The deleterious effects of iron overload in patients with myelodysplastic syndromes

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Summary  Many patients with myelodysplastic syndromes (MDS) have severe anaemia. However, regular blood transfusions, which are widely used to maintain quality of life and prevent anaemia-related morbidity and mortality, have a negative impact on survival as a result of iron overload. Retrospective surveys have shown an association of transfusion dependence with hepatic, pituitary, and pancreatic dysfunction, cardiac failure, and cardiac death. Survival is significantly decreased in transfusion-dependent patients, and the main cause of non-leukaemic death is cardiac failure. However, iron chelation therapy reduces serum ferritin levels and is associated with significantly improved survival in patients with MDS. Current guidelines recommend starting iron chelation therapy after 25–50 units of blood have been transfused, or when serum ferritin levels rise above 1,000–2,000 μg/L. The patients who are most likely to benefit from iron chelation therapy are those who have low-risk disease (International Prognostic Scoring System low or intermediate-1 risk) with a life expectancy of more than 1 year. More specific studies in patients with MDS are needed to evaluate the impact of iron chelation therapy on morbidity and mortality, and provide a stronger evidence base for treatment guidelines.

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Introduction

Myelodysplastic syndromes (MDS) are a group of clonal haemopoietic disorders characterized by ineffective haemopoiesis, bone marrow dysplasia, and an increased risk of transformation to acute myeloid leukaemia (AML). Survival after diagnosis of MDS varies from a few months to several years. A number of prognostic scoring systems have been developed to predict the outcomes of MDS, of which the International Prognostic Scoring System (IPSS) is the most widely used to predict survival and the risk of progression to AML.1 The large majority of patients with MDS are anaemic and eventually up to 90% of them require regular transfusions. In 50–60% of patients, anaemia is severe (haemoglobin level below 10 g/dL)1 and is associated with decreased physical performance and quality of life,2 and increased cardiac morbidity and mortality.3–5

The aim of blood transfusion therapy is to maintain quality of life and prevent anaemia-related morbidity and mortality. Several studies have now shown, however, that transfusion dependence has a negative impact on the survival of patients with MDS (Figure 1). 3,6 Although a number of factors may contribute to the decreased survival of transfusion-dependent patients, it has clearly been shown that mortality correlates with higher serum...
Figure 1. Overall survival of patients with myelodysplastic syndromes grouped according to cytogenetic risk, defined according to the International Prognostic Scoring System as (A) good (low) risk, (B) intermediate risk, and (C) poor (high) risk, and development of transfusion requirement. Patients with isolated 5q− syndrome were excluded from the cytogenetic good-risk group. The survival curves in this graph do not account for time dependency of the transfusion requirement. Reprinted with permission from Malcovati L, et al. J Clin Oncol 2005;23:7594–7603. © 2008 American Society of Clinical Oncology. All rights reserved.

ferritin levels in patients with MDS, and is likely to be a consequence of iron overload.3,7

This article briefly reviews the mechanisms of iron overload and its clinical consequences in patients with MDS. It also discusses who can benefit most from iron chelation therapy, and reviews current knowledge on iron chelation therapy in patients with MDS.

Mechanisms of iron overload in MDS patients

Several mechanisms play a role in iron loading in patients with MDS, who start accumulating iron even before they are in need of regular blood transfusions. At this stage of the disease, iron accumulation is probably the result of ineffective erythropoiesis, which stimulates increased iron absorption by the small intestine. The mechanism of iron accumulation at this stage is unclear, but downregulation of hepcidin, an important modulator of serum ferritin levels, is probably important.8,9 By the time of diagnosis, i.e. before transfusions begin, the serum ferritin level has usually risen to about 500–600 µg/L, but seldom exceeds this value.

