Survival outcomes in iron chelated and non-chelated patients with lower-risk myelodysplastic syndromes: Review and pooled analysis of observational studies

1. Iron overload in patients with myelodysplastic syndromes

From 60% to over 90% of patients with myelodysplastic syndromes (MDS) develop anemia, of which up to 60% may present hemoglobin levels (Hb) <10 g/dL [1–4]. Most patients will require red blood cell transfusions to correct low Hb concentrations, prevent anemia-related comorbidity, preserve physical performance, and enhance quality of life [5–7]. Especially for the 40% of patients for whom RBC transfusions are the only therapeutic option, the benefits of transfusions are impaired by the complications from iron overload, the increased risk of disease progression, especially to acute myelogenous leukemia, and shorter overall survival (OS) [8–12].

One unit of blood contains between 100 and 250 mg of iron [13]. After 10–20 transfusions MDS patients develop iron overload at an estimated rate of 0.5 mg/kg/day [10]. In turn, this may cause organ damage to especially the heart, liver, and the endocrine glands [7,14]. Mortality hazard rates rise by 30% for each increase in serum ferritin concentrations of 500 μg/L above 1000 μg/L [8].

Guidelines recommend iron chelation therapy (ICT) to manage iron overload in transfusion-dependent lower-risk MDS patients, especially those with sustained elevated serum ferritin levels or high transfusion needs [2,15–18]. The rationale for ICT in transfusion-dependent MDS patients is compelling but has not been evaluated in prospective randomized trials [19]. The ongoing TELESTO study (NCT00940602), a multicenter, double-blinded randomized controlled trial (RCT) of deferasirox versus placebo in the management of transfusional iron overload in lower-risk MDS patients, is estimated to complete data collection for the primary outcome in early 2018.

In the interim, the empirical evidence in support of ICT in transfusion-dependent MDS patients has come from observational studies. In this issue of Leukemia Research, Lyons and colleagues [20] present 5-year data from their prospective registry of transfusion iron overload in MDS patients, i.e., those lower-risk patients with an International Prognostic Scoring System (IPSS) score of Low or Intermediate-1 risk. This brings to seven the number of observational studies on ICT in lower-risk patients [6,20,21,22–24,25], three of which were published in this Journal [6,20,23] – not counting reports on intermediate analyses for three studies [5,26,27].

Awaiting the findings of the TELESTO trial, but also considering the difficulties in patient recruitment in this trial and the potential impact on statistical power [19], this is an opportune time to evaluate what has been learned from these seven observational studies about the OS benefit of ICT in lower-risk MDS patients. Here, we review these studies in terms of design, chelation agents studied, total and stratified sample sizes, and total and stratified OS results. We also extend a meta-analysis by Mainous et al. [28] of observational studies up to 2014. This meta-analysis, published as Correspondence and therefore rather succinct in methodological detail, included three reports of intermediate analyses [5,25,26]. As we could not replicate this meta-analysis due to missing information in the publication [28], we calculated the pooled OS effect estimate for the seven studies using an approach for combining median survival estimates proposed by Simes [29].

2. Methods

2.1. Study selection

Eligible studies were retrospective or prospective observational studies; evaluating at least 1 of 3 chelating agents (deferoxamine; deferasirox; deferasprone); assessing lower-risk (IPSS low or intermediate-1) MDS patients; some of whom received ICT while others did not; reporting sample sizes for both cohorts; and reporting median OS in either months or years. For those studies for which intermediate results were reported, we used the data from the most recent report. Studies including patients with higher IPSS risk level were eligible if they provided carve-out data for lower-risk patients in both the ICT and non-ICT sub-cohorts.

