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Invited editorial

Iron overload in myelodysplastic syndromes: A Canadian consensus guideline

Richard A. Wells [a,*], Brian Leber [b], Rena Buckstein [a], Jeffrey H. Lipton [c], Wanda Hasegawa [d], Kuljit Grewal [e], Karen Yee [c], Harold J. Olney [f], Loree Larratt [g], Linda Vickars [h], Alan Tinmouth [i]

[a] *Myelodysplastic Syndromes Program, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada*
[b] *Hamilton Health Sciences and McMaster University, Hamilton, Ontario, Canada*
[c] *University Health Network, Princess Margaret Hospital, Toronto, Ontario, Canada*
[d] *Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada*
[e] *Health Sciences Centre, St. John's, Newfoundland, Canada*
[f] *Centre Hospitalier de l'Université de Montreal, Hôpital Notre-Dame, Montreal, Quebec, Canada*
[g] *University of Alberta, Edmonton, Alberta, Canada*
[h] *BC Cancer Agency, Vancouver, British Columbia, Canada*
[i] *Ottawa Hospital, Ottawa, Ontario, Canada*

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Abstract

In December 2005, 11 Canadian hematologists met to develop an evidence-based clinical practice guideline that would address the diagnosis, monitoring, management, and rationale for the treatment of transfusional iron overload in patients with myelodysplastic syndromes (MDS). This Expert Panel consisted of hematologists from across Canada, each with an active practice in a major population centre or a rural area. Based on an extensive literature search and years of clinical experience, their mandate was to address common clinical practice questions, particularly why treat, whom to treat, when to initiate treatment, and how to treat iron overload in patients with MDS.

Keywords: Myelodysplastic syndromes; Iron overload; Secondary hemosiderosis; Iron chelation; Deferoxamine; Deferasirox; Desferal; Exjade; Deferriprone; Ferriprox; Transfusion; Prognosis; Guideline

1. Introduction

The prevalence of MDS has not been rigorously documented, although a recent analysis suggests it may affect as many as one in 1000 Canadians over the age of 65 years [1]. The main clinical feature of MDS is anemia, which is present in about 80% of patients at diagnosis and varies in severity. Although novel therapies are being developed that enhance bone marrow function and reduce or obviate the need for blood transfusion, currently more than 80% of MDS patients require chronic red blood cell transfusion as the cornerstone of treatment [2]. As a consequence, transfusional iron overload is a very common complication of MDS. It is widely thought that this complication of MDS is physiologically important and that the use of iron chelation therapy to prevent or ameliorate iron overload is a key consideration in the management of MDS patients [3], although this is not universally accepted. In this paper we provide a critical review of the basis in evidence for iron chelation in MDS, and provide guidelines for clinical practice.

2. Methodology

In December 2005, the Expert Panel reviewed national and international data on the contribution of transfusional iron overload to the morbidity and mortality of patients with MDS, the underlying

* Corresponding author. Tel.: +1 416 480 5248; fax: +1 416 480 6002.
E-mail address: rwells@sri.utoronto.ca (R.A. Wells).

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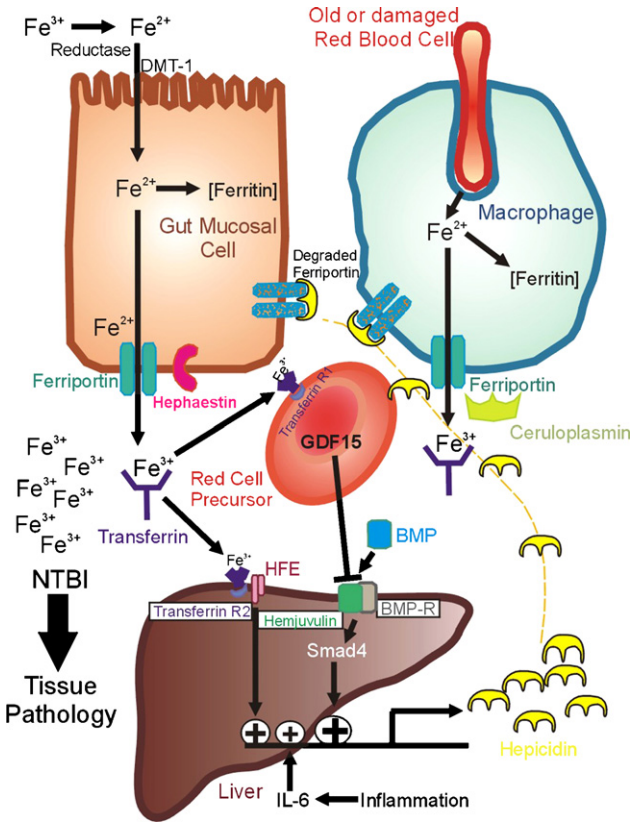

Fig. 1. Overview of Mechanisms Iron Transport. Iron enters the central transport and utilization compartment through two portals: as elemental iron that must be reduced from ferric (3+) to ferrous (2+) before transport though the DMT-1 transporter into Gut Mucosal Cells (or alternatively as heme iron through a selective heme receptor – not shown), and within the hemoglobin when old or damaged red cells are engulfed and digested by Macrophages. The latter entry point carries ~100–1000 times more iron flux than through the gut, especially in heavily transfused patients like those with MDS. In these cells, intracellular iron concentrations control the production of Ferritin, which sequesters iron in stores for later use, whereas unsequestered iron may be transported out of the cell. Iron exits the cell via Ferriportin, an activity which requires an associated oxidase – this function is performed for gut cells by the membrane bound Hephaestin, while for macrophages it is the plasma protein Ceruloplasmin. The oxidase activity allows the binding of ferric (3+) iron to Transferrin which tranports iron in blood and tissue fluid to its sites of use, predominantly Red Cell Precursors where it is taken up by Transferrin Receptor-1 and ultimately used to make hemoglobin. Iron egress from the portal cells is controlled by the liver protein Hepcidin, which acts as a plug to prevent iron release from these cells by binding to Ferriportin and targeting it for proteosomal destruction. Hepcidin production is controlled by many factors including inflammation through the IL-6 receptor, hypoxia through HIF1α (not shown) and at least two pathways that sense body iron load. One of these pathways involves Transferrin binding to hepatic Transferrin Receptor-2 which forms a complex with the HFE gene product to turn on hepcidin transcription; the other, stronger pathway is mediated by members of the Bone Morphogenetic Protein (BMP) family binding to one of the TGF receptors (BMP-R) in concert with Hemjuvulin; receptor binding activates the SMAD-4 transcription factor to make more Hepcidin. Recently it has been shown [82] that red cell precursors contain GDF15, that when released from these cells during the intramedullary hemolysis associated with ineffective erythropoieisis in thalassemia and some cases of MDS, prevents the Hemjuvulin/BMP upregulation of Hepcidin; this then causes increased iron uptake and overload. Inherited loss of function mutations in HFE, Hemjuvulin, Hepcidin, Transferrin Receptor-2, Ferriportin and Ferritin are associated with hereditary hemochromatosis types I, IIA, IIB, III, IV and V, respectively. In all cases of iron overload, whether hereditary or due to transfusion, the egress of iron from the portal cells overwhelms the ability of Transferrin to bind to iron (Fe3+) leading to free, Non-Transferrin Bound Iron (NTBI), that mediates the Tissue Pathology.

pathology of iron-related tissue and organ damage, and the current evidence for iron chelation therapy in patients with MDS. The panel examined existing clinical guidelines, discussed standard practices in Canada, and devised a comprehensive outline to guide their investigation. This work focused on the critical questions mentioned above: why, whom, when, and how to treat iron overload in patients with MDS.

