation. Another advantage of this study is that it looked at survival from the point in time when patients reached the eligibility criteria for iron chelation. Therefore, long-lasting stable intervals between diagnosis and onset of transfusion dependency were not counted and thus not misinterpreted as prolonged survival due to iron chelation. Short of a randomized prospective trial, these data may come as close as possible to reflecting the true survival benefit of iron chelation in lower-risk MDS.

It is difficult to pinpoint why iron chelation provides a survival advantage to MDS patients. Data from a US registry showed that the rate of cardiac causes of death was somewhat lower, infections occurred less frequently, and other malignancies were very rare [43]. However, the differences were not statistically significant. The IRON2 study from Spain, which found a significantly longer overall survival and leukemia-free survival in chelated patients with lower-risk MDS, also demonstrated a highly significant difference regarding the median event-free survival related to cardiac complications [44]. As already alluded to, it may be important to pay attention to iron overload not only as a cause of cardiomyopathy but also as an aggravating factor of atherosclerosis.

Clinical data regarding a beneficial effect of iron chelation on AML transformation are controversial. While the data from the Düsseldorf MDS Registry did not suggest a tangible effect [38], the abovementioned US registry found that iron chelation delays AML transformation [43].

8.6 How Is Iron Overload Diagnosed in MDS?

A suitable and widely used method to measure iron overload is to measure serum ferritin (SF), which generally shows good correlation with liver iron content as well as total body iron. However, serum ferritin can be influenced by inflammatory conditions. Therefore, it is important not to place too much emphasis on single measurements. More important is the trend of SF over time, which should be monitored monthly. Measurement of transferrin saturation (TfS) may also be useful because values above 70–80% are associated with the appearance of non-transferrin-bound iron (NTBI) and labile plasma iron (LPI), leading to increased iron uptake and oxidative stress in parenchymal cells of various organs.

Liver iron concentration can be assessed using magnetic resonance imaging (MRI). Although this is a very useful method that avoids the sampling errors and risk of complications associated with liver biopsy, MRI is not readily available everywhere.

It should be noted that there may be substantial discordance between liver and cardiac iron content, prior to and during iron chelation therapy. Iron accumulates in the liver first but later goes to the heart as well. During iron chelation therapy, removal of iron from the liver is much faster than from the heart. Furthermore, it is easier to improve cardiac iron overload if the liver is not grossly iron overloaded. A high liver iron content seems to prevent iron chelators from suppressing LPI and removing much iron from the heart [47, 48]. If cardiac iron overload is suspected, cardiac MRI should be performed. If this is not available, serial monitoring of cardiac function by echocardiography can be useful. In order to detect iron-related organ damage, laboratory tests of liver function and endocrine function should be done.

8.7 When and How to Treat Iron Overload in Patients with MDS?

Iron chelation therapy in patients with transfusion-dependent MDS has been shown to be safe and effective [31, 49, 50]. Numerous national and international guidelines have been written on the use of iron chelation therapy in MDS. They are often included in guidelines on MDS treatment in general. For example, the European LeukemiaNet guideline on the diagnosis and treatment of primary myelodysplastic syndromes in adults includes a short segment on ICT [51]. The expert panel agreed that iron chelation should be considered in transfusion-dependent patients with RA, RARS, or MDS with isolated 5q deletion and a serum ferritin level higher than 1000 ng/mL after approximately 25 units of red cells. In addition, MDS patients who are potentially candidates for allo-SCT can be considered for appropriate iron chelation therapy prior to the conditioning regimen for transplantation. Guidelines on ICT in MDS are similar in different countries. They usually recommend chelation therapy for patients who have a certain transfusion history (usually at least 20 or 25 pRBC units), whose serum ferritin levels exceed a certain threshold (1000 or 1500 ng/μl) and who have lower-risk MDS with a reasonable life expectancy because such patients often receive long-term transfusion therapy that puts them at risk of developing clinical complications of iron overload.

Nowadays, the most commonly used iron chelator is deferasirox. Most physicians experienced in the field of iron chelation have adopted a gentle approach when starting the treatment [52]. Instead of using the recommended dose of 20 mg/kg/day, it is advisable to start at a lower dose, i.e., a fixed dose of 500 mg/day (nowadays 360 mg/day with the new film-coated tablets). Patients are monitored regarding drug tolerability, and the dose is increased in weekly increments of 5 mg/kg, with a target dose of 20 mg/kg in patients with a low transfusion frequency of <2 pRBC per 4 weeks, 30 mg/kg in patients with an intermediate transfusions frequency, and 30–40 mg/kg in patients with a transfusion frequency of >2 pRBC. This approach helps to avoid unpleasant gastrointestinal adverse events after treatment initiation and is intended to strengthen compliance, which is known to decay as a result of AEs and the lack of symptoms from iron overload.