The main cause of iron overload is transfusion therapy. Each unit of blood transfused delivers 200–250 mg of iron, and therefore after only 20 units of blood have been transfused, 4,000–5,000 mg of iron are delivered to the body. As a consequence, the serum ferritin level rises to about 1,000 µg/L,3 and the capacity of transferrin to bind iron is exceeded. Reactive non-transferrin-bound iron (NTBI) is then generated,10 favouring oxidative DNA damage and apoptosis.11,12 NTBI levels are significantly elevated compared with normal even in non-transfused patients with MDS, while patients with higher NTBI levels show a higher level of apoptosis in the bone marrow.13

Consequences of iron overload in MDS patients

In 1981, it was reported that patients with refractory or aplastic anaemia who had received a mean of 120 blood transfusions had 7–26 times the normal amount of iron in the liver and typically displayed focal portal fibrosis.14 Although left ventricular cardiac function was impaired in only the most heavily transfused patients or in those with coexisting coronary artery disease, all patients had glucose intolerance associated with significantly reduced insulin output, compared with controls. The pituitary reserve of adrenocorticotropic hormone was limited in 10 of 12, and that of
gonadotrophin in 5 of 13 patients. This pattern of organ involvement resembles that encountered in idiopathic haemochromatosis. An early autopsy series also showed that grossly visible cardiac iron deposits in patients who had received blood transfusions for idiopathic haemochromatosis or chronic anaemia were associated with cardiac dysfunction and usually with chronic cardiac failure. A number of retrospective studies have highlighted the contribution of iron overload to the morbidity and mortality associated with MDS. More than 20 of 46 patients with MDS who had received more than 50 units of blood showed signs of heart failure, sometimes with cardiac arrhythmias, and 14 patients died with congestive heart failure secondary to haemochromatosis. In another small study, 34 of 43 patients with the 5q− subtype of MDS were transfusion-dependent at diagnosis, and 40 patients were eventually transfusion-dependent. Haemosiderosis was diagnosed in 12 patients by iron studies, and was associated with congestive heart failure or exertion intolerance, abnormal liver function tests, cirrhosis, diabetes, and skin changes.

Data from 374 patients with MDS have shown that once these patients develop a need for regular transfusions, their probability of survival decreases (hazard ratio for death, 1.58; p = 0.005). In a survey of 467 patients with MDS followed from diagnosis to death or progression to leukaemia, 51% of non-leukaemic deaths were due to cardiac failure and 8% were due to hepatic cirrhosis. Furthermore, cardiac failure was a significantly more common cause of death among MDS patients who were transfusion-dependent than among those not receiving regular transfusions. Iron overload was a major contributor to this increased mortality. Similarly, in a retrospective Japanese study of 292 patients with MDS and other transfusion-dependent anaemias, cardiac and hepatic dysfunction were present in 21.9% and 84.6%, respectively, of patients studied. Of the patients who died, 24.0% had cardiac failure and 6.7% had hepatic failure; 97% of those who died had serum ferritin levels above 1,000 μg/L.

Data from the US Medicare database also show that cardiac disease is a major comorbid condition in patients with MDS, occurring in nearly three-quarters of patients (Table 1), compared with under half of the general Medicare population. In this cohort of 705 patients with MDS, cardiac events occurred in significantly more patients who were receiving transfusions than in those who were not receiving transfusions (79% vs 54%; p = 0.0001). It was noted that of the 54% of patients with MDS who did not have pre-existing cardiac disease, 60% developed cardiac disease.

In a large retrospective study of 840 consecutive patients with MDS, heart failure (28% vs 18%; p = 0.001) and cardiac death (69% vs 55%; p = 0.03) were significantly more common in transfusion-dependent patients relative to those who were not transfusion-dependent. In a Cox analysis with time-dependent covariates, the risks of non-leukaemic death (hazard ratio 2.12; p < 0.001), heart failure (hazard ratio, 1.34; p = 0.03), and cardiac death (hazard ratio 2.99; p = 0.01) were all increased in transfusion-dependent patients. The development of secondary iron overload significantly increased the risk of non-leukaemic death (hazard ratio 1.25; p < 0.001), and specifically increased the risk of developing heart failure (hazard ratio 1.17; p < 0.001).

Transfusion dependency may be a reliable indicator of the severity of the disease. However, it must be recognized that the limited survival of patients with MDS may be at least partly caused by a deterioration of their stem cell disorder (progression of MDS to AML) and the presence of comorbidities, in addition to the direct effect of iron overload as a result of blood transfusions.