The Expert Panel was divided into four subgroups, each responsible for the investigation of one key question. Each subgroup was assigned the task of conducting an extensive search and thorough review of the medical literature pertaining to their question. The Expert Panel agreed on a protocol for the literature search and review, which included an extensive search terminology and the ranking of clinical evidence according to currently accepted standards as outlined by the British Committee for Standards in hematology [4]. The literature search considered all articles on MDS published prior to January 2006 (EMBASE, Ovid MEDLINE®) and key abstracts from annual meetings of the American Society of Clinical Oncology (ASCO) and American Society of Hematology (ASH), dating from 2000, and the 8th International MDS symposium in 2005. The search was designed to unearth clinical studies of any size dating from 1980, physiological studies dating from 1960, and review articles. Each subgroup presented their findings to the Expert Panel for discussion. A second scan for recent clinical studies was performed in December 2007, encompassing publications in 2006 and 2007.

In February 2006, the Expert Panel reviewed the results of the literature search and proposed recommendations for clinical practice. Based on the clinical evidence in the literature, and on expert opinion in areas where this evidence was lacking or rated as poor, the Expert Panel reached a consensus on recommendations for iron chelation in patients with MDS. These recommendations are presented in this article.

To aid this project, Novartis Canada provided an educational grant to support the cost of meetings and literature searches.

3. Why treat iron overload in patients with MDS?

Since each unit of red blood cells (RBCs) contains 200–250 mg of iron, approximately 100 times the normal daily iron flux, patients who require chronic blood transfusions are prone to develop iron overload. In addition to transfusional iron loading, MDS patients have increased intestinal absorption of iron, similar to patients with hemoglobinopathies and genetic hemaochromatosis (HH) [5]. Hence, MDS patients may show evidence of iron loading even prior to initiation of transfusion therapy.

Iron overload may cause or contribute to organ failure and is associated with a variety of disorders, including infections, renal disease, liver disease, and malignancy. Most evidence pertaining to transfusion-associated hemosiderosis is derived from the hemoglobinopathy literature. Zurlo et al. evaluated

the cause of death in 1087 Italian patients with thalassemia major who were born after January 1, 1960 [6]. In this patient population iron-related heart disease was the most common cause of death (64%) and was present in 76.8% of the patients who died. There is irrefutable evidence that iron chelation with deferoxamine (DFO) improves overall survival, as well as endocrine and gonadal function in thalassemia [7]. However, what evidence is there to indicate that iron chelation is necessary in MDS patients? The answer lies in the evaluation of the following questions.

3.1. How does excess iron cause organ damage?

Iron metabolism is complex and highly regulated (Fig. 1) [8,9]. While common mechanisms operate in all types of iron overload, specific features may predominate in different clinical conditions, e.g., genetic hemochromatosis, transfusional iron overload in marrow failure syndromes, and transfusional iron overload in hemoglobinopathies.

Total body iron balance depends on two physiologic processes: the absorption of exogenous iron from dietary sources and the recycling of endogenous iron from the hemoglobin of senescent or damaged red blood cells [8]. Intestinal absorption of iron is achieved via the divalent metal ion transporter (DMT-1) and heme receptors [10] and is regulated by intracellular iron pools. Quantitatively, iron recycling is more important, as basal levels of iron ingestion in the Western diet amount to 1–2 mg/day, whereas the recycling of iron from red cells accounts for 20 mg/day and is undertaken by the macrophage, whose activity is under complex control [9].

The absorbed or recycled iron is largely used by three major cell types:

- hepatocytes that require heme for cytochrome reductases,
- red blood cells that are composed mostly of hemoglobin,
- muscle cells that use heme in myoglobin.

All of these cell types absorb iron primarily through a plasma membrane receptor that binds the iron transport protein transferrin. The transferrin/receptor complex is endocytosed, and after acidification of the vesicle, iron is pumped into the cytosol via DMT-1, the same transporter that is found on the luminal surface of enterocytes. Once inside cells, iron may be transported out of cells, stored in ferritin, or remain in the labile intracellular pool for the incorporation into protoporphyrin, other small molecules and enzymes.

Iron egress from cells follows a common pathway in all cell types through ferroportin, a plasma membrane channel. The dysregulation of iron egress is common to both genetic hemochromatosis and transfusional iron overload [11]. The common feature involves hepcidin, a peptide synthesized by the liver that binds to the ferroportin, causing its internalization and proteosomal degradation [12]. Thus, conceptually hepcidin functions as a “plug” for the ferroportin “hole”.

In genetic hemochromatosis, levels of hepcidin are inappropriately low, allowing continual iron absorption in the presence of total body iron overload. The two major syndromes of genetic hemochromatosis are determined by the magnitude of hepcidin dysregulation [12]. In adult-onset hemochromatosis the HFE gene product, which weakly upregulates production of hepcidin, is dysfunctional. In juvenile hemochromatosis, which has an earlier onset and predominant cardiotoxicity (versus the hepatotoxicity of adult-onset hemochromatosis), hepcidin itself has point mutations. In other cases hemojuvelin, which strongly regulates hepcidin transcription, is absent or abnormal [13].

Hepcidin is also sensitive to inflammation and hemolytic anemia, which both decrease hepcidin production and are dominant over the upregulation caused by iron overload [14]. Consequently, when anemia, hypoxia, or hemolysis are present, iron is overabsorbed, even when total body iron stores are inappropriately high. This process explains the increased absorption of iron in thalassemia, where total body iron stores are massively increased through recycling of transfused and hemolyzed red cells.

Recent studies have revealed that, although there are diverse routes to iron overload, in all cases, there is a common mediator of tissue damage – non-transferrin-bound or “free” iron. Breuer et al. [15–17] showed that patients with poorly controlled hemochromatosis and transfusional iron overload secondary to thalassemia had increased non-transferrin bound iron (NTBI), whereas normal controls and patients with appropriately phlebotomized hemochromatosis did not. Furthermore, after treatment with DFO, there was a marked decrease in NTBI followed by a rapid rebound at 1 h post-infusion [18]. The rapid removal and rapid rebound in NTBI to pre-infusion levels is an important contribution to our understanding of appropriate dosing and scheduling of iron-chelating agents. These changes are paralleled by changes in iron pool kinetics in iron overloaded patients treated with chelators [19]. In patients receiving oral deferiprone (DFP), NTBI rapidly decreased with a half-life of 2–3 months, followed by a stable plateau at low basal levels, compared to a decrease in red blood cell membrane iron and serum transferrin with a half-life of 5–7 months. These results are consistent with the findings of Jensen et al. [20,21] who evaluated hepatic and myocardial iron and cellular damage during iron chelation with deferrioxamine (DFO) in adult patients with transfusional iron overload caused by acquired anemias, and showed that that the size of the chelatable, labile iron pool, as reflected by the urinary iron excretion, is pivotal for development of myocardial siderosis and for liver dysfunction caused by transfusional iron. Overall, these data strongly suggest that in order for iron chelation to be effective, it must achieve early control of NTBI, and especially of the pathophysiologically relevant NTBI subfraction known as labile plasma iron (LPI) [17,22].