2.2. Data sources

Relevant studies were identified by searching PubMed, EMBASE, and Cochrane Database of Systematic Reviews up to 7 February 2017. In addition, we used our (I.A., K.M., S.Y., A.M.) familiarity with the literature and reviewed the reference lists of retrieved articles. Two reviewers (I.A., K.M.) independently extracted data with a piloted extraction form. Any disagreements were resolved by consensus or escalated to two adjudicators (S.Y, A.M.).
2.3. Data extraction

The following data were extracted from individual study reports: year of publication; study design (retrospective vs. prospective, with duration in months for the latter); ICT agents investigated; sample sizes (total, ICT, non-ICT); and median OS (in, or converted to, months). As available, we also extracted sample size and OS data from stratified analyses (ICT treatment for ≥6 months, chelation quality [adequate versus weak], and IPSS risk status). Where the Kaplan-Meier results of individual studies revealed that the median OS was not reached, we used the last month count in the analysis.

3. Review of studies

As shown in Table 1, two studies were prospective while the remaining had a retrospective design. All studies included defer-oxamine as (one of the) agents, 6 also investigated deferasirox, and 2 also evaluated deferiprone. Sample sizes used in the analyses ranged from 36 to 599, with the proportion of ICT-treated patients in each study varying from 41.0% to 63.0%. Three studies included sub-analyses for patients receiving ICT for ≥6 months, two studies differentiated between weakly and adequately-chelated patients, and one study presented stratified data for IPSS low-risk and IPSS intermediate-1 risk patients (Table 2).

All but one study reported statistically significant better median OS rates for ICT-treated patients compared to patients in the non-ICT cohort (Table 2). Chelating patients longer (≥6 m) and/or adequately was also associated with better OS outcomes, but these were not markedly different from ICT in general (a selection bias cannot be excluded). The one study comparing low with intermediate-1 risk patients showed that both groups benefitted from ICT but with longer OS for low-risk patients.

4. Pooled analysis evaluating the overall survival benefit of ICT

4.1. Statistical analysis

In their meta-analysis report, Mainous et al. [28] did not specify how they converted the median overall survival data for patients treated with and those not treated with ICT for each study into odds ratios, associated 95% confidence intervals, and p levels; only that their analyses used a random-effects model and that weights for each study were based on the study’s inverse variance. We could not replicate their analyses and therefore adapted an approach for combining median survival estimates described by Simes [29]. We present this with some algebraic detail to enable independent verification.

We calculated the pooled estimate $R_{\text{survival}}$ of the ratio of the median survival of the ICT-treated patients ($\text{Mdn}_{\text{ICT}}$) and the non-ICT-treated patients ($\text{Mdn}_{\text{nonICT}}$) and its 95% CI. In this, $R_{\text{survival}}$ is defined as the weighted sum of the log-ratio of the median survival estimates for the ICT and non-ICT groups. It can be interpreted as the odds ratio quantifying the relative median survival effect of treating versus not treating patients with ICT.

Specifically, defining the median survival log ratio for the $i$th study as $r_i = \ln(\text{Mdn}_{\text{ICT}})_{ij}/\text{Mdn}_{\text{nonICT}}(i,j)$ and the relative weight for the $i$th study as $w_i = 1/n_{1ij} + 1/n_{2ij}$, then the median survival log ratio estimates $R$ for a set of $k$ studies can be specified as the ratio of the weighted sum of the $k$ estimates of $r_i$ over the sum of the $k$ weights $w_i$: $R = \Sigma w_i r_i / \Sigma w_i$. The pooled estimate $R_{\text{survival}}$ is defined as the exponent of $R$, or $R_{\text{survival}} = \exp(R)$. Also following Simes [29], we estimated the 95%CI of $R_{\text{survival}}$ on the
Table 2
Overall survival estimates reported in individual studies.

