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Iron chelation therapy in myelodysplastic syndromes: where do we stand?

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Abstract

Anemia leading to transfusion dependency (TD) and iron overload (IO) is commonly observed in patients with myelodysplastic syndromes (MDS). In MDS, TD and IO have been retrospectively associated with inferior survival and worse clinical outcomes, including cardiac, hepatic and endocrine dysfunction, and, in some analyses, with leukemic progression and infectious complications. Although suggested by retrospective analyses, clear prospective documentation of the beneficial effects of iron chelation therapy (ICT) on organ function and survival in MDS patients with TD and IO is currently lacking. Consequently, the role of ICT in MDS patients with TD and IO remains a very controversial aspect in the management of MDS. In this review, the authors summarize the current knowledge regarding IO in MDS and the role of ICT.

Keywords

anemia; iron chelation therapy; iron overload; myelodysplastic syndromes; transfusion dependency

In contrast to the proven clinical benefits of iron chelation therapy (ICT) in thalassemia-related transfusional iron overload (IO), the clinical utility of ICT in myelodysplastic syndrome (MDS) patients with red blood cell (RBC) transfusion dependency (TD) and resultant IO is one of the most controversial issues in the management of MDS [1]. An accumulating body of evidence describes the association between TD and secondary IO and inferior survival in MDS patients [2–4]. The combination of suggestive retrospective data, lack of randomized trials supporting the effectiveness of ICT on clinical outcomes in MDS patients [5–8] and the recent approval of two effective oral chelators, deferasirox (DFX) and deferiprone (DFP), have fueled the debate [7,9–11]. Reflective of this therapeutic equipoise of the use of ICT in MDS, the published guidelines and consensus statements for managing

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IO in MDS lack uniform recommendations. They differ as to how best to monitor IO, when to initiate ICT, how to assess response to therapy and adjust drug dosages. Therefore, clinical practices have varied significantly on physician, institution and country levels [1,12,13].

In the following sections, the authors review the adverse effects of anemia and TD on clinical outcomes and survival in MDS patients, summarize the available evidence of detrimental effects of IO in MDS patients, discuss the possible pathogenic mechanisms underlying iron-mediated damage in MDS and evaluate the trials that investigated the role of ICT in MDS.

Myelodysplastic syndromes

Epidemiology, prognosis & management of MDS

MDS encompass a group of heterogeneous clonal hematopoietic stem cell neoplasms characterized by dysplastic changes, ineffective hematopoiesis, cytopenias in peripheral blood (PB) and an increased risk of progression to acute myeloid leukemia (AML). Approximately 15,000 new cases of MDS are diagnosed in the USA each year [13]. Although MDS can occur in all age groups, median age at diagnosis ranges between 71 and 76 years [14,15]. A number of prognostic tools have been developed to separate MDS patients into subgroups with different natural histories and clinical outcomes [16]. In addition to providing prognostic data, the models have also been used to generate risk-adaptive therapeutic strategies [17]. The International Prognostic Scoring System (IPSS) is the most widely used prognostic tool for newly diagnosed MDS patients [18]. The IPSS defines four risk categories: low, intermediate-1 (INT-1), intermediate-2 (INT-2) and high-risk with different median survivals and risk of leukemic progression. The median survivals were 5.7, 3.5, 1.2 and 0.4 years for low, INT-1, INT-2 and high-risk IPSS groups, respectively [18]. The IPSS risk group is determined by a total score based on bone marrow (BM) blast percentage, the number of cytopenic cell lines in PB and the cytogenetic aberrations. The IPSS has recently been revised, but it remains to be seen how the IPSS-R will be incorporated in treatment guidelines [19]. Another commonly used classification schema is the WHO Prognostic Scoring System (WPSS), which additionally accounts for the prognostic effects of the morphologic class and TD [2] and can be applied throughout the natural history of MDS, unlike the IPSS which is modeled only at diagnosis.

Despite the approval of three disease-modifying drugs (azacitidine, decitabine and lenalidomide), allogeneic hematopoietic stem cell transplant (alloHSCT) remains the only known curative treatment modality. Unfortunately, only a minority of patients are eligible for alloHSCT due to advanced age, co-morbidities and limited donor availability [20]. As most patients are not treated with curative intent, supportive care measures continue to play a major role in the management of patients with MDS. Risk stratification status of the patient, co-morbidities, performance status, age and the patient’s preference all factor in determining the therapeutic strategy for the individual [16]. Traditionally, MDS patients are grouped into two broad prognostic classes: lower-risk (LR)-MDS, defined by IPSS low and INT-1 risk classes, and higher-risk (HR)-MDS, defined by IPSS INT-2 and high-risk categories.

In HR-MDS, expected survival is significantly limited; therefore, management goals focus on prolonging survival in patients able to tolerate aggressive therapy. Since patients with LR-MDS have a relatively longer expected survival, the goals of care emphasize quality of life improvements [16]. This is usually achieved by alleviating symptoms of anemia, reducing transfusion needs with erythropoiesis-stimulating agents (ESA) or lenalidomide therapy, controlling infections with antibiotics, transfusion of RBC or platelets as needed, and removing excess iron with ICT [7,16].

Anemia & RBC TD in MDS

Anemia is the most frequently noted cytopenia in MDS [21]. An estimated 80–90% of patients with MDS develop anemia during the course of their disease [18]. More than 50% of these patients present with hemoglobin (Hb) levels below 10 g/dl and 27% present with a Hb less than 8 g/dl [7,18,22,23]. MDS-associated anemia results from complex multifactorial processes including ineffective erythropoiesis and suboptimal responses to endogenous erythropoietin [15].

The frequency of transfusions for MDS patients varies from patient to patient but most will require RBC transfusions at some point and up to 40% will develop TD [3]. Approximately one-third of patients with LR-MDS and approximately two-thirds of HR-MDS are transfusion-dependent [3,7]. A number of treatment options are available for managing MDS-associated anemia. About 20–30% of MDS patients and approximately 40% of patients with LR-MDS achieve objective erythroid responses with ESA therapy; however these effects are limited with a median duration of 2 years [24]. Patients with LR-MDS, lower endogenous serum erythropoietin levels and those with lower RBC transfusion needs are more likely to respond to ESA therapy [15,24]. In addition, two-thirds of patients with transfusion-dependent LR-MDS and deletions in the long arm of chromosome 5 (del-5q) achieve RBC transfusion independence (TI) with lenalidomide therapy, with the median response duration longer than 2 years [25,26]. Unfortunately, erythroid responses to both ESA and lenalidomide therapy are eventually lost and patients will require other treatment options. Additionally, many MDS patients are still mainly treated with RBC transfusions as a palliative intervention [21,22].

