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ORIGINAL ARTICLE

Systematic review and meta-analysis of the effect of iron chelation therapy on overall survival and disease progression in patients with lower-risk myelodysplastic syndromes

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Abstract

The impact of iron chelation therapy (ICT) on overall survival (OS) and progression to acute myeloid leukemia (AML) in patients with iron overload and International Prognostic Scoring System low- or intermediate-risk myelodysplastic syndromes (MDS) is not well understood. We conducted a systematic review and meta-analysis of published studies of ICT in patients with MDS to better elucidate these relationships. We searched PubMed, EMBASE, Cochrane databases, and the World Health Organization Clinical Trial Registry for studies reporting the impact of ICT on OS in patients with low- or intermediate-risk MDS. Studies were examined for demographics, effect measures, and potential bias risk. Fixed and random-effects models were used to calculate adjusted OS and adjusted hazards ratio (aHR) estimates, respectively, among the different studies. Nine observational studies (four prospective and five retrospective) were identified. For patients with MDS, ICT was associated with an overall lower risk of mortality compared with no ICT (aHR 0.42; 95% confidence interval (CI) 0.28–0.62; $P < 0.01$); however, there was significant heterogeneity across the studies. In studies reporting progression to AML, ICT was not associated with decreased risk of progression (odds ratio 0.68; 95% CI 0.31–1.43; $P < 0.030$). This systematic review and meta-analysis of nine nonrandomized trials demonstrated significant reduction in risk of mortality in patients with iron overload and low- or intermediate-risk MDS treated with ICT; however, a causal relationship cannot be established. Randomized, controlled trials are needed to more definitively evaluate the relationship between ICT and survival in patients with iron overload and low- or intermediate-risk MDS.

Keywords Iron chelation therapy · Iron overload · Myelodysplastic syndromes · Acute myeloid leukemia · Survival

Introduction

Myelodysplastic syndromes (MDS) comprise a clinically and biologically heterogeneous group of hematopoietic stem cell malignancies characterized by ineffective hematopoiesis and abnormalities in proliferation, differentiation, and apoptosis [1–4]. These disorders also confer an increased risk of cell transformation to acute myeloid leukemia (AML) [5]. The incidence of MDS has been reported to be approximately three to four cases per 100,000 people each year, with a higher incidence in men than women, and the highest incidence among those over 80 years of age (approximately 35 cases per 100,000/year); however, many believe that this is an underestimate due to underreporting [6, 7].

Chronic anemia is a frequent occurrence in MDS, with many patients requiring regular red blood cell (RBC) transfusions. While the immediate benefit of these transfusions in improving symptoms of anemia and quality of life is apparent, dependence on transfusions is a negative prognostic factor for survival [8, 9]. This could be due to the association between disease severity and the number of transfusions required, but may also be related to complications associated with transfusions such as delayed hemolytic transfusion reactions, febrile reactions, allergic reactions, allo-immunization, transfusion-related acute lung injury, and transfusion-related iron overload and its subsequent complications. Excess iron can lead to

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accumulation of iron in the liver, lung, kidney, heart, pancreas, and endocrine glands, resulting in oxidative stress and disruption of heme synthesis, Fe-S clusters of some enzymes, and ultimately end-organ damage [7, 8, 10–13].

Iron overload in MDS may also contribute to poorer disease outcomes, thereby including inferior overall survival (OS) [13, 14]. In the general population, elevated iron levels have been linked to increased morbidity and mortality [15]. Furthermore, transfusional iron overload is common in chronically transfused patients with severe anemia [8], and it often occurs in patients with MDS [16]. An increased incidence of progression to AML has also been associated with iron overload, but it is currently unclear whether this is due to the toxic effects of iron overload itself or is a consequence of the increased severity of the underlying MDS in these patients [13].

Iron chelation therapy (ICT) is commonly used in patients with transfusional iron overload in chronic transfusion-dependent anemias such as sickle cell disease or β-thalassemia, and is also used in some patients with MDS [17–20]. In the absence of randomized controlled trials, data on the efficacy of this approach in management of MDS are restricted to observational studies. Several observational studies have examined the relationship between ICT (using deferoxamine, deferasirox, or deferiprone) in patients with MDS and survival, the results of which have consistently suggested a survival benefit [21–29]. However, the selection bias that inevitably occurs in observational studies has been a concern for many hematologists/oncologists and has contributed to a lack of wide-scale use of ICT in eligible patients with lower-risk MDS [30]. To further explore the relationship between ICT and clinical outcomes in patients with MDS, we performed a systematic review and meta-analysis of the literature, focusing on studies that examined the association between ICT and survival and/or the association between ICT and rates of progression to AML. Given the observational nature of the studies, we used adjusted effect measures whenever possible to account for the potential confounding of the results.

Materials and methods

Data sources and search strategy

The present systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines [31, 32]. PubMed, EMBASE, Cochrane Library, and the World Health Organization Clinical Trial Registry electronic databases were searched with no language restriction from inception through 7 August 2017, with search terms "MDS" OR "myelodysplastic syndrome" AND "Iron Chelation" OR "Iron Chelating" OR "Iron Overload" AND "survival" OR "death" AND "study" OR "trial." References from the above selected publications were subsequently hand searched to identify any additional studies. Inclusion of published abstracts was permitted if the primary outcomes of interest were reported. If two or more papers were published from the same cohort, the publication with the longer follow-up or more patients was included. Two investigators (Dr. Zeidan and Dr. Duong) independently performed the database search and agreed on the final study selection.

