Iron Overload, Chelation Therapy and Survival in Lower-Risk Myelodysplastic Syndromes: State of the Evidence

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Author’s contribution

RML developed the concept for the paper, critically revised drafts, and read and approved the final manuscript.

ABSTRACT

Myelodysplastic syndromes (MDS) are clonal stem cell disorders that primarily affect older persons and are associated with peripheral blood cytopenias, increased risk of conversion to acute myeloid leukemia and shortened survival. Treatment strategies in MDS are guided by patient risk categories, with higher-risk patients receiving more aggressive interventions. Patients with lower-risk MDS receive less aggressive therapies or supportive care/red blood cell transfusion. Transfusion-dependent patients with lower-risk MDS are likely to develop iron overload because of their longer predicted survival and, hence, greater transfusion burden. Transfusion requirement and elevated serum ferritin further complicate the treatment landscape because they have dose-dependent effects on overall and leukemia-free survival, with increasing serum ferritin levels associated with increased risk of death. Lower iron burden could provide a survival benefit, and an association with improved survival has been shown in retrospective studies. However, lack of random assignment to treatment is the major flaw in these studies, which potentially introduces patient selection bias. Despite the lack of randomization and other issues with trial design, available studies have shown consistent results, which suggest a survival benefit in transfusion-dependent patients with MDS who have received chelation therapy. Prospective studies are needed to confirm this observation. The possible mechanisms by which chelation therapy appears to benefit patients with MDS need further research. The data suggesting a survival benefit from

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chelation therapy in lower-risk, iron-overloaded patients with MDS are reviewed, including the strength of evidence, recent scientific advances and ongoing clinical trials.

Keywords: Myelodysplastic syndromes; iron overload; chelation; survival; leukemia.

ABBREVIATIONS


1. INTRODUCTION

Myelodysplastic syndromes (MDS) are clonal stem cell disorders that affect at least 3-4 persons per 100,000 of the general population and 75 persons per 100,000 who are 65 years or older. Median age at diagnosis ranges from 71 to 76 years in the United States [1,2]. MDS results in peripheral blood cytopenias and increased risk of conversion to acute myeloid leukemia (AML). Most patients with MDS will have anemia at diagnosis: 48% with hemoglobin ≤100g/l and 17% with hemoglobin <80g/l [3]. Traditionally, patients with MDS were categorized during diagnostic evaluation by French-American-British criteria into 5 subtypes of disease based on morphologic features: refractory anemia (RA), RA with ring sideroblasts (RARS), RA with excess blasts, RA with excess blasts in transformation and chronic myelomonocytic leukemia [4]. In the late 1990s, the World Health Organization (WHO) developed a refined diagnostic scheme with additional MDS subtypes, including refractory cytopenia with unilineage dysplasia, MDS unclassifiable and isolated del5q syndrome [5,6]. The WHO scheme is now used by the majority of practitioners.

Patients with MDS are also stratified into risk categories according to predicted survival. The International Prognostic Scoring System (IPSS) classifies patients as low, intermediate-1, intermediate-2 or high risk based on marrow blast percentage, cytogenetic subgroup and number of cytopenias [7]. Limitations of the IPSS are that it does not identify lower-risk patients who have a poor prognosis and can only be used at initial diagnosis [6,8]. The newer WHO Prognostic Scoring System (WPSS) allows dynamic estimation of prognosis during the course of MDS, taking into account morphologic categories, IPSS cytogenetic categories and transfusion dependence [9]. Currently, there is some debate about whether WPSS offers an advantage over IPSS, and the WPSS has not been widely accepted [6]. The revised IPSS scoring system includes more comprehensive cytogenetic scoring, with prognostic subgroups ranging from “very good” to “very poor” based on the presence of single or multiple abnormalities associated with increased risk [3], but it does not include newer genetic risk factors [10,11]. It can be used for prognosis throughout a patient’s course.

The identification of patients with disease characteristics that increase the risk of poor outcome has treatment implications. At present, treatment options for higher-risk patients with MDS are somewhat limited. Younger, healthier patients with higher-risk disease are good candidates for aggressive leukemia chemotherapy and/or hematopoietic stem cell transplantation, which provides the only potential cure. For those patients who are not transplant candidates, treatments include hypomethylating agents, immunomodulatory agents, transfusion and supportive care [6]. Hospice may be a reasonable option for those with poor performance status. Patients with lower-risk MDS typically receive erythroid-
stimulating agents, transfusions, immunomodulation, immunosuppression and supportive care [6]. Patients with del5q syndrome are generally treated with lenalidomide as their initial therapy [6].