Anemic MDS patients have been shown to have a higher mortality rate than non-anemic MDS patients, chiefly due to cardiovascular (CV) causes [3,23,27–29]. In order to compensate for the impaired tissue oxygenation, chronic anemia results in increased cardiac output which leads to left ventricular hypertrophy [22]. A statistically significant association between lower Hb levels and worse CV outcomes has been documented in MDS, including cardiac remodeling due to increased pre-load and decreased after-load, congestive heart failure (CHF), coronary artery disease, myocardial infarction (MI), arrhythmia and heart valve disease [27]. The inclusion of RBC transfusions into MDS prognostic systems such as the WPSS reflects the negative prognostic impact of TD in MDS. TD has been associated with increased risk of disease progression, leukemic transformation and reduced survival [3]. A retrospective study of the US Medicare Beneficiaries which included 512 MDS patients found that the 3-year survival rate was significantly lower in transfused MDS patients (40.9%) than non transfused MDS patients (69.0%; $p < 0.001$) [29]. MDS patients

with TD experienced higher rates of cardiac events, diabetes, infections and transformation to AML. After adjusting for age, TD was shown to be associated with an increased risk of death (hazard ratio [HR]: 2.41; $p < 0.001$). It is a matter of debate whether the increased adverse outcomes associated with TD reflect worse disease biology or results from the harmful effects of severe anemia, transfusions and their associated complications. In fact, the WPSS has been revised to include severity of anemia as a prognostic factor in lieu of TD [28].

IO in MDS

Iron homeostasis in MDS

Iron is essential for life but is harmful in excess. Since there is no physiological mechanism to excrete excess iron from the human body, iron homeostasis is tightly regulated. The normal iron content in the body is approximately 3–4 g, most of which is stored as intracellular ferritin [30]. A small amount of iron, approximately 1–2 mg, is absorbed daily from the GI tract, while about 20 mg of iron is recycled daily from Hb in senescent erythrocytes after phagocytosis by reticuloendothelial macrophages [31]. Since each unit of packed RBC contains 200–250 mg of elemental iron, approximately 100 times the normal daily intake of iron, it is inevitable that transfusion-dependent MDS patients who live long enough will develop IO [1,3,29,32].

Iron homeostasis, which is controlled primarily by the protein hepcidin produced in the liver, is affected by many factors including hypoxia, iron deficiency, IO and inflammation [30,33]. Hepcidin is a key negative regulator of cellular iron export from duodenal enterocytes, macrophages and hepatocytes [30,32,33]. It acts by downregulating ferroportin, the transmembrane iron carrier protein that mediates iron export from these cells [32,33]. When cellular iron stores are adequate or high, increased hepcidin levels decrease intestinal iron absorption and reduce the release of recycled iron from macrophages by causing degradation of the iron exporter ferroportin [30,32,33]. Conversely, when iron stores are low, hepcidin production is suppressed enabling increased intestinal iron absorption and mobilization of iron from macrophages [31,33].

The reticuolendothelial system has the capacity to store 10–15 g of iron which equates to about 40–50 RBC units [7]. Once the macrophages reach full capacity, the iron is transported into the plasma by ferroportin, where it binds to transferrin [34]. The hepatocytes also serve as additional storage sites for the excess iron. With continued transfusion, the macrophages, hepatocytes and transferrin become saturated resulting in formation of non-transferrin-bound iron (NTBI) and labile plasma iron (LPI) in the plasma. When transferrin saturation exceeds 75%, NTBI might be detected and results in formation of LPI and reactive oxygen species (ROS) [10]. LPI is the toxic, cell-penetrating, redox-active component of NTBI [11,35]. Although chronic transfusion therapy is the main cause of IO in MDS patients, other contributing factors include increased absorption of iron from the gut due to ineffective erythropoiesis, reduced hepcidin production and possibly the presence of hemochromatosis genes polymorphisms or mutations in some patients [11,36,37].

Mechanisms of iron-mediated damage in MDS

Iron-induced damage occurs as a direct result of iron accumulation in the tissues and also results from the toxic effects of molecules that amass when the capacity of transferrin to carry iron is exceeded, such as NTBI and LPI. LPI is rapidly taken up by cells causing a rise in the labile iron pool and the production of harmful ROS [38]. The resultant oxidative stress and associated decrease in the antioxidant glutathione causes damage to lipids, proteins, DNA and subcellular organelles [38]. The damage caused by oxidative stress probably results in cell death, organ damage, genomic instability and leukemic transformation [11,34,35,39,40].

Many transfused MDS patients lack evidence of significant cardiac iron deposition on imaging but still demonstrate marked hepatic iron accumulation, suggesting that other factors such as NTBI and LPI might be important mediators of cardiac dysfunction in these patients [7,41]. In addition to cardiac toxicity, elevated NTBI/LPI levels and oxidative stress have been suggested to mediate, at least partially, the increased risk of infection, accelerated transformation into AML, increased mortality after alloHSCT and damage to other target organs [11,42,43]. ROS have been shown to be increased in $CD34^+$ cells in MDS patients with IO [44]. This increase in intracellular ROS is hypothesized to cause further impairment of hematopoiesis via stem cell exhaustion and promote accumulation of DNA damage increasing the risk of leukemic transformation [44,45]. IO also can damage erythroid progenitor cells and thus contribute to the already impaired hematopoiesis proliferation [46].