Study selection and endpoints

Eligible studies had to have a comparator group (i.e., ICT and non-ICT groups) and should have reported at least one prespecified survival outcome. ICT was defined as the use of either deferasirox, deferoxamine, or deferiprone. Studies must also have reported outcomes for patients with low- to intermediate-risk MDS. Given the observational nature of the studies, an adjusted hazard ratio (aHR) was utilized for comparison of survival in the two groups in order to account for potential confounding of the results.

The primary outcome of interest was survival reported as either median OS or aHR (adjusted for confounders as defined by each study) between the two groups (i.e., ICT vs. non-ICT groups). Secondary outcomes of interest included the AML progression rate and the incidence of end-organ damage (liver cirrhosis, cardiac injury, arthropathy, etc.). Safety data were also evaluated where available.

Data extraction

Two investigators (Drs. Giri and DeVeaux) extracted data from the selected studies in duplicate using a standardized data-extraction form, and a third investigator (Dr. Zeidan) performed a cross-check for data accuracy. Information abstracted from the selected publications included data relating to study characteristics (study design, patient selection, follow-up duration, and number of patients), patient characteristics (age, sex, and MDS type, including International Prognostic Scoring System (IPSS) category), outcome measures (mortality and progression to AML), and measures of effect (calculated odds and hazard ratios (HRs), and the confounding variables for adjustment).

Quality assessment

The Newcastle-Ottawa Scale was used to assess the quality of studies [33]. This scale, which has three components, grades studies on the selection of study groups, the comparability of the groups, and the ascertainment of outcome of interest. Specifically, for the selection of the study groups, a maximum of four stars could be awarded per study for fulfilling the

following criteria: representativeness of the treated cohort and untreated cohort, ascertainment of treatment, and demonstration that the outcome of interest was not present at the start of the study. For comparability of the groups, a maximum of two stars could be awarded, with one star being awarded for adjustment or matching based on age or IPSS status, and a second star being awarded for adjustment or matching of at least one additional confounder. A maximum of three stars could be awarded for ascertainment of the outcome of interest based on how the outcome was assessed, if the follow-up time was long enough for the outcome to occur (at least 24 months), and follow-up of the cohorts was adequate (less than 10% of subjects lost to follow-up). If any of these points were not addressed in the study, a star could not be awarded. Two authors (Dr. Giri and Dr. DeVeaux) assessed the quality of the included studies. Generally, a score of 7 or higher is considered a high-quality study.

Statistical analysis

Following the method of Simes, a pooled estimate of the ratio of median OS for ICT vs. no ICT was calculated using a sum of the log-ratio of individual study estimates, weighted by sample size [34]. A 95% confidence interval (CI) was constructed using a fixed-effects model. Heterogeneity of studies included in the meta-analysis was determined using Cochran Q and I^2 indices, with a view to further exploring significant heterogeneity (defined as $I^2 > 60\%$) with sensitivity analyses. Given our findings of heterogeneous results for the primary outcome ($I^2 > 60\%$), aHRs were pooled using a random-effects model. Subgroup analyses were planned based on study design (prospective vs. retrospective), publication status (abstract vs. peer-reviewed publication), and adequacy of chelation (adequate chelation vs. any chelation). Sensitivity analysis was performed for the overall summary effects by removing one study and re-running the meta-analysis for every study in the analysis. Publication bias was evaluated visually by drawing funnel plots, and further quantified using the Egger's regression model. Statistical analyses were performed with Comprehensive Meta-Analysis (CMA 2.2, Biostat) and Review Manager (RevMan 5.3, Cochrane Collaboration, Nordic Cochrane Center).

Results

Description of included studies

The PRISMA flow diagram of study selection is shown in Fig. 1. An electronic search of PubMed, EMBASE, the Cochrane Library, and the World Health Organization Clinical Trial Registry plus a manual search retrieved a total of 649 publications.

After removal of duplicates, 537 citations were screened for eligibility, and 23 were identified for full-text review. Finally, the reviewers identified nine publications for qualitative and quantitative analysis. Reasons for rejection of studies not included in the final review were lack of comparison between chelated and nonchelated groups, evaluation of patients with AML rather than MDS, no IPSS risk category given, heterogeneous populations with multiple hematologic malignancies (including MDS), no documentation of survival, subjects undergoing stem cell transplantation, population not restricted to low- or intermediate-risk MDS, analyses based on ferritin rather than the effects of chelation, and multiple presentations of the same study.

Characteristics of the included studies are shown in Table 1. Of the nine included studies, all of which were observational in nature, there were four prospective studies [21, 24, 26, 28] and five retrospective studies [22, 23, 25, 27, 29]. There were no randomized clinical trials that met the inclusion criteria. Two studies were published in abstract form only [28, 29], while the remaining seven studies were available as peer-reviewed publications [21–27].

