

Clinical consequences of iron overload in myelodysplastic syndromes and treatment with chelators

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The myelodysplastic syndromes (MDS), a heterogeneous group of related hematological disorders, are primarily a disease of the elderly. Most MDS patients with chronic anemia become dependent on blood transfusions to maintain or improve quality of life and ultimately, to survive. Iron overload is an inevitable consequence of transfusion therapy and can lead to serious clinical sequelae. However, there remains some debate over which MDS patients will survive long enough to develop clinically relevant iron overload and therefore potentially benefit from iron chelation therapy; prognostic evaluation may serve to answer this question.

Introduction to MDS

MDS comprises a group of closely-related heterogeneous disorders characterized by impaired production of blood cells by the bone marrow. The median age of diagnosis is between 65 and 75 years, and more than 90% of patients are aged over 50 years [1,2]. The bone marrow in MDS patients is typically more active than normal, yet the numbers of circulating blood cells are reduced since their progenitors in the bone marrow are defective and many are destroyed before entering the bloodstream [1]. A fall in the number of red blood cells will eventually lead to anemia; 90% of MDS patients with chronic anemia become dependent upon blood transfusions to maintain or improve their quality of life (eg, reduce fatigue) and ultimately, to survive.

Iron overload in MDS

Iron overload is an inevitable consequence of transfusion therapy as every unit of transfused blood contains approximately 200 to 250 mg of iron [3] and natural iron losses equal only 1 mg per day [4]. If a patient with MDS receives, on average, two units of blood per month, they will receive 24 units per year and approximately 100 units every 4 years. This rate of iron loading is equivalent to approximately 20 to 25 g of iron in 4 years and is approaching levels at which clinical sequelae start developing; normal body iron levels are between 3 and 4 g.

Although transfusion therapy is the primary cause of iron overload in MDS, it is not the only contributing factor. Iron

starts to accumulate before transfusion therapy is initiated due to the stimulation of intestinal iron uptake by ineffective erythropoiesis [5]. Despite many years of research, the molecule that produces this stimulation has not yet been identified.

A commonly used method for evaluating iron levels is the assessment of serum ferritin [6]. In patients with MDS, body iron levels tend not to be excessively elevated prior to the initiation of transfusion therapy. The Düsseldorf MDS Registry recorded serum ferritin at diagnosis in 650 patients and found that levels were around or below 1000 ng/mL in more than 95% of patients. There were a small number of outliers with ferritin levels above 3000 ng/mL, but these patients were thought to be transfusion-dependent before diagnosis.

Clinical consequences of iron overload in MDS

A recent study demonstrated that transfusion dependency in patients with MDS is associated with a decreased probability of survival [7]. However, this may also be due to factors other than iron overload, such as more severe bone marrow failure leading to infectious and hemorrhagic complications. Although it is well established that iron overload primarily affects the heart, liver, and endocrine tissues [8], no studies have directly compared the frequency of these disorders in iron-loaded MDS patients and age-matched controls. Thus, it is unclear whether these complications are more common in MDS patients than in a normal elderly population.

One study assessed the clinical outcomes of iron overload in 15 nonthalassemic adult patients [9]; iron loading had been present for less than 4 years in 14 of the patients. Endocrine abnormalities were the most prominent manifestations possibly attributable to iron overload, with diabetes and inadequate hypothalamic-pituitary-adrenal reserve being of particular clinical importance. Impaired glucose tolerance was also observed, even in patients with a relatively short exposure to excess iron levels. Left ventricular dysfunction and supraventricular arrhythmias were reported in heavily transfused patients, while clinical heart failure and ventricular arrhythmias were observed in patients with concomitant coronary artery disease. The authors noted, however, that it was difficult

to separate the relative contributions of myocardial iron deposition and chronic anemia from the development of functional abnormalities.

Another study identified 46 patients with MDS who had received at least 50 units of packed red blood cells (range 50-155, mean 79) [10]. Twenty patients developed clinical signs of iron overload and all experienced heart failure, accompanied by arrhythmias in some cases. Twelve patients suffered from hepatic impairment and five developed diabetes mellitus. Refractory congestive heart failure was the cause of death in 14 patients, whereas none died from hepatic insufficiency. This suggests that cardiac abnormalities are the most frequent and serious clinical complications in patients with MDS.