Measuring IO in MDS

The exact prevalence of IO in MDS patients in not well reported with figures ranging from 50 to 80% [32,47]. Serum ferritin (SF) levels are frequently used to estimate the extent of IO. Although SF is a simple test to perform, it is not specific for IO as SF is an acute phase reactant that can rise as a result of inflammation and infection [11]. Some authors have defined IO as an elevated SF over 1000 ng/ml [32]. MDS patients with TD develop IO typically after 20 RBC transfusions [21]. Malcovati *et al.* found that ferritin levels increased to over 1000 ng/ml after patients had received a median number of 21 RBC units which was reached in a median period of 10.8 months [3]. However, depending on MDS subtype and frequency of transfusions, the extent of IO in MDS patients may not correlate exactly with the number of RBC units transfused. Some patients with refractory anemia with ring sideroblasts (RARS) can develop IO even in absence of RBC transfusions [33]. This finding is probably due to increased GI absorption of iron. Transferrin saturation is also another measurement of body iron, although it is not usually used to define IO in the context of MDS.

The heart and liver have been found to be the best organs to demonstrate the association between iron levels and degree of pathology due to IO [7,29,33,48]. The liver contains more than 70% of total body iron and has been shown to correlate significantly with SF levels [49]. This fact is being exploited in the development of more sensitive and specific tests to assess IO. The gold standard for investigating IO is liver iron content (LIC) as assessed on in a liver biopsy [32]. However due to the invasiveness of this procedure and the frequent presence of thrombocytopenia, liver biopsies are not usually performed to assess LIC in

MDS patients. Non-invasive methods of determining LIC include superconducting quantum interference device (SQUID) biosusceptometry. SQUID biosusceptometry has been shown to correlate extremely accurately with liver biopsy LIC. Unfortunately, this test is extremely costly and is not readily available [7,32,50]. Another non-invasive method is T2* ('T-two-star') MRI which assesses iron concentration in the liver and heart [50]. T2*MRI imaging has successfully shown liver iron accumulation in heavily transfused patients, including MDS patients [21,41,49,51]. However, despite the high incidence of cardiac events in transfusion-dependent MDS patients, cardiac T2*MRI imaging did not demonstrate significant cardiac accumulation [41,49,51]. In thalassemia patients, more transfusions are required to cause IO in the myocardium [41], with a transfusion burden of over 100 units needed before significant iron accumulation was detected on cardiac T2*MRI imaging [51].

IO is associated with inferior outcomes & survival in MDS

The lack of prospective studies makes it difficult to conclusively determine the association of IO on the morbidity and mortality in MDS patients. However, the preponderance of retrospective evidence suggests that organ dysfunction and inferior survival occur at a higher incidence in MDS patients with TD and IO compared with non-transfused MDS patients [2]. Nonetheless, an analysis of patients with RARS did not show a correlation between survival and the number of transfused RBC units or SF levels [52].

IO & survival in MDS—Retrospective studies show that LR-MDS patients with elevated SF levels have significantly worse overall survival (OS) [3,4,53]. A Japanese study found that 37 of the 38 MDS patients who died had a SF greater than 1000 ng/ml, with liver and cardiac dysfunction being the primary cause of death in these patients [4]. A study from Italy showed that MDS patients with TD had significantly shorter OS compared with non-transfused patients (HR: 1.36; $p < 0.001$), with cardiac events as the leading cause of death [3]. They also found that for every 500 ng/ml rise in SF above the threshold level of 1000 ng/ml, the HR for death significantly increased by 30% ($p < 0.001$). In patients in whom SF was normal or near normal (<350 ng/ml) at the time of diagnosis, SF increased to over 1000 ng/ml after a median number of 21 RBC units. IO was mainly seen in patients with LR-MDS such as refractory anemia (RA) and RARS, as these subtypes are typically associated with a relatively longer median survival and therefore received more RBC transfusions (HR: 1.51; $p < 0.001$). OS was affected by the total number of RBC units received during the course of the disease (HR: 1.21; $p = 0.02$). A review of 902 patients published only in abstract form showed that TD significantly impacts survival with median OS for transfusion-dependent patients at diagnosis and during evolution and non-transfused patients reported at 19, 60 and 96 months, respectively ($p < 0.0001$) [54]. The development of IO and TD were strongly associated with adverse OS (HR: 52.4; $p < 0.0001$ and HR: 8.8; $p < 0.001$, respectively).

Not all studies demonstrated a survival detriment in MDS patients with incremental RBC transfusion and secondary IO. In a retrospective study of 126 patients with RARS, the need for RBC transfusion at time of diagnosis but not the total number of transfused RBC units correlated independently with worse survival [52]. There were also no correlations between SF levels measured at diagnosis or during follow-up and inferior survival, suggesting that

secondary IO is not necessarily a negative prognostic factor in some subsets of MDS patients like those with RARS [52].

Cardiac effects of IO in MDS—Cardiac complications are increased in MDS patients, especially those with TD and IO. A US-based Medicare study showed that 73.2% of MDS patients suffered a cardiac event with 59.2% of these patients having no past medical history of cardiac problems ($p< 0.001$) [29]. Cardiac events experienced included arrhythmias (51.2%), CHF (48.2%) and MI (19.3%). Also MDS patients who received RBC transfusions had a significantly higher incidence of a cardiac event over the 3-year follow-up period (82.4 vs 67.1%; $p < 0.001$). Cardiac failure is a common cause of mortality (51%) and it was significantly more frequent in transfusion-dependent LR-MDS and the leading cause of death after leukemia [3]. A retrospective Japanese study noted cardiac failure accounted for 24% of deaths in patients with chronic acquired anemic patients, including MDS, with TD and IO [4]. Another study found a significantly increased risk of arrhythmias in MDS transfusion-dependent patients ($p = 0.0005$) [55].

A study assessing IO by T2*MRI in transfusion-dependent MDS patients found less myocardial IO than expected and SF was not significantly correlated with cardiac T2*MRI ($p = 0.24$) [51]. This suggests that cardiac iron deposition is not linearly proportional to the number of RBC transfusions received in MDS [56]. Indeed, many transfused MDS patients lack evidence of significant cardiac iron deposition on imaging, in contrast to marked hepatic iron accumulation, suggesting a long latent period and that other factors such as NTBI/LPI may mediate the cardiac dysfunction in these patients [7,41,49]. Not all studies demonstrated an increased number of CV events in the non-leukemic cause of death in LR-MDS patients [57].