Some patients may also present with iron overload. Transfusion-dependent patients in this population are at further increased risk for iron overload owing to their predicted longer survival and, hence, greater transfusion burden. Prospective trials have shown that preventing or reversing iron overload in patients with β-thalassemia major is associated with improved outcomes [12,13]. The iron chelators deferoxamine and deferasirox are approved for first-line treatment of patients with transfusional iron overload, and a third chelator, deferiprone, is approved for second-line treatment of iron overload in patients with thalassemia syndromes [14-16]. Recently, the US Food and Drug Administration has extended the indication for deferasirox to include prophylactic removal of iron in patients with non-transfusion-dependent thalassemias [15]. However, the evidence for benefit from iron chelation in patients with MDS is less convincing than in patients with thalassemia, perhaps because of the retrospective nature of available studies.

To date, studies in MDS have shown that lower iron burden itself is associated with improved outcome. Malcovati et al. [17] reported that patients with relatively lower serum ferritin have a better prognosis than those with higher levels. Malcovati estimated that every 500-µg/l increase in serum ferritin above a 1000-µg/l threshold was associated with a 36% increase in risk of death. Further, a transfusion requirement and elevated serum ferritin have dose-dependent effects on overall and leukemia-free survival [17].

Nevertheless, there are no prospective data for chelated patients with MDS that show iron chelation has an independent effect on outcomes, making interpretation of the available data challenging. The major flaws in completed studies include the lack of random assignment to treatment, which introduces the possibility of patient selection bias whereby healthier patients are assigned to chelation therapy because they are expected to survive longer and will receive more transfusions. Age-related comorbid conditions may also confound study results. Current prognostic classification schemes do not take comorbidities into account [3,7,18]. Therefore, the contribution of comorbidities to patient risk is not well understood, which makes it difficult to distinguish age-related comorbidities from the adverse effects of iron overload in these typically older patients, especially those who may not have been optimally chelated.

Despite the shortcomings in trial design, available studies have shown consistent results, suggesting a survival benefit in transfusion-dependent patients with MDS who have received chelation therapy. Herein, those data are reviewed and the strength of evidence is discussed in the context of recent scientific advances and ongoing clinical trials.

2. CHELATION THERAPY STUDIES IN PATIENTS WITH MDS

At present, the evidence for increased survival in transfusion-dependent, chelated, lower-risk patients with MDS comes from retrospective and observational studies Table 1. With 2 exceptions—a Medicare database analysis and an ongoing prospective observational registry—these studies typically enrolled low numbers of patients. These factors, along with differences in study design, limit meaningful comparison and application of study results to practice.
Table 1. Clinical outcomes for lower-risk MDS patients in iron chelation studies

<table>
<thead>
<tr>
<th>Study design (n)</th>
<th>Patient selection criteria</th>
<th>Prognostic criteria</th>
<th>Chelation treatment duration, mo, median (range)</th>
<th>Serum ferritin, median</th>
<th>Survival outcome, mo, median</th>
<th>Leukemic transformation, n/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leitch et al. [20] Retro matched-pair analysis, chelated (18) vs non-chelated (18)</td>
<td>Chelation treatment: ferritin &gt; 2000 µg/l, ≥ 20 RBC units, clinical evidence of iron overload</td>
<td>IPSS low or Int-1</td>
<td>21.6 (1.3-151.0)</td>
<td>Chelated: BL 4215 µg/l; FU 2659 µg/l</td>
<td>Chelated: &gt; 226, median not reached</td>
<td>Chelated: 1/18 (5.6%) Non-chelated: 4/18 (22.2%)</td>
</tr>
<tr>
<td>Rose et al. [26] Prospect analysis, chelated (53) vs non-chelated (44)</td>
<td>Patients receiving outpatient transfusions</td>
<td>IPSS low or Int-1</td>
<td>36 (6≥ 113)</td>
<td>Chelated: BL&lt;sup&gt;b&lt;/sup&gt; mean 1491 µg/l; FU mean 2790 µg/l</td>
<td>Chelated: 124 Non-chelated: 53</td>
<td>Chelated: 9/53 (17%) Non-chelated: 15/44 (34%) P = .087</td>
</tr>
<tr>
<td>Raptis et al. [24] Retro chart review, chelated (32) vs non-chelated (46)</td>
<td>Chelation eligible: ≥ 2 ferritin measurements &gt; 1000 µg/l or ≥ 20 units transfused</td>
<td>IPSS low or Int-1: 19% ↑risk; 16% unknown risk; 5% other anemia</td>
<td>Mean 1.2 y</td>
<td>Chelated: BL mean 2031 µg/l; FU mean 1949 µg/l</td>
<td>Chelated: 8.7 y&lt;sup&gt;d&lt;/sup&gt;</td>
<td>NA</td>
</tr>
</tbody>
</table>

