

Iron Overload in Allogeneic Hematopoietic Cell Transplantation Outcome: A Meta-Analysis



Philippe Armand^{1,*}, Haesook T. Kim², Johanna M. Virtanen³, Riitta K. Parkkola³, Maija A. Itälä-Remes⁴, Navneet S. Majhail⁵, Linda J. Burns⁶, Todd DeFor⁷, Bryan Trottier⁶, Uwe Platzbecker⁸, Joseph H. Antin¹, Martin Wermke⁸

¹ Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts

² Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, Massachusetts

³ Department of Radiology, Turku University Hospital, Turku, Finland

⁴ Department of Medicine, Turku University Hospital, Turku, Finland

⁵ Department of Blood and Marrow Transplant Program, Cleveland Clinic, Cleveland, Ohio

⁶ Department of Medicine, Blood and Marrow Transplant Program, University of Minnesota, Minneapolis, Minnesota

⁷ Biostatistics Core, Masonic Cancer Center, University of Minnesota Medical School, Minneapolis, Minnesota

⁸ Department of Medicine I, University Hospital C.-G.-Carus, Dresden, Germany

Article history:

Received 1 April 2014

Accepted 17 April 2014

Key Words:

Allogeneic hematopoietic cell transplantation
Iron overload
Serum ferritin

ABSTRACT

An elevated ferritin level before allogeneic hematopoietic cell transplantation (HCT) is an adverse prognostic factor for overall survival (OS) and nonrelapse mortality. Because ferritin is an imperfect surrogate of iron stores, the prognostic role of iron overload remains unclear. We conducted a patient-level meta-analysis of 4 studies that used magnetic resonance imaging to estimate pre-HCT liver iron content (LIC). An elevated LIC was not associated with a significant increase in mortality: the hazard ratio (HR) for mortality associated with LIC > 7 mg/g dry weight (primary endpoint) was 1.4 ($P = .18$). In contrast, ferritin > 1000 ng/mL was a significant prognostic factor (HR for mortality, 1.7; $P = .036$). There was, however, no significant association between ferritin > 2500 and mortality. This meta-analysis suggests that iron overload, as assessed by LIC, is not a strong prognostic factor for OS in a general adult HCT population. Our data also suggest that ferritin is an inadequate surrogate for iron overload in HCT.

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INTRODUCTION

The toxicities of iron overload in patients with benign diseases overlap with some of the most severe toxicities of allogeneic hematopoietic cell transplantation (HCT), which has led to the hypothesis that iron overload could be common and deleterious in patients with hematologic malignancies undergoing HCT. A large body of evidence has shown that an elevated serum ferritin (SF) before HCT is associated with inferior overall survival (OS), an effect that, in most studies, appears mediated by an increase in nonrelapse mortality (NRM) [1-15]. Although those studies vary in their study population and choice of SF cutoff, they almost universally agree that a high SF is associated with an adverse prognosis. A more direct estimate of total body iron burden may be obtained by measuring liver iron content (LIC), which may be assessed noninvasively by magnetic resonance imaging (MRI) [16,17]. In HCT studies evaluating both LIC estimated by MRI and SF, the correlation coefficient between the two is around .6 to .8 [12,13,18-21], implying that ferritin is an acceptable but imperfect surrogate of true iron burden.

Alternatively, because ferritin is an acute phase reactant, its elevation in serum may betray inflammatory states, including active infection or more advanced disease status, which are expected to confer an adverse prognosis in HCT independent of iron overload. There are at present 4 published studies that have directly assessed the impact of pre-HCT LIC on outcome, but they differ in their conclusion despite their generally similar design [4,14,15,22]. We, therefore, undertook an individual patient data meta-analysis of all 4 studies, with the aim of clarifying whether pre-HCT LIC is, like SF, associated with worse OS or NRM.

METHODS

We obtained patient-level data from the 4 published prospective studies [3,12,13,22]. Survivors with < 6 months of post-HCT follow-up were excluded. We conducted a meta-analysis for OS and NRM. NRM was calculated in the competing risks framework, treating relapse as a competing risk. Within each study as a whole or for a subgroup of interest, we calculated the hazard ratio (HR) and associated P value for mortality using a univariable proportional hazards model and for NRM using a competing risks regression model [23]. The HRs were pooled with inverse variance weighting, using a random effects model [24]. Heterogeneity was assessed using the Cochran's Q statistic and the I^2 calculation [24,25].