Hepatic effects of IO in MDS—A small number of studies have shown that liver iron loading and hepatic complications are increased in MDS patients who have received RBC transfusions during the course of their disease [3,4,29]. The Medicare study found that liver disease was more common in MDS patients (0.8%) compared with the rest of the Medicare study population (0.2%; $p = 0.0108$) and even more common in transfusion-dependent MDS patients (1 vs 0.7%; $p = 0.68$) [29]. The Japanese study found abnormal liver function in 84.6% of all of the MDS and aplastic anemia patients assessed [4]. Liver enzymes were raised, indicating hepatic cellular damage, in the transfused patient compared with the non-transfused patient. The elevated aspartate aminotransferase (AST) and ala-nine aminotransferase (ALT) levels correlated with transfusion frequency, transfusion history and elevated SF. Approximately 8% of non-leukemic deaths in MDS patients with TD in the Malcovati *et al.* study were due to liver cirrhosis [3]. In addition to direct toxicity from hepatic iron deposition, the elevated NTBI/LPI levels and resultant oxidative stress likely contribute to the injury of the hepatocytes [3,58]. The interaction of hepatic IO in MDS patients with other liver diseases such as viral hepatitis needs further evaluation.

Endocrine effects of IO in MDS—IO secondary to RBC transfusions has been shown in endocrine organs, including the pancreas, thyroid and pituitary [59]. The Medicare study found a significantly higher prevalence of diabetes in MDS patients compared with the rest of the Medicare study population (40 vs 33.1%; $p < 0.001$) [29]. Also MDS patients who

had received a RBC transfusion had a greater prevalence to develop diabetes than non-transfused MDS patients (44.4 vs 37.1%; p = 0.01). The Japanese analysis found elevated fasting blood glucose levels in 54.0% of transfused MDS patients compared with 39.1% in non-transfused patients [4]. Autopsy data in 36 cases with transfusional IO demonstrated iron accumulation in the beta islet cells of the pancreas which may explain the increased incidence of endocrine complications including hyperglycemia and diabetes in patients with MDS and TD [60].

Infections & IO in MDS—Infectious complications are a common cause of death in MDS patients. Malcovati *et al.* found that infections accounted for 31% of the non-leukemic causes of death [3]. Several infectious organisms have been found to grow well in iron-rich environments [11]. *In vitro* studies showed that NTBI and LPI augment the growth of several microorganisms, including *Candida* and *Staphylococcus* [1,7,11]. Transfused MDS patients were found to be at a greater risk of developing infections compared with non-transfused MDS patients (81 vs 55.7%; p < 0.001) [29]. In patients with IO, iron might mediate immune system suppressive effects including functional impairments of the neutrophils, macrophages and natural killer cells, which might contribute to an increased risk of infections [7,61].

Leukemic transformation & IO in MDS—An increased incidence of disease progression has been correlated with elevated SF and TD in MDS patients (HR: 6.6; p < 0.0001 and HR: 3.5; p = 0.003, respectively) [54]. Other studies have also shown an increased incidence of progression to AML in transfused versus non-transfused MDS patients (18.0 vs 3.9%; p < 0.001) [29]. Rose *et al.* found a trend for higher incidence of AML progression in non-chelated MDS patients with 34% of this group displaying leukemic progression compared with 17% of chelated patients, although this trend was not statistically significant (p = 0.087) [5]. This group was substantially iron overloaded with a mean SF of 2786 ng/ml. Malcovati *et al.* showed that the acute leukemia-free survival of transfusion-dependent MDS patients were significantly worse than that of non-transfused patients (HR: 2.02; p < 0.001) [3]. It is unclear whether these findings are directly due to the toxic effects related to IO or reflect the more aggressive underlying MDS biology in these patients. Increases in intracellular ROS can cause genomic instability through DNA, RNA and protein damage and thus possibly accelerate progression to AML [7,44].

IO & outcomes of alloHSCT in MDS—Studies of MDS patients with IO undergoing alloHSCT suggested worse OS and increased transplant-related mortality (TRM) due to higher rates of infectious complications and hepatic venoocclusive disease (VOD) in these patients [62,63]. A retrospective study of 590 patients by Armand *et al.* showed that MDS patients with elevated pre-transplant SF had higher TRM and poorer outcomes compared with patients with normal levels, with infections as the leading cause of these poorer clinical outcomes [64]. The 5-year OS for patients with pre-transplantation SF 0–231 ng/ml was 54%, 232–930 ng/ml 50%, 931–2034 ng/ml 37 and 27% in over 2034 ng/ml (p < 0.001). There was a higher incidence of VOD in MDS patients with the highest SF range (p = 0.054). Alessandrino *et al.* found an association between transfusion burden and post-transplant mortality, with survival being significantly worse in patients with a long history

of TD and who had received more than 20 RBC units (HR: 1.47; p = 0.038 and HR: 1.34; p = 0.10, respectively) [65]. The incidence of graft-versus-host disease (GVHD) was significantly increased in MDS patients with IO prior to transplantation in some studies [65]. Increased oxidative stress, due to LPI, could potentially explain this association between IO and GVHD [65]. LPI has been shown to increase significantly after myeloablative-conditioning regimens used prior to transplant (reviewed in [66]). However, these findings were not replicated in other analyses [67]. While some studies demonstrated that IO pre-transplant correlated with an increased risk of relapse after alloHSCT [62,64,67,68], other studies did not find this association [65,69]. The administration of ICT in the pre-transplantation period might reduce LPI, ROS and possibly improve alloHSCT outcomes, however this question remains to be evaluated in a prospective fashion.

Iron chelation therapy in MDS

Iron chelators & MDS

There is scarcity of prospective data regarding the effects of ICT on clinical outcomes in patients with MDS and IO. Although randomized studies in thalassemia have shown that ICT significantly reduces the morbidity and mortality associated with IO [31,70], extrapolation of these results to IO in MDS is problematic due to differences in the underlying disease processes, pathogenesis of IO, co-morbidities and life expectancy. Despite the detrimental effects associated with IO in MDS, retrospective studies investigating the effects of ICT in MDS have not produced consistent data. The inconsistencies may be partly explained by the inherent biological heterogeneity of MDS and the retrospective study design [71].