<sup>a</sup> Median ferritin values in µg/l at baseline (BL) and follow-up (FU) for Leitch et al. [20] and Rose et al. [26].

<sup>b</sup> Mean ferritin values in µg/l at baseline (BL) and follow-up (FU) for Raptis et al. [24].

<sup>c</sup> Mean chelation duration in years (y) for Raptis et al. [24].

<sup>d</sup> Median survival outcomes in months (mo) for Leitch et al. [20] and Rose et al. [26].

<sup>e</sup> Unadjusted risk ratio for leukemic transformation for Leitch et al. [20] and Rose et al. [26].
**Table 1 continued……………….**

<table>
<thead>
<tr>
<th>Study</th>
<th>Methodology</th>
<th>Iron overload: ferritin ≥ 1000 µg/l or multiple prior transfusions and ferritin ≥ 500 µg/l</th>
<th>IPSS low to high; 83% ↓risk</th>
<th>Mean &gt; 28</th>
<th>Chelated: BL mean 2400 µg/l</th>
<th>Non-chelated: BL mean 980 µg/l</th>
<th>Chelated: 75(^a)</th>
<th>Non-chelated: 49(^a)</th>
<th>P = .002</th>
<th>IPSS ↓risk, P = .008</th>
<th>No difference between groups</th>
<th>P = .73</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neukirchen et al. [23]</td>
<td>Retro matched pair analysis, chelated (94) vs non-chelated (94)</td>
<td>Iron overload: ferritin ≥ 1000 µg/l or multiple prior transfusions and ferritin ≥ 500 µg/l</td>
<td>IPSS low to high; 83% ↓risk</td>
<td>Mean &gt; 28</td>
<td>Chelated: BL mean 2400 µg/l</td>
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<td>Chelated: 75(^a)</td>
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<td>No difference between groups</td>
<td>P = .73</td>
</tr>
<tr>
<td>Leitch et al. [21]</td>
<td>Retro chart review, chelated non-RARS (19) and RARS (19) vs non-chelated non-RARS (79) and RARS (22)</td>
<td>Iron overload: ferritin ≥ 1000 µg/l or multiple prior transfusions and ferritin ≥ 500 µg/l</td>
<td>IPSS low or Int-1</td>
<td>Non-RARS: 12 RARS: 19</td>
<td>Non-RARS</td>
<td>Chelated: BL 397 µg/l; FU 2208 µg/l</td>
<td>Non-chelated: BL 337 µg/l; FU 1394 µg/l</td>
<td>Chelated: not reached</td>
<td>Non-chelated: 44 RARS</td>
<td>Chelated: 134.4</td>
<td>Non-chelated: 99</td>
<td>P&lt; .001</td>
</tr>
<tr>
<td>Komrokji et al. [19]</td>
<td>Retro database review, chelated (45) vs non-chelated (52)</td>
<td>Ferritin ≥ 1000 µg/l</td>
<td>IPSS low or Int-1</td>
<td>NA</td>
<td>Chelated: BL 2680 µg/l</td>
<td>Non-chelated: BL 3038 µg/l</td>
<td>Chelated: 59</td>
<td>Non-chelated: 33.7</td>
<td>P = .013</td>
<td>Chelated: 15.6%</td>
<td>Non-chelated: 21.1%</td>
<td>P = .33</td>
</tr>
</tbody>
</table>
Table 1 Continued