It is difficult to assess the relative contribution of transfusional iron overload to these events in patients with MDS. The complications reported in both these studies were primarily attributed to iron overload as all patients had laboratory evidence of excess iron. However, it is unclear how many of these problems were actually caused by other factors such as chronic anemia, concomitant diseases, complications of bone marrow failure, or even as a result of the normal aging process. For example, chronic anemia necessitates an increased cardiac output in order to compensate for impaired tissue oxygenation, and can consequently lead to heart complications. Increased cardiac output raises the heart rate and increases ventricular preload, which can result in a dilated, strongly contractile left ventricle with gradual deterioration of the contractile reserve [11]. An overstrained ventricle may then be more susceptible to the effects of iron overload.

Current treatment of iron overload

Deferoxamine

The current reference standard therapy for the treatment of iron overload is deferoxamine (Desferal[®]), a hexadentate iron chelator that binds iron in a 1:1 ratio and forms a stable complex that is excreted either in the bile or urine. More than 35 years of clinical experience with deferoxamine has established iron chelation therapy as a highly effective approach to preventing and treating iron overload [12,13]. The clinical evaluation of deferoxamine specifically in MDS patients has, however, been limited to a small number of studies, which suggested that deferoxamine treatment may also improve hemopoiesis in MDS patients with transfusional iron overload [14,15]; the mechanisms behind this effect are not fully understood. In one of these studies, eleven patients were followed for up to 60 months during and after deferoxamine therapy [15]. A greater than 50% reduction in transfusion requirements was observed in seven patients (63.6%), five of whom (45.5%) became completely transfusion independent. Platelet counts increased in seven patients (63.6%), while neutrophil counts increased in seven of nine evaluable patients (77.8%). Improved erythropoietic output was observed in all patients who were effectively chelated.

The limitations of deferoxamine therapy are well established. The compound has a poor oral bioavailability and short plasma half-life [16], which necessitates a slow, subcutaneous infusion over 8 to 12 hours, 5 to 7 times each week. This

demanding regimen, combined with an incidence of injection site reactions, means that administration is inconvenient for many patients and is exacerbated by the fact that the equipment required to deliver the deferoxamine infusion is not widely available in many countries. These factors contribute to poor patient compliance and a consequential increase in morbidity and mortality [17-19].

Deferiprone

To date, the only commercially available alternative to deferoxamine is the bidentate oral chelator, deferiprone (Ferriprox[®]). This compound is less iron-specific than deferoxamine and binds iron in a 3:1 ratio before being excreted in the urine [20]. However, deferiprone is more lipid-soluble than deferoxamine, meaning that it is rapidly absorbed from the gastrointestinal tract.

Although deferiprone has been licensed by the European Medicines Agency for the treatment of iron overload in thalassemia patients when deferoxamine therapy is contraindicated or inadequate [21,22], it has not been approved for use in the United States by the Food and Drug Administration. This is due to the incidence of adverse events (AEs) that necessitate weekly monitoring of a patient's neutrophil count [23], the most serious of which is severe agranulocytosis (occurring in approximately 0.5% of patients). Mild neutropenia has also been reported in approximately 8.5% of patients [24]. There is debate regarding the long-term efficacy of deferiprone; its long-term safety continues to be evaluated [25-27].

To date, few clinical studies investigating the use of deferiprone in patients with MDS have been completed. One pilot study, reporting just three patients dosed at suboptimal levels, was ended prematurely due to concerns over the risk of agranulocytosis [28]. A second study evaluated deferiprone in mainly nonthalassemia patients with transfusional iron overload, including 18 patients with MDS [29]. Mean serum ferritin levels in the MDS patients decreased by 25% during up to 1 year of treatment. Agranulocytosis developed in one MDS patient (deferiprone was immediately withdrawn) and a slight decrease in platelet levels was observed in two patients, although this was considered due to the underlying disease.

A new therapeutic option?

The limitations of current therapeutic options highlight the unmet medical need for an effective and convenient iron chelation therapy suitable for long-term use. A new option in advanced clinical development is the oral chelator ICL670 (deferisirox, Exjade[®]) which is representative of a new class of tridentate chelators, the N-substituted bis-hydroxyphenyl-triazoles [30,31]. ICL670 binds iron in a 2:1 ratio before being excreted, primarily in bile.

Phase II and III clinical trials in iron overloaded pediatric and adult patients with transfusion-dependent anemia, such as β -thalassemia, MDS and Diamond-Blackfan anemia, have shown that ICL670 is effective with an acceptable safety profile [32-35]. The largest of these studies was an open-label, 1-year, multicenter study that compared ICL670 (n = 296) and deferoxamine (n = 290) in iron overloaded patients with β -thalassemia

[32]. Daily ICL670 doses of 20 (which corresponds to 40 mg/kg of deferoxamine) and 30 mg/kg induced stable or falling liver iron concentration (LIC) levels, effects that were mirrored by changes in serum ferritin. ICL670 doses of 5 and 10 mg/kg/day were not sufficient to induce or maintain a negative iron balance in these patients.