A number of approved iron chelators effectively reduce IO by binding the iron and allowing for excretion from the body. Deferoxamine (DFO), the first iron chelator approved, requires daily parenteral infusion for 8–10 h for effective use due to its short half-life. The logistics of DFO administration, its side effects and concerns about patient compliance have contributed to low levels of use in transfused MDS patients [31]. In 2006, the oral iron chelator DFX was approved for managing IO associated with TD. Side effects include a maculopapular rash, GI disturbances, including nausea and diarrhea and renal dysfunction. The unpleasant GI side effects may lead some patients to discontinue with the drug [43]. There have been reports of acute renal failure, acute liver impairment and GI bleeding in association with DFX use, prompting the US FDA to issue a black box warning regarding these adverse events [31]. Since many MDS patients are elderly with reduced renal reserve, particular attention should be paid to monitoring of renal function while on DFX therapy. Nonetheless, most creatinine level elevations that occur with DFX therapy are temporary and improve or resolve completely with dose adjustment or drug discontinuation [56,72]. DFP is another oral chelator available which has only recently been approved for use in the USA. DFP has been reported to cause granulocytopenias, including agranulocytosis and neutropenia, which can be particularly concerning in MDS patients. However, an analysis in 48 MDS patients demonstrated that it could be considered as an alternative ICT if either DFO or DFX were not tolerated [73]. Particular attention should be paid to monitoring white blood count and its differential if DFP is used.

ICT & survival in patients with MDS & IO

Several retrospective studies have suggested that ICT may improve survival in MDS patients with IO, most of whom had LR-MDS (Table 1) [5,6,74–76]. Despite matching and controlling for patients characteristics, selection bias is likely a significant limitation [48]. In addition, these studies used different definitions for IO, included different proportions of patients with HR-MDS, differed in use of iron chelation agent and had variable follow-up.

In a French study, 97 patients with LR-MDS and TD were followed up 2.5 years later [5]. The median OS was 53 months for the non-chelated group versus 124 months in chelated patients ($p < 0.0003$). Adequate chelation was the strongest independent factor associated with better OS, even after controlling for known prognostic factors and co-morbidities. In this study, adequate ICT was arbitrarily defined in the study as using DFO subcutaneously at 40 mg/kg/day infused over 8–12 h for 3 days or more per week, the use of oral DFX at 20–30 mg/kg/day or the use of DFP at 30–75 mg/kg/day. However, the study found no significant differences in cardiac, hepatic, infectious or leukemic causes of death between the chelated and non-chelated MDS patients despite the survival advantage, raising the possibility of selection bias affecting the results. A recently published German matched-pair analysis showed a median OS advantage for the chelated versus non-chelated patients (75 vs 49 months, respectively; $p = 0.002$) [75]. The median SF was 1954 ng/ml in the ICT group compared with 875 ng/ml in the control group. The OS difference between the two groups was limited to patients with LR-MDS ($p = 0.008$) with no significant survival advantage associated with ICT use in patients with HR-MDS. Infection was the most common cause of death in both groups while there was no significant difference in risk of leukemic progression between the two cohorts.

ICT & organ dysfunction in MDS

Limited data, mostly retrospective, are available on the ICT effects on organ function in MDS patients with IO. Two prospective trials, EPIC and US03, demonstrated decreased SF levels, NTBI and LPI after ICT with DFX in MDS patients [43,72]. The US03 trial enrolled patients with LR-MDS who had a SF ≥1000 ng/ml and had received more than 20 units of RBC with ongoing transfusion requirements [43]. The initial DFX dose was 20 mg/kg/day which could be increased up to 40 mg/kg/day, if required. One hundred and seventy-three patients who received ICT had a median baseline SF 2771 ng/ml and had received a mean number of 69 RBC units prior to the study. Ninety-one patients who completed 1 year of ICT experienced a 23% reduction in median SF ($p < 0.001$). The dose had to be increased to at least 30 mg/kg/day in more than 40% of patients because of persistently elevated SF levels. Withdrawal rates were high in this trial with 45% of patients not completing 1 year of ICT due to adverse events. The most common drug-related adverse effects were GI disturbances and increased creatinine levels. Eighty-three patients who completed 1 year of ICT entered the extension study and median SF levels were found to continue to decrease.

The prospective 1-year EPIC trial enrolled 341 MDS patients [72]. Unlike the US03 trial, patients were eligible even if they had a SF level less than 1000 ng/ml but T2*MRI indicated IO in the liver. Patients receiving 2–4 RBC units per month were treated at an initial dose of 20 mg/kg/day of DFX, whereas those with lower or higher transfusion needs

started at 10 or 30 mg/kg/day, respectively. The dose of DFX was titrated according to SF trends and safety markers. Their baseline median SF was 2730 ng/ml and at 1 year it had significantly decreased to 2280 ng/ml ($p = 0.002$). The reduction of median SF during 1 year was 35% in new chelated patients and 22% in previously chelated patients. However, this reduction was only significant in the new chelated patient group ($p = 0.004$). Decreases were dependent on dose adjustments and ongoing RBC transfusions. The rate of withdrawal in this study was also high with 166 (48.7%) patients dropping out due to similar adverse events as reported in the US03 trial. Raised creatinine was an issue once again but they found no evidence indicating an increased risk of progressive renal damage in MDS patients who had normal baseline serum creatinine. These findings are supported by more recent smaller scale studies [38]; [77–79].

ICT & cardiac dysfunction in MDS—No studies to date have found that ICT causes an improvement in cardiac function. List *et al.* reported that 25% of patients had experienced some form of cardiac event, including arrhythmias and MI, in the 3-year follow-up period but none were thought to be related to DFX [43]. However, due to there being no comparator arm in this study it was difficult to fully assess the impact of DFX on cardiac outcomes. *In vitro* data suggest that ICT may improve cardiac function by increasing the contractibility of the myocardiocytes [7].

ICT & liver dysfunction—Takatoku *et al.* showed that SF, AST and ALT all significantly decreased in the group of MDS patients receiving DFO continuously rather than via an intermittent infusion ($p > 0.05$) [4]. In the German matched-pair analysis, a lower risk of hepatic-related deaths was observed among chelated versus non-chelated patients [75]. The EPIC study showed that ALT significantly reduced from baseline after 1 year of ICT with DFX ($p < 0.0001$) [72]. This decrease in ALT was dependent on the dose of DFX received. A significant correlation between the absolute decrease in SF and ALT was found ($p < 0.0001$), which indicated a decrease in SF of 500 ng/ml was associated with a decrease in ALT of 21.6 U/l. The US03 study also showed a significant reduction in SF levels and an improvement in hepatic enzymes ($p < 0.001$) [43]. DFX caused a decrease in LIC as determined by T2*MRI within 4 weeks before the decline of ferritin levels in one study [80]. These data suggest that ICT may have a beneficial effect in reducing hepatocyte damage which could prevent dysfunction and cirrhosis.