There were a total of 2450 patients in the nine included studies, of whom 942 (38.4%) received ICT. The weighted overall mean age was 72 years. Most of the patients in the included studies had IPSS scores of low- or intermediate-1, with the remainder ($n = 52$) being uncertain. The duration of follow-up of individual studies ranged between 24 months and 4 years where reported. Median OS was reported by eight studies, of which quantitative analysis could be done for six studies, one of which also provided a corresponding 95% CI. The aHR was also reported by seven studies. The studies by Delforge et al. [27] and Rose et al. [21] also reported separate survival analysis for patients who were adequately chelated, where adequate chelation was defined by the authors as receipt of deferoxamine subcutaneously (40 mg/kg/day via slow infusion over 8–12 h for at least 3 days per week), deferasirox (20–30 mg/kg/day), or deferiprone (30–75 mg/kg/day); weak chelation treatment was considered to be less than 3 g per week of deferoxamine.

Assessment of study quality and publication bias

We classified six of the nine studies as high quality according to the Newcastle-Ottawa Scale (Fig. 2). Publication bias was assessed graphically with funnel plots and statistically with Egger's regression intercept. There appeared to be an element of publication bias, with smaller studies toward the bottom of the funnel plot not being symmetrical around the mean effect size. This suggests that these studies were more likely to be published if they had a much larger effect size (Fig. 3). Similarly, Egger's regression intercept was statistically significant, which also suggests a significant element of publication bias ($P = 0.007$).

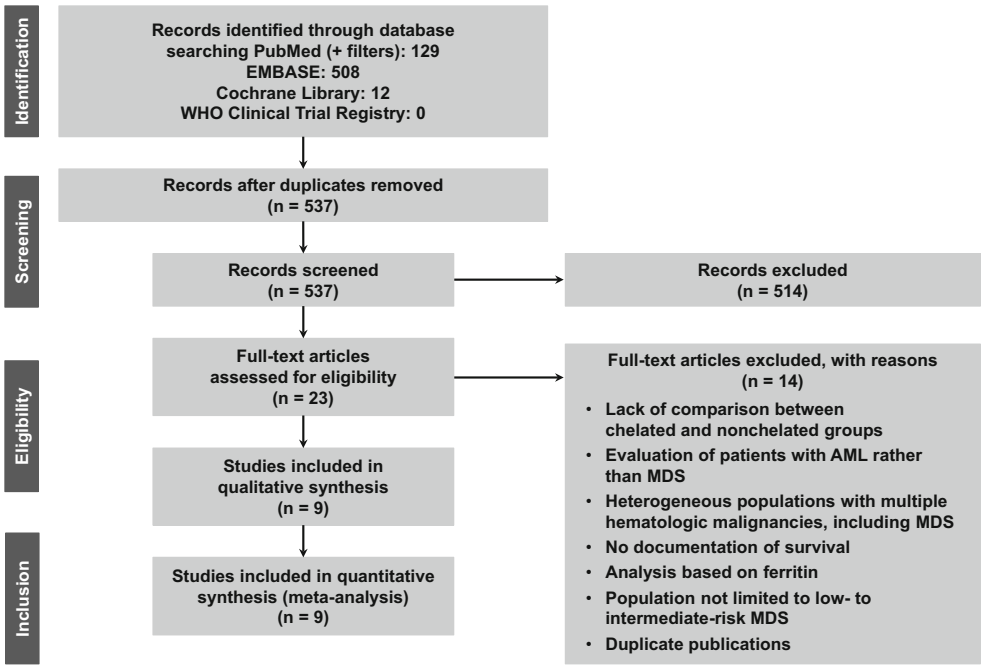

Fig. 1 PRISMA flow diagram. *AML* acute myeloid leukemia, *MDS* myelodysplastic syndromes, *WHO* World Health Organization

Overall survival

The median OS among patients receiving ICT and patients receiving no ICT was reported for six studies, one of which also provided a corresponding 95% CI. The median OS among patients receiving ICT was consistently longer than that in the non-ICT group (Fig. 4). The pooled estimate of the ratio median OS was 2.10 (95% CI 1.77–2.56), indicating that the median OS for patients receiving ICT is approximately twice that of patients receiving no ICT. It should be noted, however, that these estimates of median OS are unadjusted.

For patients with low- to intermediate-1-risk MDS, ICT was associated with an overall lower risk of mortality (aHR 0.42; 95% CI 0.28–0.62; $P < 0.01$; total studies = 7). Although the nine studies consistently favored longer OS with ICT, there was evidence of significant heterogeneity across studies for this outcome measure with I^2 of 68% and Cochran's Q statistics of 19.2 ($P = 0.004$).

Table 1 Characteristics of included studies

Author, year	Study type	Sample size (ICT vs. non-ICT)	Mean/median age in years	IPSS risk category	Median follow-up
Rose et al., 2010 [21]	Prospective	97; 53 vs. 44	72	Low 45 Int-1 52	
Remacha et al., 2015 [22]	Retrospective	263; 146 vs. 117	72	Low 218 Int-1 0 Uncertain 45	41 (19–80) months
Leitch et al., 2012 [25]	Retrospective	182; 38 vs. 144	69.5	Low 74 Int-1 101 Uncertain 7	28 (0.1–245.9) months
Komrokji et al., 2011 [29]	Retrospective	97; 45 vs. 52	67 vs. 65.5 (mean)	Low 24 Int 1 73	85.7 months
Lyons et al., 2014 [24]	Prospective	599; 270 vs. 329	75 vs. 77	Low 113 Int-1 181	
Raptis et al., 2010 [23]	Retrospective	78; 32 vs. 46	66.1 vs. 70.2	Low or Int-1 76	4 years in ICT 2.1 years in non-ICT
Delforge et al., 2014 [27]	Retrospective	127 (80 vs. 47)	72	Low 54 Int-1 73	25.4 months (SD 1.3 months)
Leitch et al., 2017 [26]	Prospective	239; 83 vs. 156	71 vs. 76	Low 73 Int-1 166	With ICT 2 (1–4) years Without ICT 1 (1–2) years
Langemeijer et al., 2016 [28]	Prospective	768; 195 vs. 573	69 vs. 73	NA	NA