3.2. Does iron overload contribute to organ dysfunction and morbidity in patients with MDS?

Schafer et al. evaluated the clinical sequelae of transfusional iron overload in 15 non-thalassemic adults aged 40–71 years who had transfusion-requiring anemias (specifically pure red cell aplasia, sideroblastic anemia, myelofibrosis, refractory anemia, and hypoplastic anemia) [23]. In the majority, the transfusion dependence was <4 years. Cardiac, endocrine, and hepatic function was assessed. Widespread subclinical organ dysfunction was evident in all patients, as summarized in Table 1.

This evidence indicates that organ dysfunction can result from transfusional iron overload. In adult patients with MDS, organ dysfunction appears to develop in a pattern that resembles organ deterioration in HH. Endocrine abnormalities, including abnormal pituitary, adrenal, and gonadotropin function tests and diabetes, were the most striking finding. This study indicates that even relatively short-term transfusional iron loading in adults may result in cumulative iron toxicity.

A retrospective German study evaluated 46 patients diagnosed with MDS over a 15-year period [24]. Two-thirds of the highly transfused patients had refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS). About 40% developed clinical signs of secondary iron overload, as shown in Table 1. The heart was the most commonly involved organ. Patients with RARS were particularly susceptible to the development of transfusion-related hemochromatosis. The authors speculated that the greater tendency to cardiomyopathy in multiply transfused MDS patients may have been attributed to coexisting cardiac disease and hemodynamic alterations induced by chronic anemia.

In a single-centre, 15 years, retrospective study of 26 chronically-transfused MDS patients with RARS, impaired glucose tolerance was found in 14, diabetes in six, abnormal liver function in 18, and cardiac failure in eight patients [25]. These complications correlated with the number of units transfused and the transferrin saturation at presentation. Furthermore, transfusion requirements of $\geq$2 units per month and transferrin saturation >60% were associated with inferior survival (log likelihood 12.3, $p < 0.032$).

Jensen et al. investigated the relationship between the extent of major organ injury and magnitude of transfusional iron overload before and after iron chelation [20]. Their studies were the first to describe the relationship between liver dysfunction and iron concentrations in the liver in patients with MDS. In addition, their work revealed that iron chelation may prevent liver damage in these patients (Table 2). Their findings suggest that there is a threshold level for hepatic iron stores; beyond which transfusional iron deposition may induce hepatocellular injury. The results of this study also indicated that iron-related liver fibrogenesis occurs in the presence of normal aminotransaminase levels, suggesting that this process is biologically distinct from iron-mediated hepatocellular damage.

The relationship between hepatic iron overload and cardiac complications in MDS patients remains unclear. In a recent study [26] magnetic resonance imaging was used to quantify myocardial iron loading by T2* in 11 transfusion-dependent good prognostic MDS, patients, nine of whom had moderate or severe hepatic iron overload. No correlation was observed between increasing serum ferritin levels, hepatic iron overload and myocardial T2*, and left ventricular function was normal in all patients. These results suggest there may be a long latent period relative to hepatic iron loading appears to predate the development of myocardial iron loading in transfusion-dependent MDS patients.

While no prospective data comparing an age-matched cohort from the general population are available to confirm the association between these morbidities and secondary hemochromatosis in MDS, a large ($n = 7113$ retrospective nested case-control study from large US health-insurance claims database of patients with a diagnosis of MDS and other hematopoetic disorders (excluding thalassemia) found that the risk of potential complications of iron overload (cardiomyopathy/heart failure, conduction rhythm disturbances, diabetes and liver disease) was significantly associated with receipt of transfusions (odds ratio [OR] 2.9, $p = 0.0008$). Risks of conduction/rhythm disturbance had an OR of 4.1 ($p < 0.005$), diabetes OR 5 ($p = 0.0025$) and liver disease OR = 3.3, ($p = 0.0008$) [27].

3.2.1. Summary

The potential risk of secondary hemochromatosis should not be neglected in patients with MDS, particularly those with favourable risk factors and who are projected to live for several years (*Evidence level III*). Complications from secondary hemochromatosis in patients with MDS may include impaired endocrine and hepatic function and shortened life expectancy, primarily due to cardiac disease.

3.3. Does iron overload influence survival in patients with MDS?

Investigations of hemoglobinopathies and HH indicate that death from iron overload is primarily due to heart or liver failure. With the rapid onset of iron overload in transfused homozygous beta thalassemia and juvenile HH, the predominating cause of death is heart failure [6,7], while in adult-onset HH, death due to hepatic cirrhosis and hepatocellular carcinoma is more frequent [28,29].

Excess mortality due to iron overload in transfusion-dependent anemias has been less extensively studied. In a retrospective study that evaluated 467 patients diagnosed with MDS between 1992 and 2002, transfusion-dependent patients had a significantly shorter overall survival (OS) than those not requiring transfusions ($p < 0.001$) with an excess of deaths from cardiac failure and cirrhosis accounting for some of the additional mortality [30] Leukemia-free survival (LFS) of transfusion-dependent patients also was significantly worse (hazard ratio [HR] 2.02; $p = .001$), rais-

Table 1
Evidence that iron overload contributes to increased morbidity, end organ damage, and mortality in MDS

Reference	*N*	Age	# of units	Assessments	Findings	LOE
Schaefer [23]	15	Mean age 54 (40–71)	120 (60–210)	– LVEF echo – 24 h Holter – Liver biopsy (10) – GTT – Metyrapone stimulation – Insulin tolerance test – LH – ACTH, TSH challenges	– 100% subclinical organ dysfunction – 50% hepatomegaly – Elevated LFTs (13) – Focal portal fibrosis and inflammation (10) – CHF (4) – 50% cardiomegaly – 8 had SVT – 100% abnormal GTT and hypothalamic pituitary axis testing	2C
Jaeger [24]	46	Mean age 69 (31–86)	79 (50–155)	– LVEF (2D echo) – Liver enzymes – Liver biopsy (3) – CT liver (2) – Autopsy (8)	– 40% ($n = 20$) had evidence of secondary hemosiderosis – Cardiac (20) – Cardiac arrhythmias (10) – 14 deaths from intractable CHF – 11 marked elevation of LFTs – 5 diabetes	2C
Cazzola [25]	26/37	Median age 64 (28–80)	Unknown	– GTT – LFTs – Cardiac function	– Transferrin saturation elevated in 21/37 at presentation – Of 26 transfused: • Impaired GTT (14) • Diabetes (6) • Abnormal liver function (18) • Cardiac failure (8) – *Multiple regression analysis* Complications correlated with # of units transfused and transferrin – Saturation at presentation – *Exponential survival probabilities*: Transfusion requirement of ≥2 units per month and transferrin saturation ≥60% associated with inferior survival (log likelihood of 12.3, $p < 0.032$)	2C
Takatoku [31]	292 (52% MDS)	<40U: 20% 4–159 U: 48% ≥160 U: 32%		– Liver enzymes – Fasting blood sugar – Cardiac function	– Liver enzyme elevation correlated strongly with transfusion history and elevated ferritin (90% >1000 μg/l) – Abnormal cardiac function in 22% (14/64) – Abnormal liver function in 73% (11/15) – Cardiac failure present at time of death in 24% – Liver failure present at time or death in 7% – Only 8.6% had continuous DFO	2C
Ferte [80]	21 with low-risk MDS, 33 controls	Median age 75	81 (6–282)	– Cardiac T2* by MRI liver content (LIC by MRI) and cardiac function by echocardiography	– 9/21 had cardiac symptoms on therapy – 6/14 had elevated LVTD – Median LIC was 350 micromoles/g/dw – Median cardiac T2* did not differ from controls – No correlation between cardiac T2*, ferritin, LIC and LVEF – 3/21 had cardiac iron overload with T2*<20; 2/3 had cardiac failure unexplained by other causes	2A