ICT & endocrine dysfunction in MDS—Takatkou *et al.* showed a decrease in fasting blood glucose levels in MDS patients receiving DFO [4]. This group of patients received DFO continuously rather than intermittently (mean one treatment per 1.9 weeks), highlighting the importance of adequate ICT dosing to gain appropriate clinical benefits (average changes −4.8 vs +31.2 mg/dl, respectively).

ICT & improvements in hematopoiesis in MDS—Lineage-specific hematologic improvements were noted in 15–22% of patients after DFX therapy in transfusion-dependent MDS patients [43,77]. Improvements to erythroid, neutrophils and platelets were observed in 21.5, 22.0 and 13.0% of patients after a median of 109, 169 and 226 days, respectively [77]. These results suggest that DFX ICT for 1 year may lead to improvements in

hematopoiesis. List *et al.* also observed erythroid improvements in 15%, neutrophil response in 15% and platelet response in 22% of patients [43]. Median time to these responses was 169 days. However, some of these patients were receiving additional MDS therapies which may impact on these findings. These improvements in hematopoiesis are consistent across trials but the exact mechanism of hematologic response is still unknown. The hematopoietic response may be associated with SF as reductions in SF were generally greater in the patients who had hematologic improvements [43,81]. A recently presented abstract reported that 19.7% of LR-MDS patients achieved TI after 12 months of DFX therapy [82].

ICT & leukemic progression in MDS—ICT can reduce the risk of progression to AML in MDS patients by decreasing oxidative stress and subsequent genomic instability [11]. As mentioned earlier, Rose *et al.* found a trend for higher incidence of AML progression in non-chelated MDS patients (34 vs 17%; $p = 0.087$) [5]. The abstract by Sanz *et al.* also demonstrated an association between reduced SF levels and lower AML transformation rates [54]. The exact effect of ICT on leukemic progression and leukemia-free survival in MDS will hopefully be better understood when the results of the ongoing prospective studies, especially the randomized studies, are available.

ICT & infections in MDS—Since iron is needed by organisms to proliferate, chelation may lead to fewer infectious complications. ICT can reduce bacterial and fungal infections in MDS patients by reducing the LPI and improving the function of neutrophils and macrophages but these benefits have not yet been confirmed [11,83]. It should be noted that DFO has been suggested to worsen fungal infections by acting as a siderophore, while DFX could be active against mucormycosis infections [84]. In the German analysis, a lower rate of infectious deaths was observed among chelated versus non-chelated patients [75]. More data are needed to clarify effect of ICT on infectious complications in MDS patients.

ICT & alloHSCT outcomes in MDS—In a retrospective study of 101 pediatric patients, pre-transplant SF >1000 ng/ml in patients who did not receive ICT was associated with lower OS ($p = 0.001$), lower event-free survival (EFS, $p < 0.001$) and increased TRM [85]. Analysis of the patients who received ICT suggested possible benefit in the outcomes after alloHSCT. Other small retrospective studies in the transplant setting used phlebotomy post alloHSCT to reduce IO which resulted in improvements in liver enzymes and possible improvements in organ function (reviewed in [7]).

Mechanisms of benefit of ICT in MDS

Although the main reason to use ICT is to remove excess iron from the body, it is proposed that ICT might cause additional beneficial effects through alternative mechanisms. Sustained reductions in NTBI, LPI and ROS, and improvements in intracellular oxidative stress parameters such as reduced glutathione and membrane lipid peroxidation have been observed within 3 months of initiating DFX therapy in MDS patients [38,43,72,81,86]. The US03 trial found that the LPI concentration was reduced to a non-detectable level in 39.3% of LR-MDS patients after 3 months of DFX [43]. They also found continued normal levels of LPI throughout the 3-year follow-up period. Greenberg *et al.* also demonstrated that DFX can effectively reduce LPI levels in addition to reducing hepatic iron concentration and SF

levels despite ongoing RBC transfusions ($p = 0.004$ at 24 weeks and $p = 0.023$ at 52 weeks) [86]. A recent prospective study showed that intracellular 8-hydroxy-2′-deoxyguanosine levels, a marker of oxidative DNA damage, significantly decreased after DFX administration in mononuclear cells of PB, suggesting that ICT reduced oxidative DNA damage in MDS patients with TD ($p = 0.002$) [87]. Selective toxicity toward MDS hematopoietic progenitors has been proposed as another rationale for ICT in MDS and could also represent one possible mechanism to explain the hematologic responses seen in some patients [43,81,88,89]. Other mechanisms suggested include a reduction in oxidative stress, altering intracellular levels of NF-κB, thereby reducing the inhibitory effect of ROS on hematopoiesis [81]. It has been shown in *in vitro* studies that DFX causes NF-κB inhibition; an effect which is not seen with other chelators and is independent of DFX effects on iron and ROS scavenging [40]. *In vitro* studies have also shown a significant time- and dose-dependent suppression of the proliferation and induction of apoptosis in $CD34^+$ MDS progenitor cells incubated with DFX compared with $CD34^+$ progenitors isolated from umbilical cord blood or normal PB [90]. However, correlation between reduced NTBI, LPI or oxidative stress parameters and improved clinical outcomes in MDS patients has not been demonstrated prospectively to date [76].

Use of ICT in MDS

Guidelines for use of ICT in MDS

The guidelines and consensus statements for managing IO in MDS patients lack uniform recommendations due to the lack of randomized evidence on the use of ICT in MDS and its effect on clinical outcomes (Table 2). Although specific details may vary, most guidelines recommend initiating ICT in LR-MDS transfusion-dependent patients with a SF level greater than 1000–2500 ng/ml. The optimal duration of ICT is unknown with some guidelines recommending continuing with ICT while RBC transfusions are ongoing, IO remains clinically relevant or until SF level falls below 1000 ng/ml [22]. There are limited data on the optimal monitoring of iron levels in transfusion-dependent MDS patients receiving ICT, with some guidelines suggesting monitoring of SF levels every 3 months. Consequently, clinical practices have often varied according to the physician, institution and country [1,12,13].