RESULTS AND DISCUSSION

The details of the 4 cohorts and the 276 patients included in this analysis have been previously published [4,14,15,22]. The median age was 52 (range, 18 to 74) years. One half had acute myeloid leukemia and 16% had myelodysplastic syndrome. Almost two-thirds received reduced-intensity conditioning (RIC). The median pre-HCT SF was 1523 (range, 20

Financial disclosure: See Acknowledgments on page 1250.

* Correspondence and reprint requests: Philippe Armand, MD, PhD, Dana-Farber Cancer Institute, 450 Brookline Ave., Boston, MA 02215.

E-mail address: parmand@partners.org (P. Armand).

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<http://dx.doi.org/10.1016/j.bbmt.2014.05.004>

Table 1
Summary Results

| Population | Outcome | Variable | HR (95 CI, P Value) |
|----------------------|----------------------|-----------------|--------------------------|
| Overall cohort | Overall survival | LIC > 5 mg/gdw | 1.0 (.6-1.5), P = 1.00 |
| | | LIC > 7 mg/gdw | 1.4 (.9-2.3), P = .20 |
| | | SF > 1000 ng/mL | 1.7 (1.0-2.7), P = .036 |
| | Nonrelapse mortality | SF > 2500 ng/mL | 1.3 (.8-2.0), P = .30 |
| | | LIC > 5 mg/gdw | 1.0 (.6-1.7), P = .90 |
| | | LIC > 7 mg/gdw | 1.7 (.9-3.3), P = .09 |
| MAC cohort | Overall survival | SF > 1000 ng/mL | 1.6 (.9-2.8), P = .14 |
| | | SF > 2500 ng/mL | 1.4 (.8-2.3), P = .30 |
| | | LIC > 7 mg/gdw | 1.3 (.4-4.4), P = .60 |
| | Nonrelapse mortality | SF > 1000 ng/mL | 1.5 (.6-3.5), P = .40 |
| | | LIC > 7 mg/gdw | Not evaluable* |
| | | SF > 1000 ng/mL | Not evaluable* |
| RIC cohort† | Overall survival | LIC > 7 mg/gdw | 1.5 (.8-2.7), P = .20 |
| | | SF > 1000 ng/mL | 1.5 (.8-2.8), P = .20 |
| | | SF > 2500 ng/mL | 2.2 (1.1-4.6), P = .026† |
| | Nonrelapse mortality | LIC > 7 mg/gdw | 1.5 (.7-3.3), P = .30 |
| | | SF > 1000 ng/mL | 1.5 (.7-3.0), P = .30 |
| | | SF > 2500 ng/mL | 1.5 (.7-3.0), P = .30 |
| Acute leukemia + MDS | Overall survival | LIC > 7 mg/gdw | 1.2 (.7-2.3), P = .60 |
| | | SF > 1000 ng/mL | 1.5 (.7-3.1), P = .30 |
| | | LIC > 7 mg/gdw | 1.5 (.7-3.0), P = .30 |
| | Nonrelapse mortality | LIC > 7 mg/gdw | 1.5 (.7-3.0), P = .30 |
| | | SF > 1000 ng/mL | 1.1 (.6-2.2), P = .70 |
| | | SF > 2500 ng/mL | 1.1 (.6-2.2), P = .70 |

HR denotes hazard ratio; 95 CI, 95% confidence interval; LIC, liver iron content; gdw, gram dry weight; SF, serum ferritin; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; MDS, myelodysplastic syndromes.

For each variable, outcome and subgroup of interest, the hazard ratio is given along with its associated 95% confidence interval and P value.

* Not evaluable because of the small number of events in this subgroup.

† See text for comment.

to 8878) ng/mL; 67% of patients had a ferritin over 1000 ng/mL, and 23% above 2500 ng/mL. The median pre-HCT LIC was 5.0 (range, .3 to 25.4) mg/g dry weight (gdw), with 82% of patients having an elevated LIC (>1.8 mg/gdw), 50% had an LIC > 5 mg/gdw, and 28% had an LIC > 7 mg/gdw. The median follow-up for survivors was 22 (range, 6 to 44) months.