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Baseline Lab</th>
<th>2-y Analysis</th>
<th>Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zeidan et al. [27]</td>
<td>Serum ferritin ≥ 1000 μg/l and/or ≥ 20 packed RBC units and/or ≥ 6 units every 12 wk</td>
<td>18.7 (0.03-146.5) at 4-y analysis</td>
<td>Chelated: 2-y analysis (median)</td>
</tr>
<tr>
<td>Retro Medicare claims database study, chelated (544) vs non-chelated (3682)</td>
<td>GL 1500 μg/l</td>
<td>Chelated: 4-y: FU 1229 μg/l</td>
<td>Chelated: 99.3</td>
</tr>
<tr>
<td>hold transfusions (16%) risk/del5q; 5% ↑risk; 79% MDS NS</td>
<td></td>
<td>Non-chelated: BL 1353 μg/l</td>
<td>Non-chelated: 52.2*</td>
</tr>
<tr>
<td>20.5 wk (mean 29.2 wk)</td>
<td></td>
<td>Non-chelated: 4-y: FU 1963 μg/l</td>
<td>Non-chelated: 4-y analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chelated: 86.8</td>
<td>Chelated ≥ 6 mo: 48.7*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-chelated: ≥ 6 mo: 108.5</td>
<td>Non-chelated: 48.7*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 6 mo: 104.4*</td>
<td>≥ 6 mo: 77.0*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-chelated: 52.2*</td>
<td>Non-chelated: 45.6*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-y analysis (median)</td>
<td>*P &lt; .001</td>
</tr>
<tr>
<td>Lyons et al. [22,28]</td>
<td>Serum ferritin ≥ 1000 μg/l and/or ≥ 20 packed RBC units and/or ≥ 6 units every 12 wk</td>
<td>2-y analysis</td>
<td>Chelated: 2-y analysis (median)</td>
</tr>
<tr>
<td>Prospect non-intervent registry, chelated (269) and non-chelated (330) (n= 4-y analysis)</td>
<td></td>
<td>Chelated: 4-y: FU 1229 μg/l</td>
<td>Chelated: 99.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-chelated: BL 1353 μg/l</td>
<td>Non-chelated: 52.2*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-chelated: 4-y: FU 1963 μg/l</td>
<td>Non-chelated: 4-y analysis</td>
</tr>
</tbody>
</table>

a: Unless otherwise specified, b: At initiation of chelation therapy and averaged for entire population (chelated and non-chelated), c: Baseline denotes first lab result after becoming chelation eligible; FU denotes first lab result after starting chelation, d: Median for all IPSS risk groups, MDS: myelodysplastic syndromes; Retro: retrospective; RBC: red blood cells; IPSS: International Prognostic Scoring System; Int-1: intermediate-1 of the IPSS; BL: baseline; FU: follow-up; Prospect: prospective; ↑: higher risk; NA: not assessed; ↓: lower risk; RARS: refractory anemia with ring sideroblasts; NR: not reported; NS: not otherwise specified; HR: hazard ratio; Intervent: interventional; Observ: observational
2.1 Heterogeneity of Chelation Studies

Patient selection criteria determine baseline disease severity and level and duration of iron overload. In the present studies [19-28], differences in patient selection criteria resulted in baseline ferritin levels ranging from 397 to 4215 µg/l, with no information on how long patients had been exposed to high levels of circulating iron, making it difficult to attribute outcomes to iron toxicity. In the majority of studies [19-22,25-28], the population was restricted to IPSS low- or intermediate-1-risk patients. In 3 studies, however, the population included higher-risk patients or was not stratified by risk category [23,24,27]. Among the patients eligible for chelation therapy in the study by Raptis et al. [24], 19% were IPSS higher-risk patients, 16% were of unknown risk status and 5% had other anemia (aplastic or Diamond-Blackfan anemia). In the study by Neukirchen et al. [23], 83% of patients had lower-risk MDS; the remaining 17% had higher-risk disease. Similarly, Zeidan et al. [27] enrolled chelation-eligible patients from a Medicare claims database, the majority of whom were not stratified by risk categories; 16% were lower risk, 5% were higher risk and 79% were classified MDS “not otherwise specified.”

Few of the available studies reported baseline comorbidities, precluding any systematic analysis of those conditions. Rose et al. [26] reported iron-overload–related comorbid conditions (cardiac disorders, diabetes mellitus, liver cirrhosis) in 30% of chelated and 21% of non-chelated patients, and non-iron-overload–related comorbid conditions in 38% of chelated and 55% of non-chelated patients. Neukirchen et al. [23] and Lyons et al. [22,28] reported the opposite trend in baseline comorbid conditions, with non-chelated patients having a higher percentage of iron-overload–related comorbid conditions (cardiac and vascular disorders) at baseline. Inconsistencies in these data confirm the difficulty in demonstrating the effects of iron toxicity in patients with MDS owing to the high frequency of age-related comorbidities across treatment groups.