<table>
<thead>
<tr>
<th>References</th>
<th>Overall survival (in median months)</th>
<th>By chelation quality</th>
<th>IPSS Low risk</th>
<th>IPSS Int-1 risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>nonICT    ICT  p   ICT ≥ 6 m p</td>
<td>adequate weak p Non-ICT ICT p</td>
<td>Non-ICT ICT p</td>
<td></td>
</tr>
<tr>
<td>Leitch et al. [21]</td>
<td>41        226ι   0.01</td>
<td>124 &lt;0.0003 124 &lt;0.0003 124 85 &lt;0.001</td>
<td>70 138 0.015</td>
<td>36 115 0.003</td>
</tr>
<tr>
<td>Raptis et al. [22]</td>
<td>71        113    0.12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rose et al. [23]</td>
<td>53        124    &lt;0.0003 124 &lt;0.0003 124 85 &lt;0.001</td>
<td>70 138 0.015</td>
<td>36 115 0.003</td>
<td></td>
</tr>
<tr>
<td>Komrokji et al. [24]</td>
<td>34        59     0.013</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delforge et al. [6]</td>
<td>37        122    &lt;0.001 126 &lt;0.001 126 52 &lt;0.001</td>
<td>70 138 0.015</td>
<td>36 115 0.003</td>
<td></td>
</tr>
<tr>
<td>Remacha et al. [25]</td>
<td>153       228ι   &lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lyons et al. [20]</td>
<td>48        86     &lt;0.0001 99 &lt;0.0001</td>
<td>70 138 0.015</td>
<td>36 115 0.003</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>48        113    0.013</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

All p values as reported by authors of studies included.
Abbreviations: ι ICT: iron chelation therapy; Int-1: intermediate-1; IPSS: Internation Prognostic Scoring System; m: month.
ι Median OS not reached at 226 months, hence 226 imputed.
ι Median OS not reached at 228 months, hence 228 imputed.

Table 3
Individual study and pooled effect estimates.

<table>
<thead>
<tr>
<th>References</th>
<th>Individual study effect estimates</th>
<th>Median survival log ratio</th>
<th>Weighted rι</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative study weight wι</td>
<td>rι</td>
<td>wι = rι</td>
</tr>
<tr>
<td>Leitch et al. [21]</td>
<td>9.000</td>
<td>1.707</td>
<td>15.363</td>
</tr>
<tr>
<td>Raptis et al. [22]</td>
<td>18.872</td>
<td>0.465</td>
<td>8.775</td>
</tr>
<tr>
<td>Rose et al. [23]</td>
<td>24.041</td>
<td>0.850</td>
<td>20.435</td>
</tr>
<tr>
<td>Komrokji et al. [24]</td>
<td>24.124</td>
<td>0.551</td>
<td>13.292</td>
</tr>
<tr>
<td>Delforge et al. [6]</td>
<td>25.606</td>
<td>1.193</td>
<td>35.320</td>
</tr>
<tr>
<td>Remacha et al. [25]</td>
<td>64.951</td>
<td>0.403</td>
<td>26.175</td>
</tr>
<tr>
<td>Lyons et al. [20]</td>
<td>148.297</td>
<td>0.583</td>
<td>86.457</td>
</tr>
<tr>
<td>Sum</td>
<td>318.891</td>
<td>5.752</td>
<td>205.818</td>
</tr>
</tbody>
</table>

Pooled effect estimates

R  Rsurvival  95%CI
0.645  1.907  1.859–1.956

basis of the critical value per the t-distribution for df=k–1 and α = 0.05, the variance sυ2 of the k estimates of rι, and the sum of all wι; specifically, \( \exp[R_{\text{survival}} \pm (t_{\text{df}, 0.025}/\sqrt{\text{var}(R)})] \) where \( \text{var}(R) = 1/(1-k) \times \bigg( \sum w_i (r_i - R)^2 \bigg) \).

4.2. Pooled effect estimates

Table 3 summarizes for each of the 7 studies the relative weight (wι) of a given study, the median survival log ratio (rι), the weighted median survival log ratio (wι ⋅ rι), as well as the sum of these estimates. From this, the pooled estimates were calculated. The R of 0.646 yielded an overall survival pooled estimate Rsurvival of 1.907 with 95% CI of 1.859–1.956. In a sensitivity analysis, including all lower-risk MDS patients who did not receive ICT in the Leitch et al. study [21] had no material effect on the pooled Rsurvival estimate.