GTT, glucose tolerance test; LFTs, liver function tests; CHF, congestive heart failure; SVT, supraventricular tachycardia; LVTD, left ventricular telediastolic diameter; Echo, echocardiography; LVEF, left ventricular ejection fraction; LIC, liver iron content; LOE, level of evidence.

Table 2
Does iron chelation work in MDS?

Reference (agent)	*N*	Patient population	Indices	Findings	LOE
Jensen [20] (deferoxamine)	39 (29 MDS)	Adults with acquired anemias (non-thalassemic)	– Aminotransferase levels	– Elevated ALT in 21 (54%)	2B
			– Liver iron concentration	– Aminotransferase levels dependent on LIC (>300 μmol/g)	
			– Serum ferritin	– Patients with serum ferritin >2500 μg/L all had elevated ALT values	
			– Urinary iron excretion	– No relationship between # of units and aminotransferase levels	
			– Transferrin saturation	– In 10 patients on DFO, urinary iron excretion was positively correlated with ALT ($R^2 = 0.64$), liver iron concentration, and serum ferritin ($R^2 = 0.5$) or transferrin saturation >0.75% ($R^2 = 0.64\%$)	
			– MRI for cardiac iron (12)	– ALT and serum ferritin fell during DFO and returned to normal by 1 year in 80%	
			– LVEF (12)	Urinary iron more directly related to the liver iron concentration than to the serum ferritin if the liver iron concentration exceeds 350 μmol/g	
Jensen et al. [21] (deferoxamine)	14 (11 MDS)	Adult patients with transfusional overload previously untreated with DFO.	– Myocardial and hepatic iron by MRI	– MRI results reproducible within 4 μmol/g in patients	1C
		Non-thalassemic	– MUGA scans	– Myocardial iron estimates at treatment start were closely related to urinary iron excretion ($R^2 = 0.69$) and to serum ferritin ($R^2 = 0.66$) but not to liver iron concentration, the number of transfused units or transferrin saturation	
			– Liver tests	– 10/14 had elevated myocardial estimates at baseline MRI	
			– Iron indices	– 6/10 normalized myocardial iron by MRI within 6–18 months	
Kersten [32] (deferiprone)	36	MDS and AA: 25/38 Thalassemia: 4/38	– Negative iron balance	– Negative iron balance achieved in 56%	1C
		Serum ferritin >1000 or >50 units of blood	– 20% decrease in serum ferritin within 1 year	– Mean serum ferritin levels declined from 3563 μg/L at 12 months (medial decrease of 39%) – 75% had declining ferritin of >20% at 12 months – 1 patient with agranulocytosis – No significant changes in liver enzymes	
Brissot [39] (deferasirox)	36	MDS as part of larger trial with beta thalassemia ($n = 278$), DBA ($n = 26$) and other transfused anemias ($n = 21$)	– Change in ferritin and ALT	– Negative iron balance was achieved in patients treated at the 20 and 30 mg/kg/day dosing after 2.5 years as evidenced by declining ferritin (decrease by 1300 μg/L) and ALT (decrease by 17 U/L).	2A
Gattermann [38]	47	MDS as part of larger trial with beta thalassemia ($n = 85$), DBA ($n = 30$) and other anemias ($n = 22$)	– Change in ferritin, LIC and iron excretion/intake ratio	– Negative iron balance achieved in most patients (absolute change in ferritin – 268 ± 2053); absolute change in LIC mg/Fe/g dw (−5.7 ± 6.3); iron excretion to intake ratio increased to 1.7 ± 0.93	2A
Greenberg [40] (deferasirox)				– Adverse events were mild and moderate; mainly GI – 2 discontinuations for toxicity	
Jensen [41] (desferrioxamine	16 (11 MDS)	Adult non thalassemic patients with transfusional iron overload treated with DFO SC 2 g daily with vitamin C 200 mg po daily added after 9–12 months in 10 patients	– LVEF by MUGA serially *q* 3–6 mos	Normal cardiac exam in 15/16 at baseline	2B
			– LIC by MRI	– No significant correlation between prestudy values of LVEF, patient age, # units, serum ferritin, MRI LIC	
			– Serum ferritin, iron saturation	– In patients not receiving vitamin C, mean LVEF of 15 patients decreased from baseline by 5% ($p = 0.04$). This decline (−7%) was restricted to patients with LIC >500 μmol Fe/g, while an increase (8.5%) in LVEF was seen in those with moderate LIC (<500 μmol Fe/g) – In 10 patients on DFO+ vitamin C, LVEF increased by 9% after 12 m – Most falls of LVEF were asymptomatic – Declines in LIC by MRI were not correlated with LVEF	

GTT, glucose tolerance test; LFTs, liver function tests; CHF, congestive heart failure; SVT, supraventricular tachycardia; LVTD, left ventricular telediastolic diameter; Echo, echocardiography; LVEF, left ventricular ejection fraction; LIC, liver iron content; DFO, desferrioxamine.

ing the possibility that transfusion burden may contribute to increased mortality by increasing the risk of leukemic transformation. The number of overall transfusions and transfusions per month affected survival. MDS patients reached a threshold ferritin level of 1000 μg/L after a median number of 21 units of RBCs. The development of secondary iron overload as indicated by serum ferritin >1000 μg/L significantly affected the OS ($p < 0.001$) with HR 1.36 for every 500 μg/L rise in serum ferritin above 1000 μg/L.

Most recently, a Japanese study [31] reported a retrospective review of morbidity and mortality in 292 transfusion-dependent adults with various bone marrow failure syndromes, of whom 152 had MDS. Fatal cardiac or liver failure was observed in 24% and 7% of patients, respectively, and these complications were seen almost exclusively in patients whose serum ferritin was greater than 1000 μg/L. Patients who received daily iron chelation therapy with deferoxamine exhibited decreases in serum ferritin levels, AST, ALT, and fasting blood sugar, and were less likely to exhibit abnormal laboratory values.