The results are summarized in Table 1. We used 2 possible prespecified thresholds for SF (1000 and 2500 ng/mL) and for LIC (5 and 7 mg/gdw), corresponding to those most often used in the HCT literature and in the primary studies. For OS, the pooled HR associated with LIC > 5 mg/gdw was 1.0 (P = 1.00) (Figure 1A); for LIC > 7 mg/gdw, the HR was 1.4 (P = .20) (Figure 1B). For ferritin > 1000 ng/mL, the HR was 1.7 (P = .036) (Figure 1C); however, there was no significant association between ferritin > 2500 ng/mL and mortality (HR, 1.3; P = .30) (Figure 1D). There was no significant heterogeneity for any of the above outcomes (Q statistic, .1 to 2.7 with 3 degrees of freedom; P values, .5 to 1.0; I² = 0 for all). There was no significant association between any of the variables studied and NRM. We also found no significant association between LIC or SF and OS or TRM in analyses restricted to patients undergoing myeloablative conditioning, or in the subgroup of patients with myelodysplastic syndrome or acute leukemia. We also conducted an exploratory analysis restricted to patients who had undergone RIC HCT. The HR for NRM associated with LIC > 7 mg/gdw was 2.2 (P = .026), although the other HRs were not significant. One of the studies in this meta-analysis only enrolled patients undergoing myeloablative conditioning HCT, and this study was, therefore, not included in this subgroup analysis. As the number of patients and of events in the analysis of NRM for RIC patients was small, those results should be interpreted with caution. However, they raise the possibility that iron overload may have a particular importance among the generally older and frailer patients undergoing RIC HCT, which deserves further study.

In summary, we did not find a significant association between an elevated pre-HCT LIC and OS or NRM overall.

Consistent with previous studies, we observed a significant association between SF and OS. However, this was only significant at a threshold of 1000 ng/mL and not at a threshold of 2500 ng/mL. This could be explained if the adverse prognosis of SF is related not to iron overload but to underlying disease-related or comorbidity-related issues that elevate acute phase reactants. In that case, the degree of elevation in SF may not be relevant, only the presence of the underlying issues reflected by any significant elevation in SF. If this were true, an SF threshold of 1000 ng/mL may better capture the patient population at risk than a higher threshold. Regardless, our results suggest that the evidence to date on SF and HCT outcome may not allow us to conclude that iron overload itself is strongly detrimental after HCT.

It is unlikely that our negative results stem from our threshold choice. Based on prior reports of the correlation between SF and LIC in this patient population [18], an SF of 2500 ng/mL corresponds to an LIC around 6 mg/gdw. Therefore, the thresholds chosen for this meta-analysis should have captured the prognostic effect previously seen with SF. It is also unlikely that our results are confounded by measurement technique. Although the MRI techniques used to estimate LIC differed among the 4 studies, they all used techniques that have been previously validated against liver biopsies.

It is possible that given the trends for increased overall and NRM for elevated LIC, our negative results reflect a sample size issue, and that a larger study would have uncovered a significant effect. Our study also lacked power to definitively study the impact of iron overload among patient subgroups. Regardless, the results presented here should not be interpreted to imply that iron is irrelevant in HCT. The trends suggest a possible prognostic effect, although it does not appear as strong as suspected based on the ferritin-related literature, and it may be restricted to certain subgroups. Moreover, iron may be related to disease pathology in ways that are just beginning to be understood. We suggest, instead, that the present study should serve as the impetus