5. Comments

Recognizing the limitations of observational studies, the seven studies on lower-risk MDS point at the therapeutic benefit of ICT in the management of transfusional iron overload in lower-risk MDS patients. While the difference of 32 months in median OS between the ICT and non-ICT cohorts in the Raptis et al. study [22] did not attain statistical significance, the results were in the direction favoring ICT. Collectively, then, the seven observational studies demonstrate a strong association between ICT and OS in lower-risk MDS patients. ICT is associated with an almost two-fold likelihood of improvement in OS (Rsurvival = 1.907), with the narrow 95% CI underscoring the precision of this likelihood estimate. The (unadjusted) difference in median OS is 74 months, indicating that ICT-treated patients tended to live 6.2 years longer than patients not given ICT.

Our results extend, in scope and analytics, those from the Mainous et al. [28] meta-analysis. These authors reported a pooled odds ratio of 1.984, though with a significantly wider 95% CI of 1.583–2.486. The (unadjusted) difference in OS of 61 months or 5.1 years was lower than in our pooled analysis. However, this may be attributable partly to our analysis including the most recent results of three studies [6,20,25] whereas the Mainous et al. [28] analysis was limited to intermediate results for these studies [5,26,27].

Our review also offers some insights into ICT practice patterns. Across studies, about half of the lower-risk MDS patients with transfusional overload received ICT whereas about half did not. This may reflect clinician reluctance, especially in the absence ofRCT efficacy data, to treat such patients routinely with ICT. It may also suggest patient-specific clinical decision-making. Further, there is evidence that patients may benefit from ICT administered over longer (≥6 m) periods of time. Though more research is needed, the Rose et al. [23] and Delforge et al. [6] studies underscore the importance of adequate chelation (i.e., slow subcutaneous deferoxamine infusions administered on multiple days per week or deferasirox at any dose). Weak chelation (i.e., deferoxamine by any other method of administration) was associated with an OS similar to non-chelated patients.

As our review was focused specifically on lower-risk MDS patients and hence required studies to either include only such patients or report subgroup analyses, we did not include two studies that bear significant relevance to the issue of iron chelation therapy. The EPIC study [30] included 341 MDS patients among...
the 1744 patients with transfusion-dependent anemias, but did not report the risk status of these MDS patients. Similarly, an analysis of 94 MDS patients receiving ICT matched to patients not treated with ICT included 17 ICT-treated patients with an IPSS Intermediate-2 or High score [31]. Even though the paper reports a statistically significant difference in median survival between lower-risk chelated and non-chelated patients (p = 0.008), no actual survival data are reported and such data should not be calculated reliably from the survival curves included.

In conclusion, while we await the results of the TELESTO trial, the seven observational studies published to date provide non-randomized, non-controlled, and non-blinded (and thus lower-grade) evidence of the OS outcomes associated with iron chelation pharmacotherapy in lower-risk MDS patients treated in routine clinical practice under conditions of significant heterogeneity in patients, clinicians, treatments, and settings. Despite the reported accrual challenges [19] the TELESTO trial should provide double-blind, placebo-controlled, randomized (and thus higher-grade) evidence of the pharmacological benefit of deferasirox under more homogeneous conditions relative to patients, clinicians, treatment protocols, and settings. Together, this evidence should provide clinicians with guidance as to the pharmacological efficacy and pharmacotherapeutic effectiveness of ICT in lower-risk MDS patients.

Disclosures

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Author contributions

I.A. and K.M. conceived the review and pooled analysis reported here.
I.A. and K.M. conducted the search, extracted the data, and compiled the data for the review.
I.A., M.A.Y., S.Y., and N.V., designed the pooled analysis.
I.A. and M.A.Y. performed the pooled analyses, which were verified by S.Y., H.K., and N.V.
I.A. and S.Y. drafted the manuscript, which was reviewed by M.A.Y., H.K., N.V., A.M., and K.M.

All authors reviewed the manuscript for scientific content.

References

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