It is important to recognize that both of these studies are limited by their retrospective design, and hence the effects of important confounding variables may be masked. In particular, it is possible that serum ferritin concentration may be associated with such factors as severity of chronic anemia or intrinsic differences in disease biology which may be the actual determinants of poor prognosis.

3.3.1. Summary

The development of iron overload, defined as a serum ferritin >1000 μg/L, may worsen overall and leukemia-free survival in patients with MDS (*Evidence level III*). This effect is more apparent in patients with low-risk or intermediate-1-risk MDS, who live long enough to experience iron toxicity (*Evidence level III*).

3.4. Does iron chelation reverse the effects of iron overload in MDS?

Few studies have evaluated the effects of reversing iron overload on survival and organ damage in MDS, leading to the extrapolation of evidence from studies of hemoglobinopathies and HH to these patients. The few available studies are reviewed here briefly and described in greater detail in Table 2.

Kersten et al. [32] led a prospective, open-label, nonrandomized, multicentre, phase II trial to evaluate the efficacy and toxicity of oral deferiprone in 38 mainly nonthalassemic patients with transfusional overload (18 with MDS; seven with aplastic anemia). Transfusional overload was defined as >50 units of blood and ferritin >1000 μg/L. Patients were treated with 3–6 g/day of deferiprone for 12 months. In 36 evaluable patients, a negative iron balance was achieved in 56%; only 20 of 38 completed 12 months of therapy with other patients discontinuing therapy due to side effects or other causes. A decline in ferritin of >20% occurred in 75% of the 20 patients at 1 year. In two patients who were no longer transfusion-dependent, ferritin normalized. Side effects leading to withdrawal included agranulocytosis (1), nausea (3), arthralgia (2), and skin rash (1). No changes were noted in cardiac function, heart size, ophthalmologic tests, and audiograms. This study demonstrated that deferiprone is an effective iron chelator in patients with transfusional hemosiderosis, including MDS; however, some concern about the safety and tolerability of this drug remains, particularly in regard to the documented propensity of this drug to cause agranulocytosis [33–37].

Gattermann et al. [38] recently reported the preliminary results of an open-label, multicentre, phase II study of 47 patients with MDS and transfusion-dependent anemia, who were treated with varying doses (5, 10, 20, or 30 mg/kg) of deferasirox (DSX), based on starting hepatic iron content. DSX produced an overall dose-dependent reduction in liver iron content (LIC) of 5.7 mg Fe/g dry weight and an overall dose-dependent decline in serum ferritin of 267 μg/L. Generally mild to moderate side effects were reported by 45 patients; the most frequent adverse event was mild, transient gastrointestinal disturbance. Based on these results, DSX appears to be a convenient, effective, and well-tolerated oral chelator for iron overload in MDS patients.

Jensen et al. [21] evaluated the relationship of hepatocellular injury and transfusional iron overload before and after iron chelation in adults with acquired nonthalassemic anemias (27 with MDS). Elevated ALT values were found in 54% at baseline. In the 12 patients chelated with DFO, ALT and serum ferritin fell and returned to normal by 1 year in 80% of the patients. DFO was also effective in lowering cardiac iron by magnetic resonance imaging (MRI) T2* in 60% after 6–18 months of therapy [22]. Significant negative iron balance, as evidenced by declining ferritin and LIC, has also been shown with both deferiprone [32] and deferasirox [39,40].

Jensen et al. studied cardiac function in a cohort of 16 patients with nonthalassemic, transfusion-dependent anemias, 12 of whom had MDS [41]. Liver iron, serum ferritin, and high urinary iron excretion were found to be predictive of high myocardial iron concentration. Although DFO was effective in reducing hepatic iron in these patients, DFO treatment resulted in significant decline in left ventricular ejection fraction (LVEF) after 12 months of chelation therapy in 15 of 16 patients. In most DFO-treated patients, a deteriorating LVEF was reversed and cardiac function improved after the addition of 200 mg/day of vitamin C. Based on observations, the authors recommended low-dose vitamin C for patients with nonthalassemic transfusional iron overload, with the caveat that vitamin C supplementation be started after 9–12 months of iron chelation to avoid the initial pro-oxidant effect of vitamin C.

3.4.1. Summary

Iron chelation in MDS can successfully lower serum ferritin as well as liver and cardiac iron content in many patients

(*Evidence level IIa*). Success is determined by drug dosing, length of drug exposure, patient adherence, and the amount of concurrent transfusional iron overload. Delayed low-dose vitamin C supplementation may augment the effectiveness of iron chelation with DFO and help to improve cardiac function, possibly via antioxidant mechanisms (*Evidence level IIb*).

3.5. Does iron chelation improve survival or hematopoiesis in MDS?

In a retrospective review of 178 MDS patients who were treated at St. Paul's Hospital in Vancouver from 1981 to 2006, the International Prognostic Scoring System [42] (IPSS) score ($p < 0.008$) and iron chelation therapy ($p < 0.02$) were the only variables predictive of survival in multivariable Cox regression analysis [43]. For patients with low or intermediate-1 IPSS scores ($n = 99/133$ measurable), median OS for patients receiving iron chelation therapy (ICT) was 160 versus 40 months for non-ICT patients ($p < 0.03$). These data must be interpreted cautiously owing to the inherent biases of the study – most importantly, that chelation therapy was offered to patients with expected survival of >5 years. Thus, while this report suggests that iron chelation therapy may have an important effect on mortality in MDS, the data must be confirmed by prospective observations.

A study supporting the results of the Vancouver study has recently been presented in abstract form by the French Groupe Francophone des Myélodysplasies [44]. These investigators identified a cohort of 170 patients with MDS referred for RBC transfusion at 18 French treatment centres during 1-month period in 2005. Survival in this cohort was followed prospectively and reanalyzed on May 15, 2007. Overall survival was superior for patients who received iron chelation therapy (median survival 115 months versus 51 months in patient who did not receive chelation; $p < 0.0001$). The results were consistent across all subgroups analyzed (IPSS low and intermediate-1, sex, age). These data also suggested a dose-response relationship, with standard chelation producing significantly better survival benefit than low-dose chelation (OS 129 months versus 69 months; $p < 0.0001$). Once again, because this study did not randomize patients into chelation and non-chelation groups, the results must be interpreted with caution owing to the possibility of selection bias.

A small, prospective, single-centre, study demonstrated improved hematopoiesis and reduced or eliminated transfusion requirements in 11 patients who were chelated with DFO for approximately 1.5 years [45]. In 64% of patients, hemoglobin requirements were reduced by >50%. Five patients (46%) became transfusion-independent after 18–26 months of DFO therapy. Platelet counts increased in 64% of patients; neutrophil counts rose in seven of nine (78%) evaluable patients. A trilineage response occurred in 5 of 11 patients, who had initial pancytopenia. Treatment response did not correlate with the amount of iron overload or duration of transfusion history, nor did the normalization of iron stores seem to be essential. This decline in transfusion requirements was seen in all patients with the highest efficacy chelation defined as a net excretion of 17.7 ± 7.2 μmol/g/month.

3.5.1. Summary

Iron chelation may have benefits beyond reducing total body iron stores (*Evidence level III, Recommendation Grade B*). Further research is needed into the oxidizing effects of iron on hemopoiesis and leukemia propagation.