ICT iron chelation therapy, *Int-1* intermediate-1, *NA* not available, *SD* standard deviation

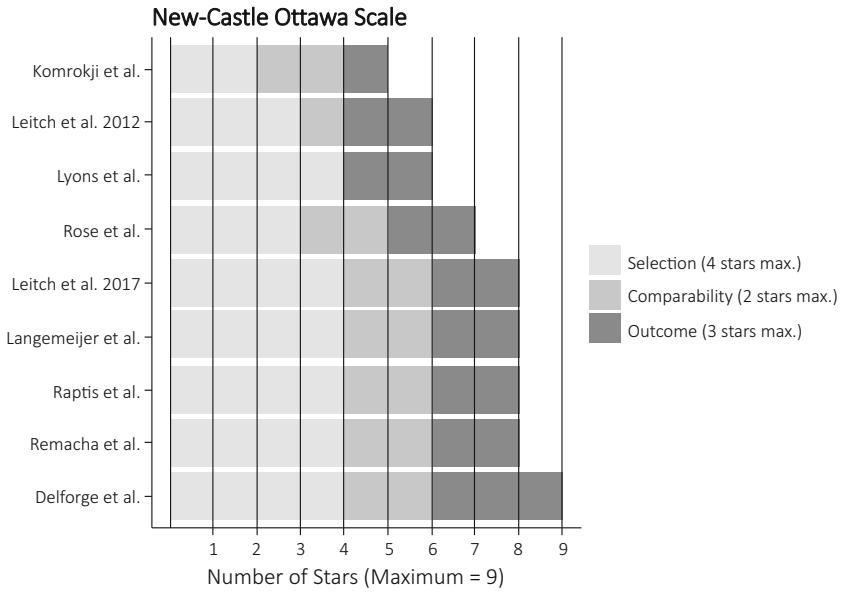

Fig. 2 Quality assessment of included studies as measured using the Newcastle-Ottawa Scale

Sensitivity analysis

Because of the significant heterogeneity among the studies included in this analysis, we explored the results further with a pre-planned sensitivity analysis. Sensitivity analysis was performed for the overall summary effects by removing each study in turn and re-running the meta-analysis for the remaining studies. This approach showed how much each study contributed to the summary effect by noting how much the summary effect changed in its absence. Exclusion of any one study did not change the overall effect direction. The study with the largest influence on OS was that reported by Langemeijer et al. [28], whose removal changed the aHR by 12% (from 0.42 to 0.37). In addition, the removal of the study by Langemeijer et al. [28] led to loss of heterogeneity (I^2 = 13.5, Cochran's Q statistic = 5.78, P = 0.328).

In addition to the above, we performed several other pre-planned sensitivity analyses. The first of these was performed based on a retrospective vs. prospective design (Fig. 5). Although the direction of effects did not change, heterogeneity was statistically significant for prospective studies (I^2 = 74%, Cochran's Q statistic = 7.65; P = 0.028), but not in retrospective studies (I^2 = 32%, Cochran's Q statistic = 4.4; P = 0.22). A second subgroup analysis was performed according to whether the study was published in a peer-reviewed journal or had only appeared as a conference abstract. Again, the direction of effects did not change and there was little heterogeneity observed in the random-effects model for either the