Myocardial accumulation of iron has not yet been extensively studied in patients with MDS, and the results that have been obtained are contradictory. For example, in an autopsy series, it was found that extensive cardiac iron deposits were always present in patients with idiopathic haemochromatosis or chronic anaemia who had received more than 100 units of transfused blood (unless bleeding diatheses coexisted), though they could also occur in patients who had received fewer than 100 units of blood. More recently, myocardial T2* magnetic resonance imaging (MRI) studies suggested that iron loading of the heart can occur after 75–100 units of blood have been transfused. However, two recent studies using T2* MRI failed to show iron accumulation in the hearts in patients with MDS after 63–90

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Incidence of cardiac events over a 3-year period among 705 patients with myelodysplastic syndromes in the US Medicare population. (Data from Goldberg et al.19)</th>
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</thead>
<tbody>
<tr>
<td>Number of patients (%)</td>
<td></td>
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<tr>
<td>Any cardiac-related event</td>
<td>522 (74)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>142 (29)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>344 (48)</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>374 (53)</td>
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<tr>
<td>Other cardiac events</td>
<td>415 (58)</td>
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units of blood, though iron accumulation in the liver was shown in all patients studied.\textsuperscript{23,24} The reason for these discrepancies is not clear, but the heterogeneity of these series (some patients received chelation therapy, while others did not) may have contributed. In addition, increased NTBI in patients with MDS may cause direct myocardial tissue damage, which cannot always be shown by MRI, which visualizes storage iron.\textsuperscript{25} Finally, it has been suggested that there may be a long latency period between iron accumulation in the liver and iron overload in the heart in patients with MDS,\textsuperscript{15} which is supported by more recent T2* MRI series.\textsuperscript{26}

**Outcomes of chelation therapy in MDS**

The positive impact of iron chelation therapy on survival has been clearly shown in a series of 97 patients with \(\beta\)-thalassaemia major, in whom maintenance of serum ferritin levels below 2,500 \(\mu\)g/L was the major determinant of cardiac-disease-free survival.\textsuperscript{27} Although there are few studies of the efficacy of iron chelation therapy in patients with MDS, evidence is slowly accumulating that efficient iron chelation could have a positive impact on survival in patients with MDS. For example, a retrospective study in 178 patients with MDS indicated that iron chelation therapy was significantly associated with improved survival in patients in the Low-risk or Intermediate-1-risk categories (classified using the International Prognostic Scoring System [IPSS]).\textsuperscript{28} In fact, the median overall survival was not reached at 160 months in those who received iron chelation therapy, whereas it was only 40 months in those who did not receive iron chelation. Furthermore, significantly more patients who received iron chelation therapy survived to 4 years (80% versus 44%; \(p < 0.03\)). Serum ferritin levels fell significantly in patients who received iron chelation therapy, and increased significantly in those who did not. In another retrospective study in 292 patients with MDS or other transfusion-dependent anaemias, effective iron chelation therapy with deferoxamine (i.e. daily or continuous chelation therapy) resulted in improved levels of serum ferritin, liver enzymes, and fasting blood sugar levels.\textsuperscript{18} Intermittent deferoxamine therapy, however, conferred no benefit.

Of course, these retrospective findings need to be confirmed by prospective studies. In a prospective cohort study that enrolled 170 patients (5 of whom were lost to follow-up) with MDS receiving regular blood transfusions, iron chelation therapy significantly improved median overall survival from diagnosis from 51 months to 115 months (\(p < 0.0001\)).\textsuperscript{29} After adjustment for other prognostic factors, such as sex, age, IPSS category, and transfusion requirement), the survival difference remained significant.

**Eligibility for iron chelation therapy**

Current guidelines for management of iron chelation therapy in patients with MDS are based on non-randomized trials, expert opinion, and the experience of iron chelation in patients with \(\beta\)-thalassaemia major.\textsuperscript{30–33} These guidelines converge towards a consensus on the subgroups of patients with MDS who should receive iron chelation therapy.