A recent Phase II multicenter study enrolled patients with transfusion-dependent anemias, including patients with MDS (n = 47) or other rare anemias (n = 52) [34]. In the β -thalassemia cohort, ICL670 5 and 10 mg/kg/day were not able to reduce LIC, while 20 and 30 mg/kg/day induced stable or falling LIC levels. However, when patients with other anemias were assessed, 10 mg/kg/day was sufficient to maintain iron balance, while 20 and 30 mg/kg/day led to a decrease in liver iron levels. A similar pattern has been demonstrated in a separate analysis of the MDS patient cohort [35].

ICL670 has been generally well tolerated in these clinical studies. The most common AEs, regardless of the relationship to study drug, were gastrointestinal disturbances such as diarrhea, abdominal pain, nausea, and vomiting. AEs were generally mild and transient.

Which patients with MDS will benefit from iron chelation?

Effective iron chelation therapy has been shown to improve survival in patients with β -thalassemia [13,17]. This effect is generally observed after 15 years of age and corresponds to around 10 years of treatment [17]. Although there is a large volume of published data relating to iron overload and chelation therapy in β -thalassemia, it is unclear whether this knowledge can be applied directly to MDS.

Since MDS is primarily a disease of the elderly and life expectancy is consequently low, there remains some debate whether patients with MDS will survive long enough to potentially benefit from iron chelation therapy. It should also be considered, however, that elderly MDS patients may be especially vulnerable to the toxic effects of iron and therefore benefit from early initiation of chelation therapy. Thus, there is a need to establish which patients with MDS would be likely to benefit most from iron chelation therapy. A reasonable way to approach this is to assess the survival of different patient groups, based on the World Health Organization diagnostic classification of MDS (Table 1) and the International Prognostic Scoring System (IPSS) risk score [36]. IPSS is calculated based upon cytogenetic, morphologic, and clinical data and is scored as either low (score 0), intermediate-1 (0.5–1.0), intermediate-2 (1.5–2.0) or high (≥ 2.5) (Table 2).

It seems probable that patients with an increased percentage of blast cells in their bone marrow (ie, refractory anemia excess blast [RAEB] I and RAEB II) would be less likely than other patients to benefit from chelation therapy due to a low probability of survival (Fig.). The MDS patients most likely to develop transfusional iron overload are those with dyserythropoiesis (ie, refractory anemia [RA] and refractory anemia with ringed sideroblasts [RARS]), as these patients have a median survival time of approximately 5 years. Patients with

refractory cytopenia with multilineage dysplasia (RCMD) and refractory sideroblastic cytopenia with multilineage dysplasia (RSCMD) also frequently require transfusion therapy and may develop iron overload. The median survival of RCMD and RSCMD patients is approximately 3 years but with a considerable risk of leukemic transformation; however, the prognosis in this patient group is extremely heterogenous. Patients with 5q-syndrome are also potential candidates for chelation therapy, although they comprise only a small proportion of the MDS patient population.

Once patients have been diagnosed and classified, the IPSS risk score is calculated. Those with a low-risk score, which equates to around 36% of patients with multilineage dysplasia, are likely to survive for approximately the same length of time as patients with RA or RARS (Table 3). Patients with an intermediate-1-risk score, around 50% of patients with multilineage dysplasia, will survive for approximately 3 years. The remaining patients (ie, intermediate-2- and high-risk) have a poor prognosis and are unlikely to survive for long enough to develop significant iron overload.

Table 1
WHO diagnostic classification of MDS

MDS categories
Refractory anemia without ringed sideroblasts (RA) with ringed sideroblasts (RARS)
Refractory cytopenia with multilineage dysplasia (RCMD)
Refractory sideroblastic cytopenia with multilineage dysplasia (RSCMD)
Refractory anemia with excess blasts with 5-10% blasts (RAEB I) with 11-20% blasts (RAEB II)
5q-syndrome
Unclassified

Table 2
IPSS classification of MDS

Prognostic variable	Bone marrow blasts (%)	Karyotype*	Cytopenias
0	<5	Good	0/1
0.5	5–10	Intermediate	2/3
1.0	–	Poor	
1.5	11–20		
2.0	21–30		
≥ 2.5	>30		

*Good, normal, -Y, del(5q), del(20q); poor, complex (≥ 3 abnormalities) or chromosome 7 anomalies; intermediate, other abnormalities.