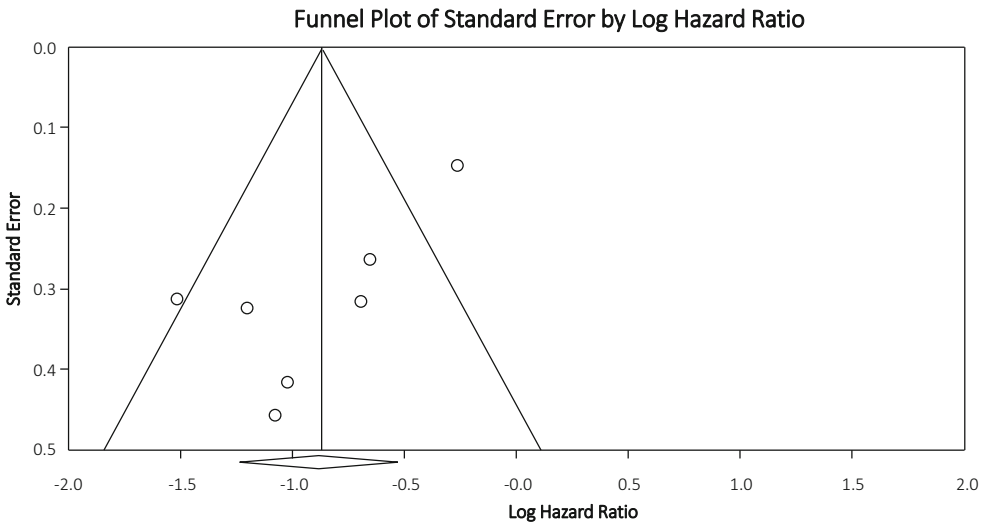

Fig. 3 Funnel plot showing publication bias

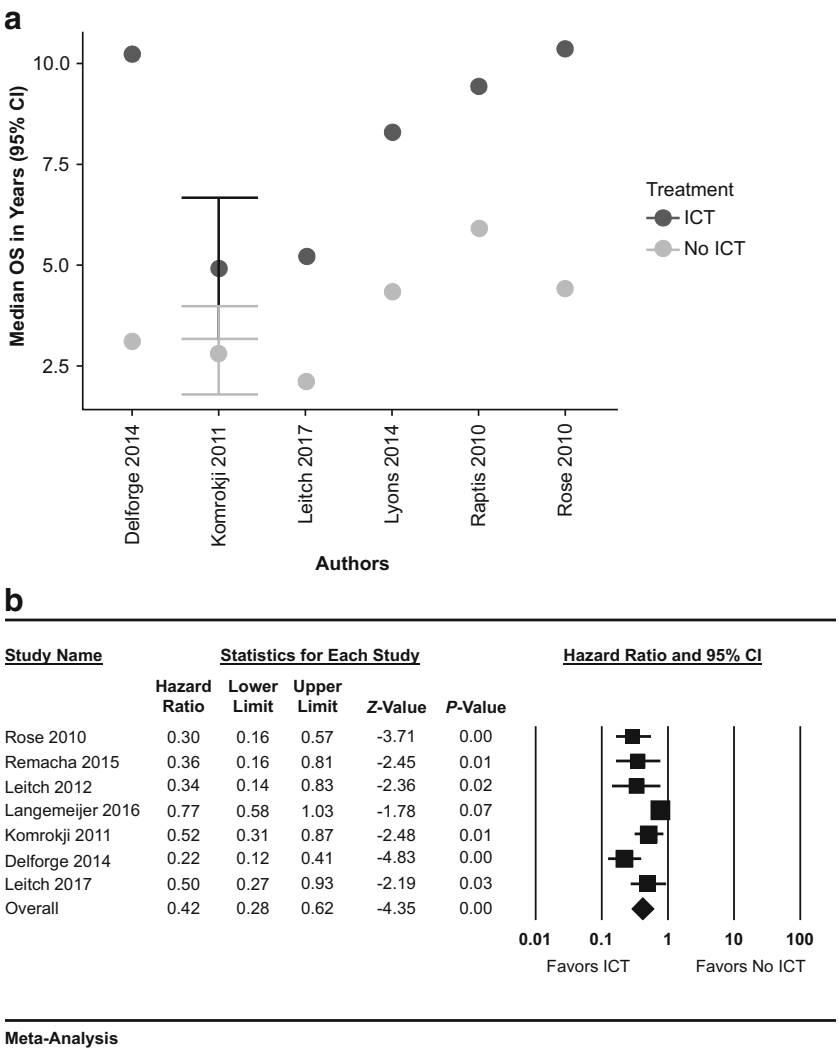

Fig. 4 OS in low- to intermediate-1-risk MDS patients treated with or without ICT: **a** median OS in years and **b** forest plot showing adjusted hazard ratio for change in risk of death associated with ICT compared with no ICT. *CI* confidence interval, *ICT* iron chelation therapy

abstracts ($I^2 = 41\%$, Cochran's Q statistic = 1.69; $P = 0.19$) or the journal publications ($I^2 = 0\%$, Cochran's Q statistic = 3.5, $P = 0.48$).

Adequate iron chelation vs. any iron chelation

Two of the studies reported the survival benefit of adequate chelation relative to no chelation [21, 27]. There was a significant survival advantage for patients who received the higher adequate dose of ICT, with an aHR of 0.26 (95% CI 0.16, 0.40; $P < 0.01$; Fig. 6). While any degree of chelation was found to confer a survival benefit (aHR = 0.55; 95% CI 0.40, 0.75; $P < 0.01$), overall, this was to a smaller degree than that seen with adequate chelation.

A sensitivity analysis was also performed according to whether patients received adequate chelation. There was little heterogeneity for studies in which patients received adequate chelation ($I^2 = 0\%$, Cochran's Q statistic = 0.47, $P = 0.49$) or for those in which they did not ($I^2 = 23.0\%$, Cochran's Q statistic = 7.8, $P = 0.25$).

Rate of transformation to AML and other outcomes

The rates of progression to AML in the ICT vs. non-ICT groups were reported by seven studies (Fig. 7). Overall, ICT was not associated with a decreased risk of progression to leukemia (odds ratio (OR) 0.68; 95% CI 0.31–1.43; $P = 0.30$). There was a significant heterogeneity among the various studies, with a Cochran's Q statistic of 30.67 ($P < 0.01$) and an I^2 statistic of 80.44.