The Italian guidelines recommend that adult patients with MDS who have previously received more than 50 units of blood and with an expected lifespan longer than 6 months should receive iron chelation therapy.\textsuperscript{30} The UK guidelines recommend that iron chelation should be considered once a patient has received 5 g of iron, which is equivalent to approximately 25 units of blood, but only if long-term transfusional therapy is likely.\textsuperscript{31} This recommendation is somewhat less stringent than the Italian guidelines as far as the transfusion history is concerned, but a little more demanding as far as the prognosis of the patient is concerned, in specifying patients requiring long-term transfusion therapy, which suggests longer than 6 months (though this is not defined). The most recent National Comprehensive Cancer Network (NCCN) practice guidelines strongly recommend that iron chelation therapy should be considered in patients who have received 20–30 units of blood and for whom ongoing blood transfusions are anticipated.\textsuperscript{33}

There are also some differences between the different guidelines with respect to the serum ferritin levels at which patients should start iron chelation therapy. For example, the NCCN guidelines recommend iron chelation therapy for patients with MDS who have a serum ferritin level above 2,500 \(\mu\)g/L.\textsuperscript{33} This represents a slight inconsistency, because serum ferritin levels of 1,000 \(\mu\)g/L are usually reached after an average of 21 units of red blood cells,\textsuperscript{3} so 2,500 \(\mu\)g/L would correspond to about 50 units of red blood cells, rather than the recommended threshold of 20–30 units. The Nagasaki consensus recommends starting iron chelation therapy when serum ferritin levels reach 1,000–2,000 \(\mu\)g/L, depending on the transfusion rate.\textsuperscript{32} Expert opinion now tends to the view that a serum ferritin level of 1,000 \(\mu\)g/L is a suitable threshold for starting iron chelation therapy...
therapy. Chelation therapy should continue for as long as transfusion therapy continues and as long as iron overload remains clinically relevant, \(^{30–33}\) with the aim of reaching and maintaining a serum ferritin level below 1,000 \(\mu g/L\).

In general, the patients who will benefit most from iron chelation therapy are those who fall into the lower risk groups or have stable disease, i.e. those who have a better expected survival rate. The NCCN guidelines emphasize that iron chelation should be particularly considered for patients with lower-risk MDS whose clinical course suggests the need for continuing red blood cell transfusions, and for those with concurrent cardiac or hepatic dysfunction. \(^{33}\) These guidelines thus recognize that patients with MDS may have additional factors that may make them more vulnerable to the toxic effects of iron overload.

The Nagasaki consensus statement provides somewhat more detailed eligibility criteria (Table 2). Patients with refractory cytopenia with multilineage dysplasia (RCMD) or refractory sideroblastic cytopenia with multilineage dysplasia (RSCMD) with a low IPSS score are also good candidates for iron chelation therapy. \(^{34}\) These patients are likely to survive for about 5 years. Patients with RCMD or RSCMD and an IPSS Intermediate-1 score who have a life expectancy of about 3 years may also benefit, though the indication is less clear. \(^{34}\)

Conclusions

Much of our current knowledge of the clinical consequences of iron overload is derived from studies in patients with \(\beta\)-thalassaemia major. The real causes of decreased survival in patients with MDS who receive regular red blood cell transfusions are difficult to assess. Just as these patients tend to have multiple clinical problems, so too the causes of decreased survival are likely to be multifactorial and not related only to transfusions. However, evidence is accumulating on the deleterious role of iron in MDS. More prospective studies are needed to identify more precisely how iron overload contributes to organ dysfunction and related mortality in this population. Current guidelines for iron chelation therapy in patients with MDS who have a reasonable survival prognosis are largely based on clinical experience and studies in patients with \(\beta\)-thalassaemia major. Experts agree though that chelation therapy should be started serum ferritin level of 1,000 \(\mu g/L\). More specific studies in patients with MDS are needed to evaluate the impact of iron chelation therapy on morbidity and mortality in these patients, and to provide a stronger evidence base for treatment recommendations.

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