In order to strengthen compliance, patients should be well informed about possible GI

adverse events. Diarrhea is the most common side effect of DFX and occurs much more frequently in elderly MDS patients than in young thalassemia patients. To manage this side effect, it is useful to discontinue any laxatives (which are commonly used by elderly patients), consider the use of loperamide, maintain hydration, and try to administer DFX at night [53].

For moderate diarrhea, it is recommended to reduce the DFX dose to 10 mg/kg/day and, for severe diarrhea, to hold the DFX dose until the diarrhea has resolved, and then try to reinitiate DFX at dose of 10 mg/day and adjust in increments of 5 mg/day each week. If that does not help, DFX should be discontinued. It is important that patients try to keep themselves hydrated (by drinking small, steady amounts of clear liquids, e.g., electrolyte solutions), because it helps to avoid additional renal problems.

The mean creatinine concentrations in MDS patients during the EPIC trial and other clinical studies showed that an initial 20% increase in serum creatinine values should be expected. However, with proper dose adjustment of DFX, this is usually followed by a new steady state rather than progressive elevation [54, 55]. According to the drug label in the USA, iron chelation with deferasirox can be used in patients with a creatinine clearance above 40 mL/min. Nevertheless, close monitoring of renal function is required in elderly MDS patients with preexisting chronic renal insufficiency, diabetes, hypertension, and congestive heart failure.

Liver toxicity is not a problem of DFX treatment in daily clinical practice. Transaminase levels actually decrease with decreasing serum ferritin levels, indicating that iron chelation is beneficial rather than toxic for the liver of iron-overloaded patients [56]. Hepatotoxicity is a rare exception, apparently confined to a few patients with preexisting liver problems.

Treating iron overload has recently become more convenient because an improved deferasirox formulation in the form of film-coated tablets is now available. The new formulation is well tolerated and can be taken with or without a meal [57, 58]. Anything that makes iron chelation easier to handle may help to improve patient adherence and thus carries the potential to improve survival.

8.8 Iron Overload in the Context of Allogeneic Stem Cell Transplantation

The incidence of iron overload in the context of allogeneic hematopoietic stem cell transplantation (HSCT) for MDS varies according to both time and method of assessment. Table 8.3 summarizes relevant data from posttransplant assessments in a series of patients undergoing allo-HSCT (in 10–20% for MDS). The incidence of iron overload ranges from 54 to 100% [59, 60, 61, 63]. There is generally a good correlation between iron overload assessed by serum ferritin, liver iron content (LIC) assessed by magnetic resonance imaging (MRI), and the number of packed red blood cell units (pRBC) transfused. However, this is true only when iron overload is assessed late after transplant in long-term survivors, and confounding factors that can influence SF levels are excluded (hepatitis, alcoholism, immunosuppressive therapy, hepatotoxic drugs, GVHD, veno-occlusive disease, inflammation, other cancers, or relapse) [63]. Iron overload appears to be more frequent in the early posttransplant phase and to decrease over time, suggesting that the confounding factors mentioned above become less prevalent over time [64].

Retrospective studies found that transfusion burden and/or ferritin levels >1000 ng/mL, assessed prior to allo-HSCT (Table 8.4), were associated with a higher risk for non-relapse mortality (NRM), acute GVHD, and severe infections [66, 67]. Specifically in MDS patients, increased risk of infection with iron overload after HSCT was seen in retrospective studies [65, 69, 70]. High NTBI levels in the early phase after HSCT have been reported to predict grade III or IV toxicity [71]. However, as ferritin is an acute-phase reactant, elevation of SF may reflect inflammatory conditions including active infection or more advanced bone marrow disease, which are expected to confer an adverse prognosis in HSCT independent of iron overload. The same caveat applies to hepcidin levels which are also influenced by iron overload as well as inflammation. In a series of 166 patients undergoing allo-HSCT, patients in the high-hepcidin group had a significantly shorter overall