4. When and in whom should iron chelation therapy be initiated?

Iron overload is an inevitable consequence of chronic transfusion therapy without concomitant blood (or iron) loss (e.g., angiodysplasia). The principle of iron chelation in MDS is to prevent the occurrence of iron-induced organ damage, thereby avoiding excess morbidity and mortality. Iron chelation should start before organ damage occurs in patients in whom the rate of transfusion and iron loading predict physiologically important tissue iron deposition. However, due to the clinical heterogeneity of MDS, the rate of transfusion varies widely among patients. The rate of iron loading per unit of transfused blood is also idiosyncratic. Therefore, the decision to begin iron chelation must be tailored to individual need.

4.1. Identification of patients likely to benefit from iron chelation therapy

Effective iron chelation is known to improve survival in patients with thalassemia, but comparatively little literature is available for patients with MDS. In patients with thalassemia, survival benefit is usually associated with 10 years of iron chelation. Since most newly diagnosed patients with MDS are >70 years of age, it is unclear whether they will survive long enough to achieve any benefit from iron chelation. Notwithstanding this fact, it is important to note that organ damage from iron overload may occur much earlier in elderly individuals with MDS than in younger patients with thalassemia and as discussed earlier, may influence hematopoiesis and leukemic transformation; therefore, the benefits of iron chelation may occur earlier in patients with MDS.

Nonetheless, for MDS patients with expected survival <1 year (IPSS: ≥2) it is unlikely based on current data that iron chelation will have a significant impact on morbidity or mortality. Iron chelation has the greatest potential for benefit in patients with the best prognosis (IPSS: low or Int-1), for whom the median survival is 3–6 years. However, while IPSS scoring is very useful for prognosis, clinical experience shows that some individuals with an unfavourable prognostic

score have a stable disease pattern with no early progression. These patients may also benefit from iron chelation, and thus decisions on which patients are candidates for chelation therapy should not be made purely on the basis of IPSS score.

Iron overload may have a detrimental effect on survival after allogeneic stem cell transplant (allo SCT) for MDS, particularly with regard to early hepatic complications of SCT. Patients who are potential candidates for allo SCT may benefit from early iron chelation to prevent the development of iron overload. A recently-published retrospective study of 590 allogeneic stem cell transplant recipients, 103 of whom had an underlying diagnosis of MDS, identified pre-transplant serum ferritin as a strong independent predictor of outcome. In the MDS subgroup, ferritin >2515 μg/L was associated with significantly increased hazard ratios for death (HR 2.6, $p = 0.003$) and for treatment-related mortality (HR = 3.2, $p = 0.002$) but not for relapse (HR = 0.8) [46]. These data suggest that iron chelation therapy might comprise an important part of pre-transplant management in this group of patients.

4.2. When should iron chelation be started?

In thalassemia, explicit clinical guidelines have established the threshold levels for hepatic iron content that trigger iron chelation. These guidelines cannot practically be applied to adults with MDS for a number of reasons. Most importantly, no evidence-based validation of this threshold has occurred in MDS patients. Liver biopsy to validate the relationship between hepatic iron levels and organ damage is often unrealistic in MDS patients, due to thrombocytopenia or neutropenia. In addition, the risk/benefit ratio of iron-chelating agents, such as DFO, is different in adults versus children; therefore, a uniform threshold for initiation of therapy is unlikely to apply. Lastly, the rates of transfusion and iron loading are much more heterogeneous in the MDS population than in thalassemia patients.

In the absence of direct measurement of total body iron burden, the decision to start chelation therapy in MDS patients is based upon the determination of actual or predicted physiologically significant iron overload. In the following sections we review the data on which this determination is made for individual MDS patients.

4.2.1. Liver iron content

Although serum ferritin and transferrin saturation are commonly used to screen for iron overload, these tests do not accurately reflect tissue iron levels. There is substantial interindividual variation in ferritin levels in patients with equivalent iron burden and other factors, such as infection, inflammation, cancer, and hepatocellular damage, may result in significant elevation of ferritin concentration in the absence of iron overload. The gold standard for body iron burden in iron overload is liver iron content (LIC). It can be determined most directly by chemical analysis of a liver biopsy sample; however, the invasiveness of this approach carries an unacceptable risk for patients with MDS, in whom neutropenia and thrombocytopenia are prevalent.

4.2.2. Non-invasive determination of LIC

The technique of biosusceptometry assesses iron burden by exploiting the paramagnetic properties of tissue iron. Non-invasive measurements by superconducting quantum interference device (SQUID) biosusceptometry correlate extremely accurately with biopsy LIC. Only five SQUID susceptometers exist worldwide; none is in Canada.

Magnetic resonance imaging has been adapted to measure LIC. A signal intensity ratio method based on T2 contrast, as studied in 174 patients who subsequently underwent liver biopsy, identified patients with significant iron loading with a sensitivity of 89% and specificity of 80% but correlated poorly with biopsy in patients with very high LIC [47]. A recently described modification of this protocol appears to improve the performance of this test at higher LIC [48,49]. Another method, based on T2-star (T2*) relaxometry, was developed primarily for measurement of cardiac iron but has been shown to have potential use in measuring LIC [50]. The most accurate and precise MRI technique for measurement of LIC was developed by St. Pierre et al., who found mean liver proton relaxation rates (R2) correlated strongly with LIC, as determined by biopsy across a broad range of LIC values [51]. Although T2, T2*, and R2 data can be acquired on standard clinical MRI apparatus, determination of LIC from these data requires specialized analytical software that is not widely available.

4.2.3. Non-invasive measurement of myocardial iron burden

Neither serum ferritin nor LIC correlate well with myocardial iron concentration [50]. A technique based on measurement of cardiac T2*, a relaxation parameter arising from local field inhomogeneities that are increased with iron deposition, has been developed for non-invasive assessment of myocardial iron [52]. This parameter correlates inversely with iron concentration, such that a T2* <20 ms indicates iron overload [52]. T2* has been shown to be more sensitive than studies of left ventricular diastolic function as an index of cardiac iron loading [53] and has proven useful in monitoring the efficacy of iron chelation therapy in patients with severe cardiac iron overload [54]. Once again, however, this technique is not yet available in Canada for routine diagnostic use.

4.2.4. Transfusion history and surrogate markers of iron stores

Since the previous gold standard techniques of hepatic and endomyocardial biopsy are unacceptably invasive in most circumstances for patients with MDS and since newer non-invasive techniques are not widely available in Canada,

current practice is to rely on transfusion history, serum ferritin, and transferrin saturation to guide the decision on when to begin iron chelation in MDS.

There is no prospectively validated threshold for the number of units of transfused blood that should trigger the initiation of iron chelation. Published recommendations, based on expert opinion, suggest a threshold ranging from 25 to 50 units of blood. However, since the rate of iron loading varies in MDS, the number of units transfused should not be the sole index of iron burden in MDS patients. In particular, some patients with MDS have elevated serum ferritin levels at the time of diagnosis even prior to the initiation of transfusion therapy, e.g. patients with RARS, in whom iron absorption is inappropriately increased. Such patients may have a more indolent course of disease and may benefit from initiation of iron chelation before an arbitrary number-of-units threshold has been reached.