Only two of the nine studies reported any data on end-organ damage or other safety data [22, 24]. The data included in these papers were insufficient to conduct any further meta-analysis. In the study by Remacha et al. [22], there was a significant increase in median cardiac event-free survival in chelated patients compared with nonchelated patients (137 vs. 96 months; $P = 0.017$). No

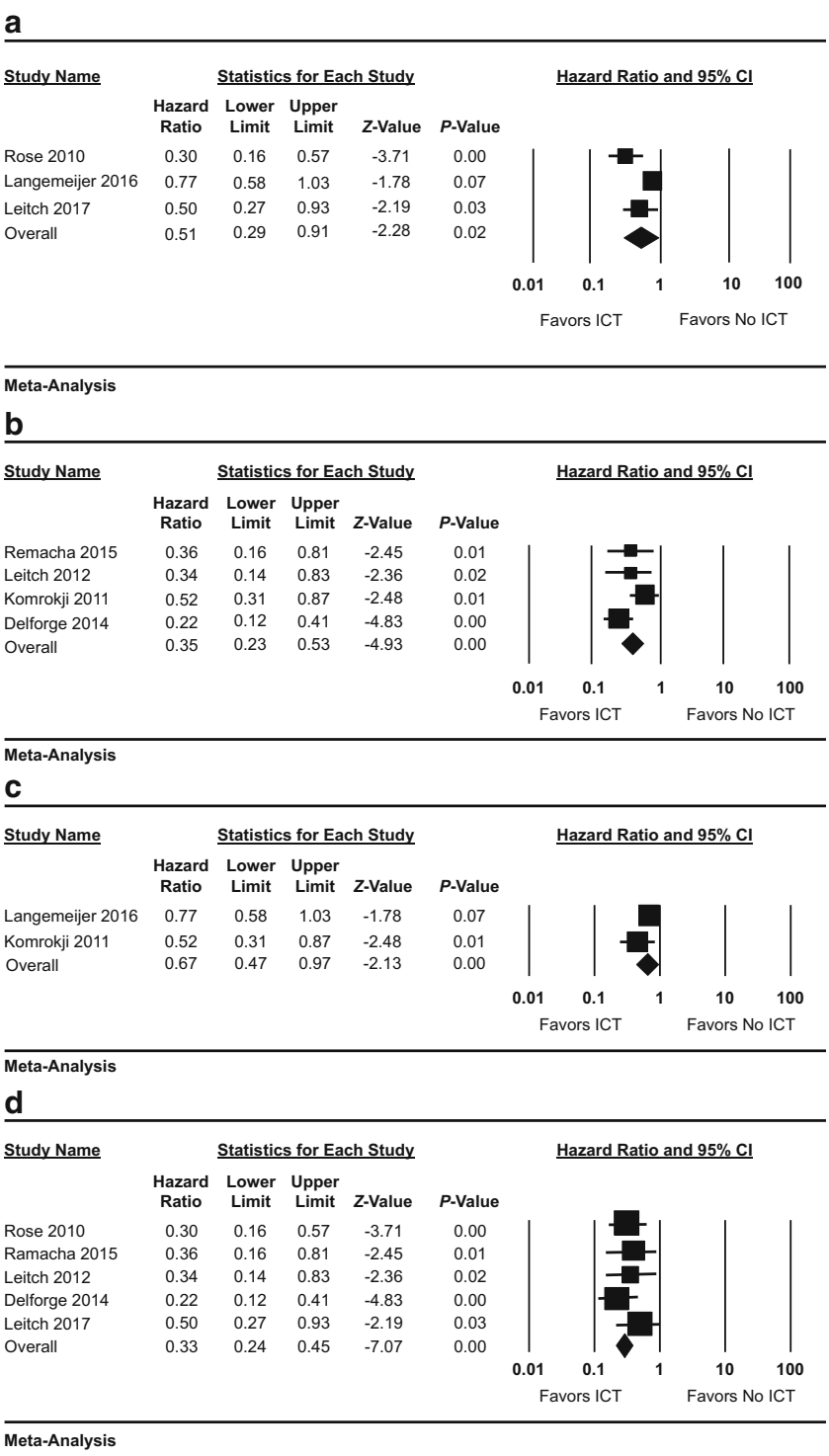

Fig. 5 Random-effects model of heterogeneity: **a** prospective studies ($I^2 = 74\%$; Cochran's Q statistic = 7.65; $P = 0.028$), **b** retrospective studies ($I^2 = 32\%$; Cochran's Q statistic = 4.4; $P = 0.22$), **c** abstracts ($I^2 = 41\%$; Cochran's Q statistic = 1.69; $P = 0.19$), and **d** published articles ($I^2 = 0\%$; Cochran's Q statistic = 3.5; $P = 0.48$). *CI* confidence interval, *ICT* iron chelation therapy

differences were observed in terms of hepatic, endocrine, or arthropathy event-free survival, primarily due to endpoints not being reached. The only other study reporting safety data noted that there was minimal change in laboratory assessments for renal and hepatic function over the course of the study among patients who were not chelated, chelated, or chelated for ≥ 6 months [24].