Table 8.3 TRM transplant-related mortality

Study	Patient population	Iron overload parameter	Time of assessment	Frequency of iron overload	Impact of iron overload
McKay et al. (1996) [59]	N = 76 allo-auto	Serum ferritin >N	1 year post T	88%	Liver dysfunction
Strasser et al. (1998, 1999) [60, 61]	Autopsies N = 10 allo	LIC BMI	50–100 days post T	100%	Liver involvement
Thomas et al. (2000) [62]	N = 106 allo	Serum ferritin > N	2 years post T	54%	Cofactor on liver dysfunction
Rose et al. (2007) [63]	N = 65 allo	Serum ferritin >N-MRI-pRBC	4 years post T	58%	Liver dysfunction
Meyer et al. (2003) [64]	N = 290	Serum ferritin, TS, pRBC	Follow-up over 60 months	Decrease over time from 100 to 5%	OS-TRM

LIC liver iron content, *BMI* bone marrow iron index, *SF* serum ferritin, *TS* transferrin saturation, *pRBC* packed red blood cell, *OS* overall survival, *TRM* transplant related

Table 8.4 Incidence and impact of iron overload assessed prior to HSCT

Study	Patient population	Iron overload parameter	Time of assessment	Frequency of iron overload	Impact of iron overload
Armand et al. (2007) [65]	N = 590 Allo-MDS	SF > 1000	3 months pre T	47%	OS-TRM
Platzbecker et al. (2008) [66]	N = 172 MDS de novo	SF > 1000 ng/mL SF > 2500 ng/mL	Pre T	47%	OS-NRM
Alessandrino (2010) [67]	N = 357 MDS allo	SF: 1900 TS med: 86% pRBC >20	Pre T	100%	OS-NRM
Trottier (2013) [68]	N = 88 Allo	SF > 500 MRI	Pre T	60/88 28/88	No impact on both OS and TRM
Armand et al. (2014) [69]	Meta-analysis of four studies	SF > 1000 ng/mL SF > 2500 ng/mL MRI	Pre T		No impact[a]

SF serum ferritin, *TS* transferrin saturation, *pRBC* packed red blood cell, *OS* overall survival, *TRM* transplant-related mortality, *NRM* non-relapse mortality

[a]Impact of ferritin level on OS but no impact of LIC assessed by MRI on OS

survival than those in the low-hepcidin group (49.2 vs. 69.0%, respectively, $p = 0.006$) [72].

In the context of myeloablative conditioning (MAC) regimens, LIC and SF levels have only been assessed regarding overall survival, showing no significant impact [64, 73, 74]. A subgroup analysis restricted to patients with MDS-AML (25%) also failed to yield significant results.

Prospective studies produced conflicting results regarding the impact of iron overload on posttransplant non-relapse mortality. Armand et al. published a meta-analysis on the four prospective studies investigating the impact of iron overload on posttransplant outcome [69]. This meta-analysis showed that SF levels >1000 ng/L were a risk factor for shorter survival in the entire cohort but did not specifically impact the non-relapse mortality. Liver iron content (>5 or >7 mg/g) had no statistically significant impact on outcome. The authors concluded that "the results should not be interpreted to imply that iron is irrelevant in HSCT." The trends suggest a possible prognostic effect, although it does not appear as strong as suspected based on the ferritin-related literature, and it may be restricted to certain subgroups. Moreover, iron may be related to disease pathology in ways that are just beginning to be understood.

In summary, MDS patients who are candidates for allo-HSCT should be considered for iron chelation therapy prior to transplantation. The indication for iron chelation therapy during conditioning and during the posttransplant remains to be defined [51, 75–77].

8.9 Future Directions and Ongoing High-Impact Patient-Centered Clinical Trials

Altogether, the side effects of oral iron chelation therapy in MDS appear to be outweighed by the survival benefit that was consistently observed in several retrospective analyses. Whether the survival benefit was solely due to iron removal or also influenced by confounding factors or biases must be settled by a prospective randomized trial. The only such trial is TELESTO, a prospective multicenter study to investigate the clinical benefit of chelation therapy with deferasirox in MDS patients (ClinicalTrials.gov Identifier: NCT00940602). It turned out to be difficult to recruit patients for this trial in countries where DFX is licensed and reimbursed, and after much discussion with the FDA, the number of patients to be recruited was reduced from 630 to 210. Meanwhile, patient accrual has been completed. While the statistical power of the trial may no longer be sufficient to provide unequivocal evidence of improved overall survival, there might still be a strong signal indicating that transfusion-dependent patients with lower-risk MDS benefit from iron chelation therapy.

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