(Data from Greenberg P, et al. International Scoring System for Evaluating Prognosis in Myelodysplastic Syndromes. *Blood* 1997;89:2079–88; with permission.)

Table 3
Survival of MDS patients with RCMD and RSCMD according to IPSS score (Düsseldorf MDS Registry, n = 1598)

	RA	RARS	RCMD	RSCMD	RAEB I	RAEB II	5q-
n	131	146	420	247	200	211	41
IPSS score		Low 36%	Int-1 50%	Int-2 13%	High 1%		
Median survival time (months)		62	36	12	7		

Abbreviations: Int-1, intermediate-risk-1; Int 2, intermediate-risk-2.

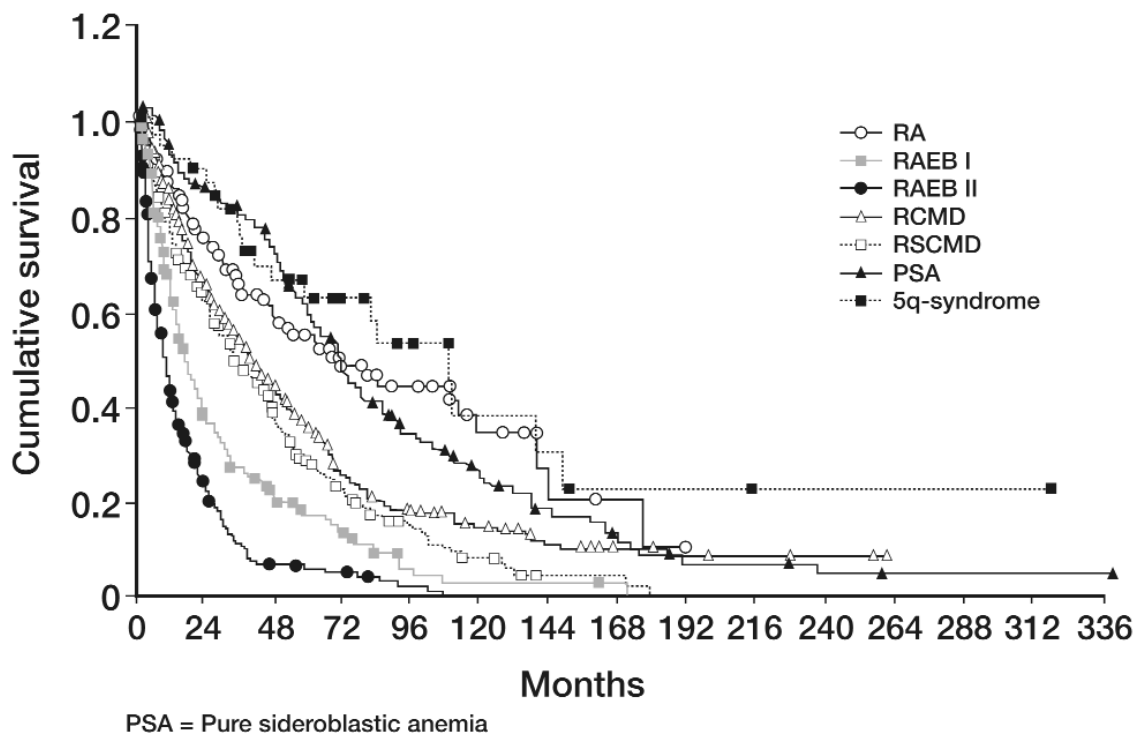


Fig. Cumulative survival of MDS patients according to WHO diagnostic classification (Düsseldorf MDS Registry, n = 1598).

As such, it is proposed that the primary MDS candidates for iron chelation therapy are patients with RA or RARS who live for approximately 5 years (~20%), and patients with RCMD or RSCMD and a low-risk IPSS score who also live for 5 years (~15%). Secondary candidates, in whom the indication for chelation therapy is less clear, include patients with RCMD or RSCMD who have an intermediate-1-risk score and live for approximately 3 years (~20%).

Conclusions

Many patients with MDS become dependent on blood transfusions to maintain or improve their quality of life and to survive; these patients are susceptible to the development of iron overload. The impact of excess iron in MDS has not yet been conclusively established. However, the prognostic assessment of MDS may

help to determine which patients will live long enough to potentially show clinical sequelae due to excess iron levels. Patients with a good prognosis are probably the best candidates to receive iron chelation therapy. Currently available iron chelators are limited, therefore the availability of newer, more convenient therapeutic options may mean that a greater proportion of transfusion-dependent patients with MDS can receive chelation therapy.

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