Differences in baseline treatment history also contribute to the heterogeneity among the patients with MDS studied. In all, 71% of patients in the study by Leitch et al. [20] received supportive care, whereas 29% of patients received some other type of therapy, including chemotherapy, stem cell transplant, immunomodulators and erythroid-stimulating agents/granulocyte-colony stimulating factor. In the study by Rose et al. [26], 50% of non-chelated patients and 67% of chelated patients received erythroid-stimulating agents, with 1 non-chelated and 8 chelated patients receiving thalidomide. Similarly, 74% of RARS and 68% of non-RARS patients received only supportive care in the study by Leitch et al. [21], with the remaining patients receiving other MDS therapies, including erythroid-stimulating agents, immunomodulators, chemotherapy or lenalidomide.

Although the length of iron chelation therapy was reported in some of the studies [20-24,26-28], mean/median dosage of iron chelator was not reported, making it difficult to determine the adequacy of chelation therapy. Of the studies reporting baseline and follow-up serum ferritin levels, 3 [20,22,24,28] showed reductions or stabilization in serum ferritin and 2 [21,26] showed increases in serum ferritin in chelated patients. These trends suggest adequate chelation intensity in a subset of studies and weak chelation in others. However, there was no systematic attempt to calculate required chelation intensity based on the rate of iron intake in these studies, further increasing heterogeneity in the data. Despite these differences, the studies showed a consistent pattern of improved outcomes in chelated versus non-chelated patients.
2.2 Survival Outcomes

A survival advantage associated with chelation therapy was first reported by Leitch et al. [20] in a retrospective matched-pair analysis of patients with lower-risk MDS. Although this was a small study (n=18 chelated patients) with some baseline differences between chelated and non-chelated groups that could have affected the outcome, survival was significantly longer in chelated versus non-chelated patients (median, >226 vs 40 months, respectively; \( P=0.003 \)). Similarly, fewer patients in the chelated group progressed to AML (n=1/18 vs 4/18, respectively).

Rose et al. [26] conducted a larger study in France that compared chelated (n=53) versus non-chelated (n=44) patients with lower-risk MDS. Baseline patient characteristics in this study were established retrospectively; however, patients were prospectively evaluated 2.5 years after enrollment. In all, 71% of patients had comorbid conditions, with a mean of 1.7 comorbidities and no significant difference in the number of comorbidities between groups. Overall survival was significantly longer in chelated versus non-chelated patients (median, 124 vs 53 months, respectively; \( P<0.001 \); Fig. 1). “Adequate chelation” was significantly associated with longer survival, as was lower transfusion requirement and lower IPSS risk status Fig.1 and Table 2. Adequate chelation was defined arbitrarily as continuous subcutaneous deferoxamine (40 mg/kg/day over 8-12 hours for at least 3 days per week), deferiprone 30-75 mg/kg/day and deferasirox 20-30 mg/kg/day, and lesser dosages were defined as “weak chelation.” There was a trend toward fewer AML transformations in the chelated versus non-chelated patients (n=9/53 vs 15/44, respectively).

Table 2. Prognostic factor analysis in patients with lower-risk MDS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>( P ) value</th>
<th>Hazard ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate chelation(^a)</td>
<td>.0003</td>
<td>0.302</td>
<td>0.16-0.58</td>
</tr>
<tr>
<td>Transfusion requirement</td>
<td>.0028</td>
<td>2.516</td>
<td>1.37-4.61</td>
</tr>
<tr>
<td>&gt;3 PRBC units/mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPSS&gt; 0</td>
<td>.0420</td>
<td>1.929</td>
<td>1.02-3.63</td>
</tr>
<tr>
<td>Age&gt;72 y</td>
<td>.2004</td>
<td>0.678</td>
<td>0.37-1.23</td>
</tr>
<tr>
<td>Comorbidities&gt;3</td>
<td>.5270</td>
<td>1.288</td>
<td>0.59-2.83</td>
</tr>
</tbody>
</table>

\(^a\): Adequate chelation was defined as continuous subcutaneous deferoxamine (40 mg/kg/day over 8-12 hours for at least 3 days/wk), deferiprone 30-75 mg/kg/day or deferasirox 20-30 mg/kg/day; MDS: myelodysplastic syndromes; PRBC: packed red blood cells; IPSS: International Prognostic Scoring System. Adapted with permission from Elsevier [26]
Fig. 1. Overall survival in lower-risk MDS patients by chelation status (a) and intensity (b)

Adequate chelation defined in Table 2, MDS: myelodysplastic syndromes, Reprinted with permission from Elsevier [26]
In a retrospective review of patient records from academic and community oncology practices, outcomes were compared between chelated and non-chelated patients with lower-risk and higher-risk MDS (N=128) [24]. A significant survival advantage was observed for chelated versus non-chelated patients in this large study population (median, 8.7 vs 4.7 years; \(P=0.02\)), irrespective of MDS risk level. There was a trend for longer overall survival in chelated versus non-chelated patients with lower-risk MDS; however, this did not reach statistical significance. Leukemic transformation rates were not evaluated.