Similarly, no prospectively validated threshold has been established for serum ferritin levels. In the literature, experts have recommended a threshold ranging from 1000 to 2500 μg/L [55–58]. Serum ferritin may be strikingly elevated in acute or chronic inflammation, despite normal iron stores. Therefore, interpretation of ferritin measurements in the context of fasting transferrin saturation is strongly recommended to confirm the presence of excess iron. Iron chelation should not be started unless transferrin saturation exceeds 0.5.

4.3. Recommendations: Patient selection for iron chelation therapy

The Expert Panel reached the following consensus on whom to recommend for iron chelation in MDS.

- Consider iron chelation in transfusion-dependent patients with MDS and a good prognosis, as indicated by an IPSS score of Low or Int-1, or WHO classification of RA, RARS, or 5q-syndrome and:
  - Serum ferritin>1000 μg/L, or
  - Who are candidates for allogeneic stem cell transplantation, or
  - Have a life expectancy >1 year.

  (*Evidence level IV, Recommendation Grade C*)
- Consider iron chelation in transfusion-dependent patients with MDS and a higher IPSS score (Int-2 or High) and:
  - Serum ferritin>1000 μg/L, and
  - Who are candidates for allogeneic stem cell transplantation, or
  - Have a life expectancy >1 year.

  (*Evidence level IV, Recommendation Grade C*)
- Based on the literature review and clinical experience, the Expert Panel recommends that, in patients with MDS who are candidates for chelation therapy, iron chelation should be initiated when transfusion-dependent patients:
  - have evidence of iron-related organ damage, or
  - have serum ferritin >1000 μg/L and fasting transferrin saturation >0.5, irrespective of the number of units of blood transfused.

  (*Evidence level IV, Recommendation Grade C*)

5. How to treat iron overload in patients with MDS?

Once the decision to treat is reached, the literature provides no specific evidence-based studies of high quality to guide the best approach to treating patients with MDS and transfusion-related iron overload. As shown above, this population represents only a minority of patients in studies of iron chelation, which include patients with diverse hematological diseases, are usually comprised of small numbers of patients, and are often retrospective analyses or phase II studies.

Three available iron-chelating agents are available: deferoxamine (DFO) deferasirox (DSX), and deferiprone (L1). In addition to these agents, physicians should be aware that in rare cases therapeutic phlebotomy may offer a more direct and rapid route to reducing iron burden [59,60]. A single case report indicates that a good response to an erythropoietic agent in MDS may permit the use of phlebotomy to unload iron from a previously transfusion-dependent patient [61]. New agents such as lenalidomide, decitabine, and azacytidine have been reported to yield significant rates of transfusion independence, and should provide further opportunities for phlebotomy in MDS patients who achieve such excellent hematological responses.

5.1. Agents available for iron chelation therapy

Most clinical experience is associated with DFO (Table 3), and the dose needed to treat iron overload adequately is well established. This agent is available only as an intravenous or subcutaneous infusion, which makes access and long-term compliance an issue. DFO 20–50 mg/kg/day may be given by 12-h subcutaneous continuous infusion or twice daily subcutaneous (SC) bolus infusion for 5 days/week. No statistical difference in levels of iron excretion has been found in comparisons of both delivery methods [62–65]. Vitamin C repletion and low-dose supplementation may be considered, if iron chelation with DFO is suboptimal [65].

Adverse effects associated with DFO are well described [66]. Allergic reactions have occurred with rapid IV injections. As a result, IM or slow SC or IV infusions are recommended. Adult respiratory distress syndrome has followed excessively high IV doses of DFO. Ocular toxicity and ototoxicity may occur and are likely reversible, if abnormalities are detected early [67]. Visual acuity tests, slit-lamp examinations, funduscopy, and audiometry are recommended periodically in patients on prolonged treatment.DFO treatment of iron overload may promote *Yersinia* infections and mucormycosis by acting as a siderophore and delivering iron to these organisms [68,69]. In such cases, DFO treatment

Table 3
Evidence in support of the beneficial effects of iron chelation in MDS

Reference (agent)	*N*	Treatment	Assessment of efficacy	Findings	LOE
Jensen et al. [45] (deferoxamine)	11	DFO SC 12 h infusions 5 day/week by CADD ($n=4$) or CADD ($n=4$) or SC bolus (1 g twice daily) ($n=7$) Vitamin C supplement 9–21 mos after DFO	– BM evaluation at baseline and repeat after 13–37 mos of treatment ($n=10$)	– Hb requirement fell in 7/11 (64%) while on iron chelation 6–60 mos	2B
			– Semi quantitative assessment of iron within BM macrophages	– Four patients became transfusion independent after 8–26 months of treatment	
			– % hematopoiesis in BM volume	– ANC and platelet counts increased in 64% of patients	
			– Blood transfusion requirements	– 4/11 had trilineage hematological improvement	
			– Clinical response defined as reduction of blood transfusions requirement of at least 50% c/w baseline	– No significant change in marrow cellularity or iron content	
			– Serum ferritin, transferrin receptor and erythropoietin	– Serum ferritin declined in 9/11 patients	
			– LIC by MRI	– Serum transferring receptors normalized in patients with progressive decline in Hb requirements	
			– Cytogenetics	– LIC declined in all patients (minor in 50%)	
			– PRINS	– Decline in transfusion requirements was seen in all patients with high efficacy chelation defined as 17.7 ± 7.2 μmol/g/month	
				– Maximal improvement in hematopoiesis was not seen until at least 1.5 years of iron chelation	
Leitch [42] (deferoxamine)	178 MDS Patients (18 who received ICT)	DFO SC 0.5 – 3 g/day Over 12 h infusion 5 days per week	– Ferritin levels	– Median ferritin pre ICT was 4215 μg/l and 2659 μg/l post ICT	2A
			– Causes of death	– Ferritin increased in non ICT patients over time	
			– Overall survival	– By cox regression analysis, IPSS score ($p<0.008$) and ICT ($p=0.02$) were the only factors independently predictive of OS	
				– For patients with Low and Int-1 IPSS, median OS for patients receiving ICT was NR at 160 mos versus 40 mos for non ICT patients	

LOE, level of evidence; BM, bone marrow; PRINS, primed in situ labeling; LIC, liver iron content; CADD, continuous administration delivery device; DFO, deferoxamine; ICT, iron chelation therapy; IPSS, international prognostic scoring system; OS, overall survival.

should be discontinued until the infection is resolved. In cases of severe chronic iron overload, cardiac dysfunction has been reported after concomitant DFO and high doses of vitamin C (>500 mg daily). This apparent paradox is explained by the fact that, while vitamin C supplementation may augment urinary excretion of iron in patients receiving deferoxamine [70], it promotes free radical production that may initiate cardiomyocyte damage [71]. Cardiac dysfunction was reversible when vitamin C was discontinued. In the presence of aluminum overload, DFO may decrease serum calcium and aggravate hyperparathyroidism. DFO may also precipitate the onset of dialysis-related dementia. In patients with aluminum-related encephalopathy, high doses of DFO may exacerbate neurological dysfunction, e.g., seizures.

