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The impact of chelation therapy on survival in transfusional iron overload: a meta-analysis of myelodysplastic syndrome

Arch G. Mainous III[1,2], **Rebecca J. Tanner**[1], **Mary M. Hulihan**[3], **Mirna Amaya**[1], and **Thomas D. Coates**[4]

Arch G. Mainous: arch.mainous@phhp.ufl.edu

[1]Department of Health Services Research, Management and Policy, University of Florida

[2]Department of Community Health and Family Medicine, University of Florida, Gainesville, FL

[3]Division of Blood Disorders, Centers for Disease Control and Prevention, Atlanta, GA

[4]Department of Pediatrics and Pathology, University of Southern California Keck School of Medicine, Los Angeles, CA, USA

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iron overload; chelation; myelodysplastic syndrome

Elevated iron has been linked to increased morbidity and mortality in the general population (Mainous *et al*, 2004). In addition, iron overload can occur as an iatrogenic consequence of red blood cell (RBC) transfusions. Transfusional iron overload is not an uncommon consequence in patients who are chronically transfused to treat severe anaemia (de Ville de Goyet *et al*, 2013), as can occur in patients with myelodysplastic syndrome (MDS). Transfusion-dependent patients have increased mortality (de Ville de Goyet *et al*, 2013). Iron chelation therapy (ICT) is a strategy to address transfusional iron overload in MDS and utilizes drugs that remove iron as the drug is excreted.

Several observational studies have examined the relationship between ICT in MDS and survival. We performed a meta-analysis of observational studies that have examined associations between ICT and survival in MDS patients, hypothesizing that patients who received ICT would have a longer median survival than patients who did not.

Pubmed and Web of Science were searched for articles published in English or Spanish, with no date restrictions, and a final search date of 25 March, 2014. We also searched the Cochrane Collaborations Cochrane Reviews for systematic reviews and meta-analyses. The

Author contributions

Arch Mainous 3rd, Rebecca Tanner, Mary Hulihan and Mirna Amaya wrote the paper. Arch Mainous 3rd, Rebecca Tanner and Mirna Amaya analysed the data. Arch Mainous 3rd, Rebecca Tanner, Mary Hulihan and Thomas Coates designed the study. Arch Mainous 3rd, Rebecca Tanner and Mirna Amaya performed the study.

Conflict of interest statement

The authors declare no potential conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

searches contained the following key words: chelat* (allowing for all variations on the word root), MDS, myelodysplastic syndrome. Abstracts and research that had been presented at meetings or published in supplemental material were also included in the search. Finally, we also hand-searched the references of every paper that met our inclusion criteria for additional studies.

A duplicate purge was conducted and the final record list examined for potential inclusion was 615 records. Two reviewers independently reviewed the retrieved documents to identify studies that met the following inclusion criteria: (i) original research with complete study design details; (ii) presence of a non-chelated comparison group; (iii) not a duplicate; and (iv) examined median overall survival (OS) as an outcome. A third member of the team acted as a final evaluator for study inclusion. The selected studies met all of these criteria (Figure S1).

For each study, data regarding median OS, study methodology, sample size, baseline characteristics of the study population (age and percent male), treatment and control group size, and outcome information were extracted. The outcome data selected was OS, the only outcome common to studies that examined ICT in MDS patients. It is also the most clinically meaningful.

Estimation of differences in median OS associated with receipt of ICT were combined using a random effects model, which weights each study based on an individual study's inverse variance. The study was the unit of analysis. Estimates of median OS differences were reported with 95% confidence intervals. Differences were considered significant using 2-sided $P \leq 0\ 05$. One study that utilized a matched pair design had the design accounted for in the analysis.

As a sensitivity analysis, we conducted a one-study-removed analysis to assess the effect of each study on the combined effect. We report odds ratios for the increased likelihood of longer survival with ICT compared with no ICT. We also report the mean of the difference in median survival between ICT and no ICT. Funnel plots were used to identify publication bias and the Egger test was used to assess the amount of asymmetry in the funnel plot. Comprehensive Meta-Analysis (CMA) Version 2 (Biostat, Englewood, UK) was used for all analyses.

Our search identified 1234 records that included meeting abstracts, news items, journal articles, editorials, book chapters, guidelines and reviews. After duplicates were purged, 612 records were reviewed for inclusion. The first exclusion resulted in the removal of 444 records because they were guidelines, book chapters, literature reviews, news items and meeting items that were not MDS- and ICT-related. The remaining 168 full text articles and meeting abstracts were read to determine whether they fitted the rest of the inclusion criteria, resulting in the inclusion of one articles and meeting abstracts for the final determination. Of the 11 studies identified, eight observational studies met the full inclusion criteria; no clinical trials were identified (Table I).

The eight observational studies identified included a total of 1562 participants (median sample size = 153; range 78–534). The use of ICT was found to result in an increased

likelihood of having a longer median survival time than nonuse of ICT (Fig 1). The mean of the difference in median OS between individuals who received ICT and those who did not was 61·2 months; with greater median survival occurring in the ICT group. Visual analysis of the funnel plot for publication bias indicated that there was possible bias towards small studies, which overrepresented positive results in the results (Figure S2), and was confirmed by the Egger test ($P = 0{\cdot}0009$).