Neukirchen et al. [23] performed a retrospective matched pair analysis in chelated (n=94) versus non-chelated (n= 94) patients with MDS. Patients in this study had IPSS low- to high-risk disease (83% lower risk). Overall survival was significantly longer in the chelated group for the overall study population (median, 75 vs 49 months; \(P=.002\)), which included higher-risk patients. When restricted to patients with lower-risk MDS, the survival advantage for chelated patients remained significant (\(P=0.008\)). No difference in leukemia transformation rates was observed between groups.

A retrospective chart review compared outcomes in transfusion-dependent patients with lower-risk MDS, stratifying patients as RARS and non-RARS and by chelation status [21]. The chelated group included 19 non-RARS and 19 RARS patients, and the non-chelated group included 79 non-RARS and 22 RARS patients. Overall survival was significantly longer in the chelated groups of both RARS (median, 134.4 vs 99 months; \(P<0.001\)) and non-RARS (median, not reached vs 44 months; \(P<0.001\)) patients, respectively. Leukemic transformation rates were not assessed.

The survival advantage observed in chelated patients in these published studies is further supported by preliminary results of other studies published in abstract form. Komrokji et al. [19] performed a retrospective database analysis in patients with lower-risk MDS wherein overall survival was significantly longer in the chelated group compared with the non-chelated group (median, 59 vs 34 months, respectively; \(P=0.013\)). Fewer patients in the chelated group had conversion to AML compared with non-chelated patients (15.6% vs 21.1%, respectively). Similarly, a retrospective observational study in patients with lower-risk MDS found overall survival was significantly longer in chelated (n=109) versus non-chelated (n=116) patients (median, 133 vs 105 months, respectively; \(P=.009\)) [25]. However, the median time to leukemia transformation was not reached in either group. Based on a retrospective Medicare claims analysis of patients with MDS who had received ≥ 20 blood transfusions, Zeidan et al. [27] reported that, relative to non-chelated patients, risk of death was reduced by 23% in patients who received 14-26 weeks of chelation therapy and by 66% in patients who received ≥53 weeks of chelation therapy. However, one of the limitations of this study was that risk was not stratified by IPSS criteria in the majority of patients.

Data are available from the largest prospective, non-interventional, observational registry to date for patients with lower-risk MDS [22,28]. At the 2-year interim analysis, overall survival was significantly longer in patients who had received chelation therapy for ≥ 6 months versus non-chelated patients (median, 104 vs 52 months, respectively; \(P<.001\); Fig. 2a) [28]. Time to AML transformation was longer in patients who had received chelation therapy for ≥ 6 months versus non-chelated patients at the 2-year analysis, although the difference was not statistically significant Fig. 2b [28]. Preliminary 4-year results from the registry study suggest similar findings [22]. Overall survival remained significantly longer in patients receiving chelation therapy for ≥ 6 months versus non-chelated patients (median, 102.5 vs 48.7 months, respectively; \(P<.001\)). The chelated ≥ 6-months group had significantly fewer deaths than the non-chelated group (52.0% vs 69.7%, respectively; \(P<.001\)), with no
significant difference in the cause of death. The difference in time to AML transformation was statistically significant at the 4-year analysis between patients receiving chelation therapy for ≥6 months versus non-chelated patients (mean, 77.0 vs 45.6 months, respectively; \( P < .001 \)).

Fig. 2. Overall survival (a) and time to AML transformation (b) in lower-risk MDS patients by chelation status and duration

AML: acute myeloid leukemia; MDS: myelodysplastic syndromes, Reprinted with permission from Elsevier [28]
Given the retrospective nature of chelation studies in lower-risk MDS patients, the results must be considered as only hypothesis-generating. Nevertheless, each study shows a survival advantage in chelated patients, regardless of the inclusion of those with higher-risk disease. In those studies performing covariate analyses, chelation therapy was shown to be independently associated with longer survival [20,26]. It remains unclear whether a benefit exists from actually lowering iron stores in total or in a compartment, and an unidentified benefit of the chelation agents other than iron reduction cannot be excluded. Thus, the possible mechanisms of benefit from iron chelation need further research.