Deferiprone (L1) is effective in increasing iron excretion; however, its efficacy has been established chiefly in patients with thalassemia and sickle cell disease, with minimal data available on its use in patients with MDS [32,72,73]. The largest clinical study of this drug included 18 patients with MDS, 12 of whom completed 1 year of therapy [32]. The median ferritin level was reduced by 25%. The safety profile of L1 is unclear; at least one severe toxicity, a reversible agranulocytosis, has been reported in MDS.

Deferasirox (DSX) has been studied in >700 adult and pediatric patients with transfusion-related iron overload complicating thalassemia, sickle cell anemia, myelodysplastic syndrome, Diamond-Blackfan syndrome, or other rare anemias, and has been shown to be a safe and effective treatment for iron overload [74–77]. Further studies of the role of deferasirox in MDS are in progress [38,41]. For patients with ongoing transfusional iron loading, a DSX dose of 20 mg/kg/day by mouth, once daily, appears to be sufficient to maintain iron levels, while a higher dose of 30 mg/kg/day is required to achieve reduction in iron stores. DSX is generally well tolerated in thalassemia patients, with the most common adverse effects being transient gastrointestinal symptoms, such as abdominal pain, nausea and vomiting, diarrhea and constipation (15.2%), and skin rash (10.8%) [74]. Dose-dependent increases in serum creatinine to twice the upper limit of the normal range were observed in 38% of patients. Postmarketing surveillance in the USA has resulted in the identification of several instances of fatal renal failure and of cytopenias following institution of deferasirox therapy. Regular follow-up of renal function and blood counts are recommended with weekly determinations of serum creatinine for at least the first eight weeks of therapy. Rare adverse events include elevated ALT (0.6%), deafness (0.3%), and cataracts (0.3%).

5.2. Choice of chelating agent: theoretical considerations

In the absence of data comparing the relative impact of the available iron-chelating agents on clinical endpoints, it is reasonable to consider the in vitro evidence. Glickstein et al. [78,79] extended the analysis of labile iron pools as the pathophysiologic mediator of iron overload by using iron-sensitive or redox-sensitive fluorophores to measure the uptake and efficacy of three iron chelators (L1, DSX, and DFO) on total intracellular and organellar iron pools in cell lines from major body tissues involved in iron trafficking and overload (cardiomyocytes, macrophages, and hepatocytes). All three drugs caused significant chelation of labile intracellular iron after 12 h of exposure at clinical doses; additionally, L1 and DSX caused a rapid drop in cytosolic iron at 30 min and were able to gain access to the intracellular pools of redox-active labile iron and restore the contractility of cardiac myocytes that had been impaired by iron overload. This pioneering work was the first to investigate the critical intracellular distribution of pathophysiologic iron and its accessibility to clinical chelating agents.

5.3. Monitoring chelation therapy

Patients undergoing iron chelation therapy require clinical and laboratory monitoring for efficacy, for adverse events related to the chelating agent, and for adverse effects related to over-chelation of iron. Serial determination of serum ferritin has been validated for the biochemical monitoring of chelation efficacy. In 1995, Jensen et al. used MRI, previously validated by correlation with liver biopsies, to measure hepatic iron in 26 adults with transfusional iron overload treated with DFO [47,81]. They compared imaging scans with the number of blood transfusions, serum ferritin levels, and transferrin saturation to determine the relationship between MRI and other measures of iron overload and showed that ferritin is a good, but imperfect, indicator of the efficacy of iron chelation.

5.4. Recommendations

Very little literature is available to guide recommendations for treatment of iron overload in patients with MDS. The following recommendations are based mainly on clinical experience and literature with thalassemia patients.

Once the decision has been made to initiate iron chelation therapy, either DFO or DSX may be used (*Evidence level IIa, Recommendation Grade B*):

- DFO 20–50 mg/kg/day by subcutaneous or intravenous infusion over 12–15 h or by BID SC bolus injections 5 days/week
- DSX 20–30 mg/kg PO QD

Before initiation of chelation therapy, the following baseline investigations should be completed (*Evidence level IV, Recommendation Grade C*):

- Ophthalmological examination (slit lamp, retinal and corneal assessments)
- Audiometry
- CBC
- Creatinine (for DSX)

Routine follow-up of patients on iron-chelation therapy should reflect Health Canada recommendations, and include (*Evidence level IV, Recommendation Grade C*):

- Clinic visit once monthly for 3 months, then quarterly (once every 3 months)
- Ferritin, TSH/T3/T4, LFTs, creatinine, glucose q3monthly (CBC and creatinine weekly for four weeks after initiation of DSX therapy and after any dose increase)
- Urinalysis (for proteinuria) monthly for DSX
- Annual audiometry and ophthalmological assessments
- 2D echo, if abnormal at baseline or if clinically indicated

Dosage adjustment:

- Reduce dose of iron chelation therapy when ferritin falls below 2000 μg/L (*Evidence level IV, Recommendation Grade C*)
- Discontinue iron chelation therapy when ferritin <1000 μg/L (*Evidence level IV, Recommendation Grade C*)
- For DSX, follow product monograph if creatinine is elevated (*Evidence level IV, Recommendation Grade C*).

Currently, no literature is available to support or guide the use of combination therapy in patients with MDS. Therefore, no recommendations are made.

6. Summary

The recommendations presented in this paper are based, for the most part, upon low-level evidence and extrapolation from data in other diseases, particularly thalassemia major, where iron chelation therapy has resulted in stunning improvements in quality and length of life. It would be of great value to have data from a prospective randomized assessment of the effects of iron chelation therapy on morbidity, mortality, quality of life, transfusion needs, and the rate of leukemic transformation. However, two impediments stand in the path of an assessment of this kind. First, the study would need to be large and would require long follow-up of patients, and would therefore be very expensive to conduct. Second, owing to the strength of data on the benefits of iron chelation in thalassemia major and in the absence of data suggesting that such benefit is absent for patients with MDS, neither physicians nor patients would be eager to submit to randomization to a 'no chelation' arm. Hence, such a study is unlikely ever to be conducted, although our Panel is exploring the feasibility of a randomized trial comparing 'early' and 'late' thresholds for initiating chelation therapy.

In the absence of a definitive clinical trial, physicians and patients must make choices regarding iron chelation therapy that are informed by the best data available. We have summarized those data here, and have presented our consensus recommendations that are based on our consideration of them. The deficiencies in the evidence basis for these recommendations preclude them being construed as the standard of care; the final decision on management of transfusional iron overload in MDS remains a matter for the joint judgment of the patient and the treating physician.

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Appendix A

Classification of Evidence levels and Grades of Recommendation (from the British Committee for Standards in Haematology) [4].

Classification of Evidence Levels	
Ia	Evidence obtained from meta-analysis of randomised controlled trials
Ib	Evidence obtained from at least one randomised controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomisation
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities

Classification of grades of Recommendations

A	Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing specific recommendation (*Evidence levels Ia, Ib*)
B	Requires the availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation (*Evidence levels IIa, IIb, III*)
C	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality (*Evidence level IV*)

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