Patterns of use of ICT in MDS

Utilization patterns of ICT among transfusion-dependent MDS patients in real-life settings have not been well studied [6,53]. Multiple studies have suggested that ICT is underutilized in patients with TD MDS [4,6,91], largely due to questions about efficacy, conflicting guidelines and logistic difficulties with administration [12,83,91,92]. Before 2006, DFO, which requires daily prolonged parenteral administration via an infusion pump for optimal effects, was the only available form of ICT in the USA. The approval of DFX as the first oral ICT in the USA renewed interest in ICT in the management of MDS patients.

ICT can be costly, with the National Comprehensive Cancer Network estimating the annual cost per patient with DFO at US$21,048 and US$46,008 with DFX [93]. However, the oral ICT DFX is suggested to be more cost-effective than DFO which requires infusion devices

for administration [57]. These possible large costs associated with ICT use is another point that might be considered in addition to the inconclusive benefits of ICT and possible adverse events when deciding on initiating ICT in MDS patients. Therefore and similar to the risk-adaptive use of other therapies for MDS [94,95], the use of ICT therapy in patients with MDS should be a decision made on a case-by-case basis based on a careful estimation of risk/benefit ratio.

Expert commentary

The beneficial effects of ICT on end organ function and survival in patients with MDS with TD and secondary IO are yet to be demonstrated prospectively in a randomized fashion. Given the possible side effects, the associated costs and the therapeutic equipoise of benefit in MDS, the use of ICT, especially for HR-MDS, remains a hotly debated issue. There is an increasing body of clinical and laboratory data detailing the adverse effects of secondary IO in MDS on survival and on organ function, including cardiac, hepatic and endocrine damage, and possibly increased infection risk and leukemic transformation. The availability of newer effective oral iron chelators has renewed interest in exploring the benefits of ICT in MDS with TD.

Retrospective data suggest that ICT in MDS with secondary IO improves survival, especially in LR-MDS, may reduce cardiac and hepatic complications, can lead to hematologic improvements and can possibly decrease leukemic transformation, infectious complications and TRM. Early data from prospective studies of ICT in MDS patients with IO show reductions in harmful iron species such as LPI, NTBI and ROS, that are believed to mediate some of the tissue damage seen with IO. Prospective data also confirm improvements of liver enzymes and hematologic improvements in a significant minority of patients using ICT in these patients. It remains to be seen whether survival advantage or improvement in target organ function can be conclusively demonstrated with longer follow-up of these studies. Due to this uncertainty, a significant variation currently exists in published clinical practice guidelines on all aspects of ICT use in MDS from when to initiate ICT, how to select patients to how to monitor response and adjust drug dosages. The existence of this therapeutic equipoise regarding the clinical benefits of ICT in patients with MDS and secondary IO should encourage enrollment of patients on randomized studies that evaluate this question.

Traditionally, ICT use in MDS has been recommended for patients with LR-MDS with significant degree of IO, usually defined by cumulative transfusion history of 20 or more units of RBC or a SF level of more than 1000–2500 ng/ml with ongoing transfusion needs. It has been argued that ICT in patients with HR-MDS with IO should also be considered in an effort to reduce infections and leukemic progression, and improve outcomes of patients who proceed to alloHSCT, although none of these benefits have been proven prospectively to date. It should be noted, although not clearly documented, that interventions which lead to restoration of normal erythropoiesis such as lenalidomide, ESA, azacitidine, decitabine or alloHSCT can allow utilization of excessive body iron stores and therefore reduce IO in patients with MDS. Until more conclusive data are available regarding survival and organ function, the initiation of ICT in patients with MDS remains a highly individualized decision

that should be made on case-by-case basis based on the risk status of the patient, degree of IO, expected survival, co-morbidities, expected risk/benefit ratio, patient's preference and possible cost.

Five-year view

More data from prospective studies such as EPIC and US03 will be available over next few years regarding survival and organ function in relation to ICT use in MDS patients with IO. Results from large randomized studies, such as the TELESTO trial (ClinicalTrials.gov identifier: NCT00940602) which is evaluating the long-term effects of ICT therapy with DFX in patients with MDS will hopefully provide more answers. These clinical results will help us better establish the best ways to apply ICT in the management of MDS patients in ways that optimize the risk/benefit ratios. Over the next years, it is expected that the mechanisms of iron-mediated damage in MDS will be dissected further and the pathogenesis of organ dysfunction will be better understood. The elucidation of the pathogenetic mechanisms of iron damage, especially at the level of dysplastic hematopoietic stem cells, progenitors and their genome and its contribution to leukemogenesis, might facilitate discovering new targets and approaches to reduce iron-mediated genetic damage, genomic instability and hopefully leukemic progression.

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Key issues

- The best use of iron chelation therapy (ICT) in myelodyspastic syndrome (MDS) patients with transfusion dependency (TD) and iron overload (IO) is a debated issue.
- Increasing evidence highlights the detrimental effects of TD and secondary IO in MDS on the survival and clinical outcomes, including cardiac, hepatic and endocrine damage, and possibly increased infection risk and leukemic transformation.
- Retrospective data suggest that ICT in MDS with secondary IO can improve survival in some patients with MDS, especially those with lower-risk MDS, may reduce cardiac and hepatic complications, lead to hematologic improvements and possibly decrease leukemic transformation, infectious complications and transplant-related mortality.
- The traditional use of ICT in MDS has been in patients with lower-risk MDS with TD, but other researchers have argued that the use of ICT in higher-risk MDS patients should be considered to possibly reduce infections, delay leukemic transformation and improve transplantation outcomes.
- The availability of two effective oral iron chelators, deferasirox and deferiprone, have renewed interest in evaluation of ICT utility in MDS.
- ICT use in MDS patients with IO significantly reduce harmful iron species such as labile plasma iron, non-transferrin-bound iron and reactive oxygen species that are believed to mediate some of the tissue damage seen with IO.
- Early prospective data confirm improvements of liver enzymes and hematologic improvements in a significant minority of MDS patients using ICT.
- The beneficial effects of ICT on organ function and survival in patients with MDS with TD and IO are yet to be demonstrated prospectively in a randomized fashion.
- Given the possible side effects, the associated costs and the therapeutic equipoise, the use of ICT in MDS remains one of the most hotly debated issues with significant variations between the different clinical guidelines.
- Until conclusive data are available, use of ICT in MDS patients should be made on a case-by-case basis in a dynamic fashion based on ongoing evaluation of risk/benefit ratio.