3. CAUSE OF DEATH IN CHELATED PATIENTS WITH MDS

When examining cause of death in chelated versus non-chelated patient groups, intriguing trends in the data can be observed Table 3. Among the 5 studies reporting cause of death, cardiac causes appeared higher among chelated patients in 3 studies [20,21,26], whereas another study [28] showed no appreciable difference. Similarly, fatal infections appeared higher among chelated patients in 3 of the 5 studies [20,23,26], with 2 studies [21,28] showing the opposite trend. The cause of death that was apparently more frequent in non-chelated patients included MDS/AML in 3 of the 5 studies [20,21,26] and bleeding in 4 studies [20,21,23,26]. Although it is tempting to assign meaning to these trends, they are likely most useful for the research questions they pose. A multivariate analysis in a well-controlled trial will be needed to account for confounding factors before differences in cause of death can be associated with chelation-therapy status. Elucidation of mechanisms underlying the potential survival benefit from chelation therapy may help explain the apparent trends in cause of death among transfusion-dependent patients with MDS.

4. FUTURE DIRECTIONS

Survival outcomes in these studies are consistent, which suggests that intervention to reduce iron burden in patients with MDS may improve outcomes. Prospective studies have shown this to be the case in thalassemia, where patients begin transfusions at a young age and, if left untreated, suffer the adverse effects of iron overload. The comorbidity burden in the older patient population with MDS, however, creates a more complex situation, making careful patient selection in clinical trials of paramount importance. Owing to differences in patient selection criteria and baseline comorbidities, it is difficult to know the relative contribution of age-related comorbid conditions and iron overload to mortality in these patients. At present, the role of iron toxicity in MDS is unknown.

Attempts have been made to identify additional risk factors in lower-risk MDS patients. Investigators at MD Anderson Cancer Center developed a prognostic model for lower-risk MDS that further stratifies patients into low-, intermediate- and high-risk categories based on cytogenetics, age, severity of cytopenias and bone marrow blast percentage [8]. This lower-risk MDS model is meant to identify those patients classified as lower risk by IPSS who are at risk for a poor outcome relative to other lower-risk patients. This model may prove useful in identifying patients who are candidates for clinical trials or stem cell transplantation.

The prognostic impact of point mutations in patients with MDS has also been studied. Mutations in 5 genes (TP53, EZH2, ETV6, RUNX1, ASXL1) were shown to be independently associated with decreased overall survival [10]. One or more of these mutations was present in 31% of patients, which may help explain the clinical heterogeneity of MDS, including those patients with lower-risk disease. To further explore the impact of mutations associated with
poorer prognosis in patients with lower-risk MDS, Bejar et al. [11] calculated prognosis using the lower-risk MDS model and determined the mutation status of 22 genes in a cohort of 288 patients. In multivariable analysis that included lower-risk MDS model categories and other mutations, only EZH2 mutations retained prognostic significance. The combination of the lower-risk MDS prognostic model and the presence of EZH2 mutations were shown to identify approximately 29% of patients with lower-risk MDS who had a poorer prognosis. A more recent analysis of mutations in patients with MDS showed that the number of mutations present provided prognostic information above that determined by the IPSS, but did not substantially improve on the prognostic information provided by a model incorporating clinical variables [29]. Four of the most commonly mutated genes (ASXL1, SRSF2, RUNX1 TP53) were associated with worse outcomes, and the mutated gene SF3B1 was associated with better prognosis. Unique patterns of subsequent mutation were associated with primary RNA splicing gene mutations, and those associated with poor outcomes had a negative impact regardless of their presence in either major or minor clones. These results suggest that longitudinal genetic characterization in MDS may improve on current prognostic models, providing more objective patient selection criteria for clinical trials and potentially informing treatment decisions.