This meta-analysis has limitations. According to our search, there have been no randomized control trials of ICT in MDS patients. Our study was only able to utilize observational studies. Second, it is possible that the increased survival in the ICT group could be caused by selection bias, where patients who had a better prognosis were more likely to receive ICT. However, seven of the eight included studies attempted to control for severity of illness by examining low-risk MDS patients. Finally, the studies included in this meta-analysis use different drugs for chelation. The differences in the drug examined in each study may impact the estimated survival in ways that this study did not account for.

This meta-analysis of eight observational studies indicates that the use of ICT in patients with MDS (particularly low-risk) is associated with a greater median survival time than non-use of ICT. A consistent pattern was found, with seven of the eight identified studies exhibiting this effect. On average, patients who received ICT lived more than 5 years longer than their counterparts who did not receive ICT. These results suggest that lowering iron has distinct and clear health benefits for this population. This meta-analysis adds to the evidence that ICT in patients who are suffering from transfusional iron overload may improve survival.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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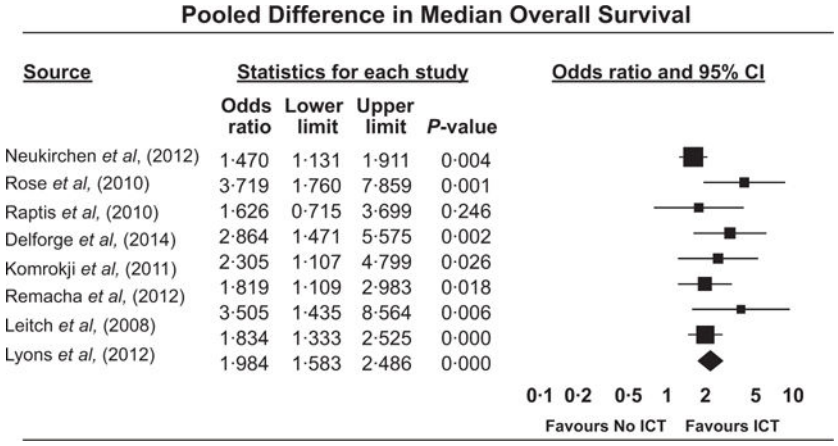

Fig 1.

Pooled differences in median overall survival. Squares represent individual studies; the size of the square represents the weight given to each study in the meta-analysis. Horizontal lines indicate 95% confidence intervals. The diamond represents the pooled results. ICT, iron chelation therapy; 95% CI, 95% confidence interval.

Table I

Study characteristics.

Reference	Country	Study design	Sample size for 2 groups	Population	Age (years)	Male Sex, %	Median OS with ICT (months)	Median OS without ICT (months)	*P* value
Lyons *et al* (2012)	United States	Prospective Non-interventional Cohort	534	Low risk MDS patients (WHO, FAB or IPSS) who received no ICT or ICT ≥ 6 months	Median age (range): No ICT = 77 (47–99); ICT = 75 (21–94); ICT ≥ 6 months = 75 (21–94)	Ratio M:F; No emsp;ICT = 1·45:1; emsp;ICT ≥ 6 months = 1·11:1	ICT = 96·8 ≥6 months ICT = 102·1	50	0·0001
Neukirchen *et al* (2012)	Germany	Retrospective Matched-Pair Analysis	188	Adults with MDS	Median age (range): No ICT = 67·5(33–89) ICT = 64(18–82)	No ICT = 48 emsp;ICT = 42	75	49	0·002
Komrokji *et al* (2011)	United States	Retrospective Cohort	97	Low/Int-1 IPSS MDS patients	Mean age: No ICT = 65·5; ICT = 67	No ICT = 63·5 emsp;ICT = 73·3	59	33·7	0·013
Raptis *et al* (2010)	United States	Retrospective Single arm Descriptive Analysis	78	ICT-eligible Low risk MDS patients (WHO, FAB, or IPSS) (subgroup analysis)	Mean age (SD): No ICT = 70·2(11·6); ICT = 66·1(11·2)	No ICT = 43·5 emsp;ICT = 46·9	Low emsp;Risk = 112·8;	70·8	0·12
Rose *et al* (2010)	France	Prospective Cohort	97	Low/Int-1 IPSS MDS patients	Mean age: All = 72; No ICT = 75; ICT = 70	All = 59·7 No emsp;ICT = 59·1 emsp;ICT = 54·7	124	53	0·0003
Leitch *et al* (2008)	Canada	Prospective Cohort	178	Low/Int-1 IPSS MDS patients	Median age at diagnosis = 69	59	>226	40	0·003
Delforge *et al* (2014)	Belgium	Follow-up, Multicentre, Observational Non-interventional Retrospective	127	Low/Int-1 IPSS MDS patients	Mean age at diagnosis (SD): No ICT = 73(9·0) ICT = 71(9·3)	No ICT = 42 emsp;ICT = 45	122·4	37·2	0·001
Remacha *et al* (2012)	Spain	Retrospective Observational Cohort	263	Transfusion-dependent MDS patients with low/int-1 IPSS who had received ≥10 RBC transfusions during at least 12 months prior to study entry	NA	NA	133	105	0·009

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OS, overall survival; MDS, myelodysplastic syndrome; WHO, World Health Organization classification; FAB, French-American-British classification; IPSS, International Prognostic Scoring System; Int-1, intermediate-1; ICT, iron chelation therapy RBC, red blood cell; SD, standard deviation; NA, not available; M, male; F, female.