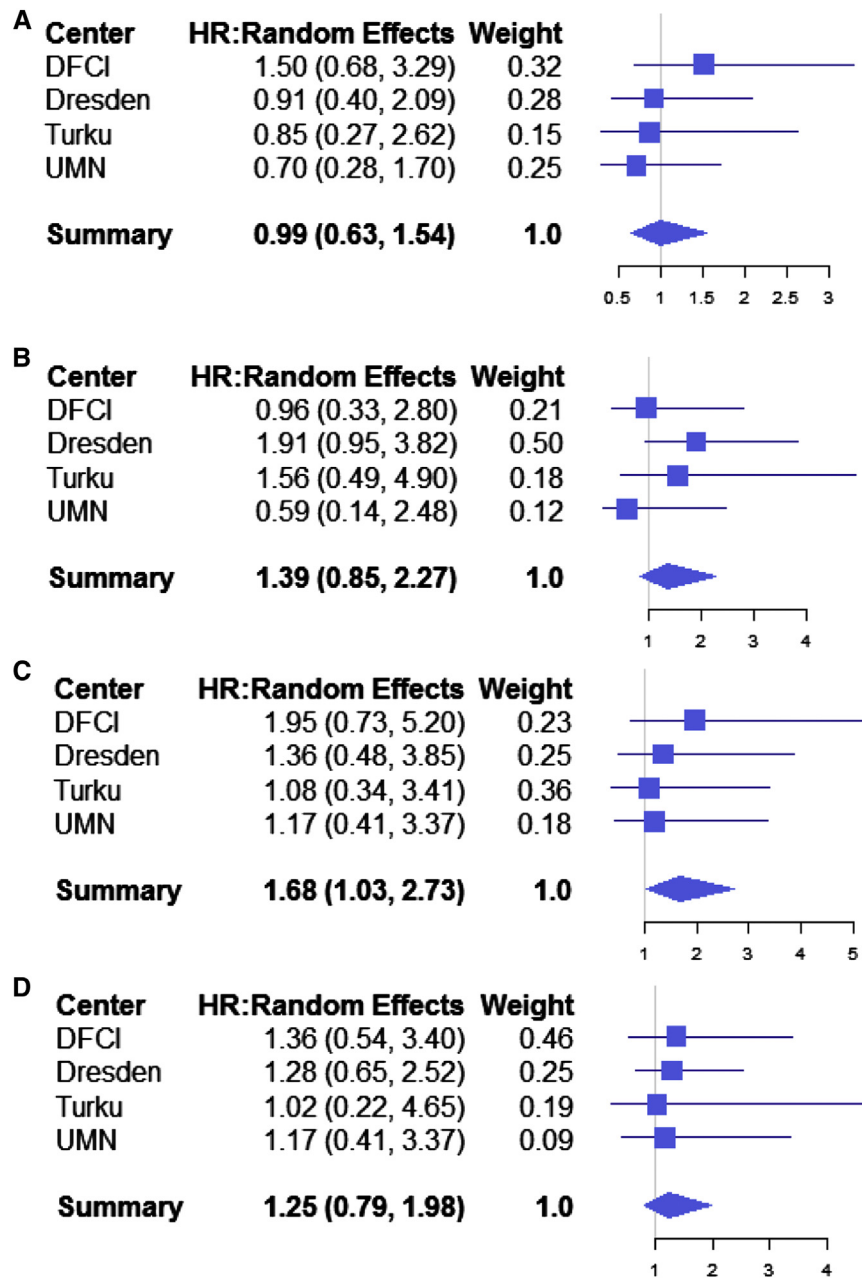


Figure 1. Forest plot of the hazard ratios for mortality associated with LIC > 5 mg/gdw (A), LIC > 7 mg/gdw (B), ferritin > 1000 ng/mL (C), and ferritin > 2500 ng/mL (D). Center names are abbreviated as follows: DFCI indicates Dana-Farber Cancer Institute; Dresden, University of Dresden; Turku, Turku University Hospital; UMN, University of Minnesota.

for the design of next-generation studies that do not rely primarily on SF measurement, and that explore, through careful and creative design, alternative mechanisms through which iron may influence HCT outcomes. Furthermore, several groups have already reported on the use of [26–30] or recommendation for [31] chelation therapy in the pre or post-HCT setting. Our results may weaken the premise for chelation studies in general transplantation populations, and they may emphasize the need to design future chelation studies with a broad array of correlative endpoints that could uncover possible effects of chelation beyond simply the reduction in iron stores.

ACKNOWLEDGMENTS

Financial disclosure: P.A. was supported by an ASCO Career Development Award. This work was also supported by National Institute of Allergy and Infectious Diseases U19 AI 29530, NCI P01 CA142106, and the Jock and Bunny Adams Research and Education Endowment.

Conflict of interest statement: There are no conflicts of interest to report.

Author contributions: P.A. designed the research, collected and analyzed the data, and wrote the paper. H.T.K. designed the research, analyzed the data, and edited the paper. J.M.V., M.A.I.-R., N.S.M., L.J.B., B.T., J.H.A., and M.W. designed the

research, collected the data, and edited the paper. R.K.P. and U.P. collected the data and edited the paper. T.D. designed the research and edited the paper.

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