Table 1

Summary of retrospective studies demonstrating a statistically significant overall survival advantage in association with iron chelation therapy in patients with myelodysplastic syndromes and secondary iron overload in the non-stem cell transplantation setting.

Study	Type of study	Participants (n)	Population	ICT agent	Median OS	Leukemic transformation	Infection-related deaths	Cardiac deaths	Hepatic deaths	Ref.
Leitch *et al.*	Retrospective	178 (18 on ICT)	LR-MDS (99); HR-MDS (34)	DFO (18)	40 months for non-ICT vs 226 months for ICT (p = 0.003)	4 in non-ICT vs 1 in ICT (p = 0.06)	2 deaths in non-ICT vs 1 death in ICT (p = 0.05)	0 deaths in non-ICT vs 2 deaths in ICT (p = NS)	NS	[74]
Raptis *et al.*	Retrospective	102 (41 on ICT)	LR-MDS (78, 32 on ICT); HR-MDS (24, 9 on ICT)	DFO (12); DFX (29)	8.7 years for ICT vs 4.7 years for non-ICT (p = 0.03)	4 in non-ICT vs 3 in ICT (p = NS)	NS	NS	NS	[6]
Rose *et al.*	Retrospective/prospective cohort	97 (53 on ICT)	LR-MDS	DFO (40); DFX (4); DFP (5); DFP + DFO (4)	53 months for non-ICT vs 124 months for ICT (p < 0.0003)	15 in non-ICT vs 9 in ICT (p = 0.087)	6 deaths in non-ICT vs 7 deaths in ICT (p = NS)	10 deaths in non-ICT vs 10 deaths in ICT (p = NS)	I death in non-ICT vs 0 deaths in ICT	[5]
Neukirchen *et al.*	Retrospective matched-pair analysis	188 (94 on ICT)	LR-MDS (78); HR-MDS (16)	DFO (53); DFX (47); DFO then DFX (14); DFO then DFP (3)	49 months for non-ICT vs 75 months for ICT (p = 0.002)	13 in non-ICT vs 12 in ICT (p = 0.73)	12 deaths in non-ICT vs 33 deaths in ICT (p = 0.03)	NS	NS	[75]
Leitch *et al.*	Retrospective	182 (38 on ICT)	LR-MDS (175)	DFO (9); DFX (19); DFO then DFX (9); DFX then DFO (1)	Non-RARS: 44 months for non-ICT vs NR for ICT (p < 0.0001). RARS: 99 months for non-ICT vs 134.4 months for ICT (p = 0.025). RA/ del-5q: 60 months for non-ICT vs NR for ICT (p = 0.017)	Non-RARS: 10 leukemic deaths in non-ICT vs 0 leukemic deaths in ICT (p = NS). RARS: 2 leukemic deaths in non-ICT vs 1 leukemic death in ICT (p = NS). RA/ del-5q: 2 leukemic deaths in non-ICT vs 0 leukemic deaths in ICT (p = NS)	Non-RARS: 10 deaths in non-ICT vs 0 death in ICT (p = NS). RARS: 3 deaths in non-ICT vs 1 death in ICT (p = NS). RA/ del-5q: 2 deaths in non-ICT vs 0 deaths in ICT (p = NS)	Non-RARS: 1 death in non-ICT vs 2 deaths in ICT (p = NS). RARS: 0 deaths in non-ICT vs 2 deaths in ICT (p = NS). RA/ del-5q: 1 death in non-ICT vs 2 deaths in ICT (p = NS)	Non-RARS: 1 death in non-ICT vs 0 deaths in ICT (p = NS). RARS: no deaths in either group. RA/ del-5q: no deaths in either group	[76]

DFO: Deferoxamine; DFP: Deferipone; DFX: Deferasirox; HR-MDS: Higher-risk myelodysplastic syndromes; ICT: Iron chelation therapy; LR-MDS: Lower-risk myelodysplastic syndromes; NS: Not stated; NR: Not reached; OS: Overall survival; RARS: Refractory anemia with ringed sideroblasts; RA/del-5q: Refractory anemia/deletion of long arm of chromosome 5.

Data taken from [5,6,74–76].

Table 2

Guidelines for the treatment of iron overload in myelodysplastic syndromes.

Guidelines	Transfusion status	Serum ferritin level (ng/ml)	Patient profile	Ref.
Italian	Received ≥ 20 RBC units	NS	IPSS low or INT-1 IPSS INT-2 or high, undergoing alloHSCT	[96]
UK	Received 25 RBC units	NS	Pure sideroblastic anemia del(5q)	[97]
Canada	Transfusion dependent	>1000	IPSS low or INT-1 IPSS INT-2 or high undergoing alloHSCT WHO RA, RARS and del-5q Life expectancy >1 year	[32]
MDS Foundation	Received 2 RBC units/month for ≥1 year	>1000	IPSS low or INT-1 WHO RA, RARS and del-5q No erythroid response to primary therapy Undergoing alloHSCT Life expectancy >1 year	[22]
NCCN	Received >20 RBC units	>2500	IPSS low or INT-1	[98]
Spanish	Transfusion dependent	>1000	IPSS low or INT-1 WPSS very low, low or INT Spanish Prognostic Index Low-risk	[99]
Israeli	Received 20–25 RBC units	>1000	IPSS low or INT-1 Life expectancy >1 year Undergoing alloHSCT	[100]
Japanese	Received >40[†] Japanese RBC units; Received >2 RBC units for ≥ 6 months	>1000	Life expectancy >1 year	[101]
Austrian	Transfusion dependent, >2 RBC units/month	>2000	Life expectancy >2 years	[102]

[†]Equivalent to 20 western RBC units.

alloHSCT: Allogeneic hematopoietic stem cell transplant; del-5q: Deletion of long arm of chromosome 5; DFO: Deferoxamine; DFX: Deferasirox; IPSS: International Prognostic Scoring System; NR: Not reported; NS: Not stated; RA: Refractory anemia; RBC: Red blood cell; SF: Serum ferritin.

Adapted from [83].