Discussion

Nine prospective and retrospective observational studies of ICT in patients with MDS were identified. All of these studies found that ICT was associated with a survival advantage, demonstrating longer median OS in patients treated with ICT than those not receiving ICT, and/or an aHR favoring ICT. All of

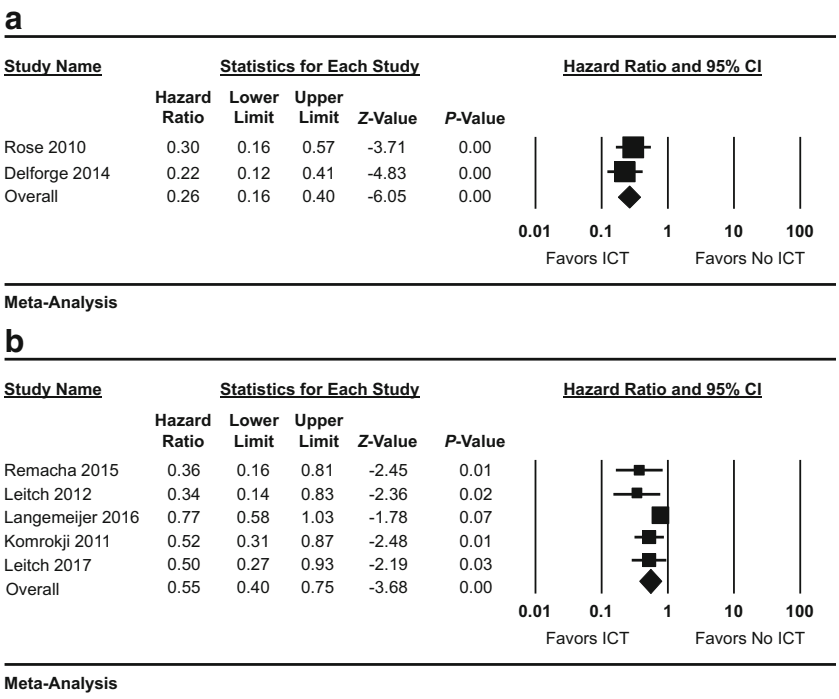

Fig. 6 Random-effects model of overall survival in patients who received: **a** adequate ICT (I^2 = 0%; Cochran's Q statistic = 0.47; P = 0.49) and **b** any ICT (I^2 = 23.0; Cochran's Q statistic = 7.8; P = 0.25). *CI* confidence interval, *ICT* iron chelation therapy

these studies focused on patients with lower-risk MDS, as defined by the IPSS [35–39]. Meta-analysis of these studies found a statistically significant benefit of ICT, with an aHR of 0.42 (95% CI 0.28, 0.62; $P < 0.01$). These data confirm the conclusions of the individual studies as well as a previous review [16, 40]. In our systematic review and meta-analysis, we controlled for study design, patient selection, follow-up duration, and number of patients, as well as patient and disease characteristics (age, sex, and MDS type, including IPSS category) and outcome measures. A recent uncontrolled retrospective study in patients with intermediate to very high IPSS scores demonstrated median OS of 24.4 months after the initiation of ICT, similar to some of the studies included in our analysis [41]. It is clear, however, that some important patient differences between chelated and nonchelated patients exist. For example, in the study by Lyons et al. [42], a greater proportion of chelated patients than nonchelated patients received RBC transfusions.

Our review identified an additional five studies that met our entry criteria, but did not report data in a manner that allowed for incorporation into the meta-analysis [43–46]. In a large Surveillance, Epidemiology, and End Results (SEER)–Medicare study of the impact of ICT in MDS, there was a significant association between the duration of ICT and the aHR for survival [43]. Neukirchen et al. [45] conducted a matched pair analysis of 188 MDS patients with iron overload who had received either ICT or supportive care only. Median OS was observed to be 75 months in the ICT group and 49 months in the supportive care group (P = 0.002). Finally, three publications were identified that did not provide sufficient detail regarding IPSS at diagnosis to be included [45–47]. In a study by Steinmetz et al. [44] that included

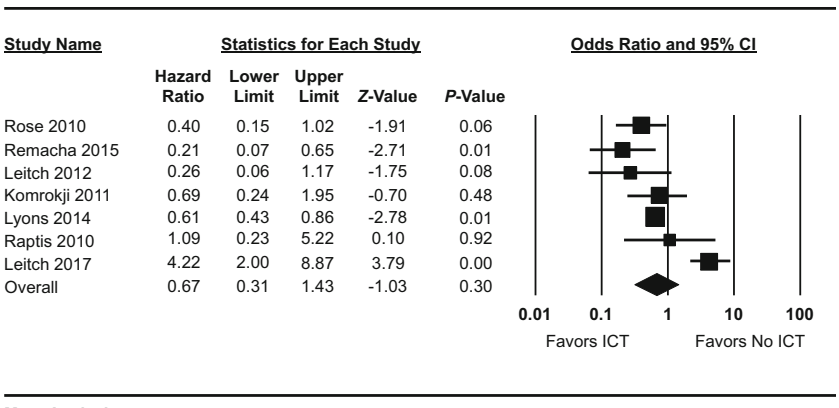

Fig. 7 Forest plot showing rate of acute myeloid leukemia transformation with or without ICT. *CI* confidence interval, *ICT* iron chelation therapy

patients with IPSS at diagnosis ranging from low- to high-risk, there was little difference in median OS between those who received ICT and those who did not (51 vs. 49 months; $P = 0.281$). In another study that included patients with IPSS ranging from low- to high-risk, Chan et al. [46] found that iron chelation was a significant predictor of OS (HR = 11.4; $P < 0.05$). A study by Hao et al. [47] that reported results from a Medicare claims database did not specify any IPSS. In this study, the 1- and 2-year death rates were 27.6 and 57.3%, respectively, for those treated with ICT, and 66.5 and 83.6%, respectively, for those who received no ICT [47].