Hematologic response to iron chelation therapy may also be a factor in patient outcomes. Studies suggest that iron chelation may improve hematologic parameters in a large subset of patients. The Gimema Trial showed reduced transfusion requirement over the study and achievement of transfusion independence in 32% (22/68) of patients who completed 1 year of chelation therapy [30]. Similarly, Gattermann et al. reported erythroid, platelet and neutrophil improvements in 21.5%, 13.0% and 22.0% of patients receiving >100 days of chelation therapy [31], and List et al. reported erythroid, platelet and neutrophil improvements in 15%, 22% and 15% of chelated patients, respectively [32]. Both Gattermann et al. and List et al. observed greater serum ferritin reduction in patients who had hematologic improvement. A smaller study in Italy showed that 29% of patients had reduced transfusion requirement following chelation therapy [33]. Erythroid responses in the Italian study were observed after serum ferritin reductions of approximately 40% from baseline levels. The consistent association between reduced serum ferritin and hematologic improvement suggests that iron toxicity may be contributing to cytopenias in patients with MDS. However, labile plasma iron levels were not different between patients with and without hematologic responses in studies measuring labile plasma iron [31,32]. At present, the potential contribution of hematologic improvement to differences in survival outcomes between chelated and non-chelated patients is unknown.

A prospective, systematic evaluation to stratify patients by disease severity, comorbidity burden and additional clinical and genetic prognostic factors will be necessary to determine if iron chelation therapy provides an independent benefit. Among these factors, organ iron load determined by magnetic resonance imaging may help identify at-risk patients as physicians gain experience with iron imaging techniques. Additional research questions also need to be addressed, including the contribution of iron toxicity to ineffective erythropoiesis and tumorigenesis in MDS. This information may be useful in redefining optimal circulating iron levels.
Table 3. Cause of death in MDS chelation trials reporting these outcomes

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<td>Infection</td>
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*a: Cumulative percentage of deaths may exceed 100% due to rounding, b: MDS/AML combined, MDS: myelodysplastic syndromes; RARS: refractory anemia with ring sideroblasts; AML: acute myeloid leukemia
Results from the TELESTO trial (ClinicalTrials.gov, NCT00940602) [34] may answer some of these outstanding research questions and guide the use of iron chelation in patients with MDS. TELESTO is an ongoing phase 3, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of deferasirox in patients with MDS. Eligible patients are ≥18 years old with IPSS low- or Int-1-risk MDS, serum ferritin >1000µg/l and a history of ≥15 transfusions with ongoing transfusion need. Outcome measures include a composite of event-free survival (combined death and non-fatal cardiac and liver function events), overall survival, endocrine function, glucose metabolism, MDS progression and hematologic function/transfusion requirement. However, the study does not include a crossover arm, which limits patient availability to therapy and precludes the opportunity to show benefit in placebo-treated patients who may have developed comorbid conditions or experienced worsening of comorbidities during the study. Depending on the rigor of the outcome measures, results from TELESTO may explain the contribution of iron toxicity to mortality in lower-risk MDS patients. Results of this trial are anticipated as early as 2018.

4.1 New Therapeutic Targets

Advances in the understanding of iron metabolism over the past decade have identified new therapeutic targets in iron dysregulation. Ferroportin and hepcidin are among several key proteins involved in iron metabolism. Ferroportin is a transmembrane protein that transports iron out of cells and into the circulation. Hepcidin binds to ferroportin and targets the protein for destruction [35]. This mechanism is an important discovery for potential treatments in both iron-deficient anemia and the iron overload associated with transfusion-dependent anemia [36].

Synthetic hepcidins are currently being studied in preclinical models. Results to date have shown reduced serum iron concentration and prevention of iron overload [35]. In thalassemic mice, genetic silencing of hepcidin inhibition reduced iron overload and improved erythropoiesis [36]. Theoretically, increased hepcidin action could also help reverse iron overload by trapping iron in the mucosal epithelium, where it is continuously lost through sloughing [35]. The clinical utility of hepcidin modulation has yet to be demonstrated in humans.

5. CONCLUSIONS

Currently, the evidence to suggest a survival benefit associated with chelation therapy in lower-risk patients with MDS comes from retrospective and observational studies. Collectively, these studies show a consistent survival advantage and a trend toward increased leukemia-free survival in chelated patients compared with non-chelated patients. Long-term outcomes in these patients deserve further study, especially with regard to the relative contribution of iron overload and age-related comorbidities to decreased survival in this older population. The only randomized, controlled trial of iron chelation therapy in patients with lower-risk MDS is currently underway, with results expected in 2018, at the earliest. An understanding of the potential role of iron toxicity in MDS outcomes may help refine treatment strategies with existing therapies and guide the appropriate use of those in development.
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CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

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REFERENCES