As expected, this systematic review and meta-analysis confirmed the lack of any published prospective, randomized controlled trials of ICT in MDS, leaving only prospective and retrospective observational studies for inclusion. As expected, this resulted in a high degree of heterogeneity among studies; however, sensitivity analyses accounting for study design (prospective vs. retrospective), whether or not patients received adequate ICT, and publication (peer-reviewed journal vs. conference proceeding), as well as a one-study-removed analysis, found no significant impact of this heterogeneity on the results of the meta-analysis. There was also some evidence of publication bias, with smaller studies tending to have greater positive results. Despite all of these potential confounding issues, the overall conclusions of the analysis were not affected. Importantly, the Newcastle-Ottawa Scale found six of the nine studies included to be of good quality. One limitation of this analysis was that only one of the nine studies presented a median OS with a 95% CI, thereby necessitating use of a fixed-effects rather than a random-effects model.

Three different agents for the management of iron overload—deferoxamine, deferasirox, and deferiprone—are available. Although deferasirox was the most commonly used treatment in seven of the nine studies, and deferoxamine in two of the nine studies, there was little attempt to compare their relative benefits. This was likely because of the small numbers receiving the second most common agent used in each study and the frequency with which patients switched from one ICT to another. In the only study comparing the clinical efficacy of two iron-chelating agents, Langemeijer et al. [28] found that deferasirox was associated with significantly better OS than deferoxamine ($P = 0.0021$).

Similarly, although most studies did not distinguish between any chelation and adequate chelation, there were two studies that did [21, 27]. These authors arbitrarily defined adequate chelation as deferoxamine subcutaneously (40 mg/kg/day in slow infusion over 8–12 h for at least 3 days per week), deferasirox (20–30 mg/kg/day), or deferiprone (30–75 mg/kg/day); weak chelation treatment was considered to be less than 3 g per week of deferoxamine. In our analysis, adequate chelation was associated with a greater OS benefit than that seen in the primary analysis of any chelation. In the study by Rose et al. [21], adequate chelation was associated with median OS of 124 months, significantly longer than the 85 months reported for weak chelation ($P < 0.001$). Delforge et al. [27] observed a similar benefit for patients who were adequately chelated ($P = 0.001$ vs. weakly chelated) but further found no significant difference in OS between weakly chelated and nonchelated patients. These results highlight the importance of maintaining compliance with ICT in MDS. However, compliance and long-term treatment is far from straightforward, with up to 80% of patients discontinuing ICT, primarily due to gastrointestinal and renal issues [48]. There is, therefore, a need for better tolerated ICT.

Previous studies have suggested that iron overload may contribute to the risk of progression to AML [13]. It is unclear whether this is due to the toxic effects of iron overload or a reflection of the severity of the underlying MDS in these patients. It has been suggested that the risk of AML transformation in patients with iron overload is increased by the presence of increased intracellular reactive oxygen species, causing genomic instability through DNA, RNA, and protein damage [13, 49]. However, in our analysis, the risk of progression to AML in patients treated with ICT was not significantly different compared with those with no ICT, with an OR of 0.68 (95% CI 0.31–1.43; $P = 0.30$). This suggests, therefore, that mitigation of iron overload through ICT is not responsible for a reduced rate of disease progression to AML. Other concomitant disease-directed therapies, such as hypomethylating agents or lenalidomide, might affect the natural history of the disease [50–54].

Although the efficacy and safety of ICT in patients with low-risk MDS have not been evaluated in a randomized, controlled trial, based on available prospective data, consensus guidelines do recommend the use of ICT in patients with low or int-1-risk MDS [55–58]. Given the lack of prospective, randomized, controlled studies, it is difficult to definitively determine the relationship between ICT and survival in patients with MDS. The results of this systematic review and meta-analysis are consistent with those of published retrospective and observational trials suggesting that ICT may improve survival in patients with MDS. Selection bias in use of ICT remains difficult to control for, and the association of ICT with reduced mortality risk does not necessarily imply causation. While the present analysis provides little insight as to the relative benefits of deferoxamine, deferasirox, and deferiprone, it does highlight the importance of achieving adequate chelation in general, and it suggests that inadequate chelation has little benefit. None of these studies looked at the effect of ICT in patients with higher-risk MDS or in the peri-transplantation setting in which the role of ICT remains to be clarified. Our analysis also did not address a number of other critical questions in the management of iron overload, including the threshold of ferritin for starting chelation therapy and the impact of ICT-associated side effects on OS and

quality of life. Randomized trials of ICT are warranted to confirm our results and to further elucidate the associated mechanisms of iron toxicity.

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Author contributions AMZ and VHD independently performed the database search and agreed on the final study selection. SG and MD extracted data from the selected studies in duplicate using a standardized data-extraction form. They also assessed the quality of the included studies. AMZ performed a cross-check for data accuracy. All authors contributed to the writing of the manuscript, and all authors approved the final manuscript.

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Compliance with ethical standards

Conflict of interest Amer M. Zeidan has received research funding from Celgene, Incyte, Takeda, Pfizer, ADC Therapeutics, Medimmune, Trovagene, AbbVie, and Merck; he has consulted for Agios, AbbVie, Otsuka, Pfizer, Gilead, Celgene, Ariad, Incyte, Takeda, and Novartis; and he has served as a speaker for Takeda. Samir K. Ballas has served on the speakers bureau for Novartis and has received honoraria from Novartis. Smith Giri, Michelle DeVeaux, and Vu H. Duong declare that they have no conflict of interest.

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