Assessing Iron Overload: Are We There Yet?

Paul C. Kruger1, Michael F. Leahy1,3, and John K. Olynyk2,3,4,5

Iron overload occurs in many hematologic disorders and causes significant morbidity. The advantages of MRI in quantifying liver iron concentration continue to mount, and the association between iron overload and increased mortality after allogeneic stem cell transplant needs further attention. Clin Cancer Res; 18(23); 6395–7. ©2012 AACR.

In this issue of Clinical Cancer Research, Wermke and colleagues (1) publish results of an observational study of MRI assessment of liver iron content (LIC) in 88 patients undergoing allogeneic stem cell transplantation (allo-SCT) for either myelodysplastic syndrome (MDS; n = 24) or acute myeloid leukemia (AML; n = 64). Systemic iron overload (SIO) in these conditions is a consequence of ineffective erythropoiesis and blood transfusions used to treat anemia due to either the disease itself or cytotoxic chemotherapy. It is a frequent and significant problem in these conditions and may result in organ damage due to iron deposition in the liver, heart, pancreas, and endocrine glands (2). Furthermore, SIO results in increased risks of serious infections. Thus, assessment of body iron stores and quantitation of LIC is a relevant part of the clinical assessment of such patients (3).

The authors measured the LIC using MRI and assessed the relationships between pretransplant LIC, serum iron biochemistry parameters [transferrin saturation (TRS) and serum ferritin], and after allo-SCT outcomes. Eighty-five of 88 patients had serum ferritin levels elevated to more than 400 ng/mL, whereas 44% had serum TRS values greater than 400 ng/mL, whereas 44% had serum TRS values of 88 patients had serum ferritin levels elevated to more than 400 ng/mL, whereas 44% had serum TRS values of 88 patients had serum ferritin levels elevated to more than 400 ng/mL. Thus, assessment of body iron stores and quantitation of LIC is a relevant part of the clinical assessment of such patients (3).

The authors measured the LIC using MRI and assessed the relationships between pretransplant LIC, serum iron biochemistry parameters [transferrin saturation (TRS) and serum ferritin], and after allo-SCT outcomes. Eighty-five of 88 patients had serum ferritin levels elevated to more than 400 ng/mL, whereas 44% had serum TRS values greater than 400 ng/mL. The median LIC was 125 μmol/g (IULN: 36 μmol/g; range 25–350 μmol/g) before allo-SCT. Positive correlations were observed between LIC and transfusion history (r = 0.67; P < 0.001) and serum ferritin (r = 0.640; P < 0.001).

The most widely available tools to assess iron overload are the indirect markers serum ferritin and TRS. However, they are sensitive but not specific as ferritin is also an acute-phase reactant, whereas TRS has a day-to-day variability. Indeed, in the current study, a ferritin value greater than 1,000 ng/mL provided a specificity of only 32% for detection of LIC greater than 125 μmol/g. More accurate quantitation of LIC is possible via noninvasive methods, such as MRI, or invasive approaches, such as liver biopsy (Fig. 1). Liver biopsy is rarely clinically appropriate in patients with MDS and AML, who are often thrombocytopenic. Liver MRI has been clearly shown to accurately assess LIC over a large range of iron concentrations (4, 5), either by signal intensity ratio or relaxometry methods (6). Of all the reported MRI methods, FerriScan has been licensed by regulatory authorities in Europe, United States, and Australia (7).

Labile plasma iron (LPI), a toxic redox-active component of nontransferrin-bound iron and a major mediator of tissue damage, was also analyzed in this study as a diagnostic tool. Nine patients tested positive for LPI with a median of 0.95 LPI units (range: 0.71–3.21 LPI units), although there was no significant correlation between pre-allo-SCT LPI concentrations and LIC, transfusion burden, or ferritin. Nor was there any correlation between enhanced LPI and these markers in over half (13/24) of the screened patients. The role of LPI as a diagnostic tool remains investigational (8). Nevertheless, LPI remains an important contributor to iron toxicity as levels increase after chemotherapy in patients with AML. Furthermore, it offers a potential target for therapy, as it is directly chelatable. Further clarification of the role of iron chelation in these conditions is required. Vigorous iron chelation in the pretransplantation period may be important, but the benefits of chelation posttransplantation are uncertain (2).

Wermke and colleagues clearly show the importance of iron status for the prediction of outcome of allo-SCT. Patients with high LIC had an increased cumulative incidence of nonrelapse mortality (at day 100, <125 μmol/g vs. ≥125 μmol/g: 4.7% vs. 27.3%, P = 0.028; ref. 1). Other studies have also documented the association between iron overload and decreased survival after allo-SCT in both malignant and nonmalignant hematologic conditions (9, 10). Although serum ferritin has been used as a marker in these studies instead of MRI assessment of LIC, it still adds to the evidence base that iron overload is a frequent and significant problem in these conditions and may result in organ damage due to iron deposition in the liver, heart, pancreas, and endocrine glands (2). Further clarification of the role of iron chelation in these conditions is required. Vigorous iron chelation in the pretransplantation period may be important, but the benefits of chelation posttransplantation are uncertain (2).
frequent and deleterious in this population of patients. Reducing the number of red blood cell (RBC) transfusions may reduce nonrelapse mortality. A Swiss study in patients receiving intensive chemotherapy for hematologic malignancy and stem cell transplantation showed that a change from a double to single unit RBC transfusion policy is safe, sufficient to treat anemia, and associated with a reduction by 25% in RBC transfusion requirements and reduction in other complications associated with RBC transfusion (11). There was no evidence of more severe bleeding or more platelet transfusions during the single unit period, and the overall survival was similar in both single and double unit cohorts. Clearly, further studies to assess the impact of reduced RBC transfusion support in intensive chemotherapy and stem cell transplantation are indicated.

The work of Wermke and colleagues adds to the growing body of literature in renal (12) and hepatologic (5) fields, which documents the nonspecificity of serum ferritin as a marker of iron overload and the superiority of MRI-based methods for documentation of LIC (4, 5, 12). While the evidence is clear, the major limitations of such noninvasive approaches relate to availability, standardization, and cost. The MRI approach described in the current study (1.5 Tesla scanner, protocol based on gradient recalled echo sequences), is not licensed by regulatory authorities and does not have internationally standardized quality controls. While FerriScan is standardized and does have regulatory approval and quality control systems, it is not reimbursable in many countries, limiting availability. However, it may be possible to mount arguments for reimbursement based on studies such as those of Wermke and colleagues, which indicate that early identification of at-risk patients and early treatment with iron-chelation therapy might reduce iron-mediated toxicity and potentially improve outcomes. This seems innately sensible given the large resource costs of allo-SCT.

Wermke and colleagues have provided compelling information on the dangers of SIO after allo-SCT, which adds to our current understanding of iron overload increasing morbidity and mortality and decreasing quality of life. Furthermore, knowledge of the dangers of SIO has ramifications for patients with nonmalignant hematologic conditions. It is now time to revise the standard-of-care for diagnosis of SIO to include liver MRI as the gold standard in assessing LIC. Such technologies will allow definitive evaluation of the impact of early-chelation treatment to reduce iron burden and ensure that patients are in optimal condition before, or
following, allo-SCT, so that transplantation outcomes can continue to improve.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: M.F. Leahy, J.K. Olynyk
Development of methodology: J.K. Olynyk
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.K. Olynyk
Writing, review, and/or revision of the manuscript: P.C. Krugler, M.F. Leahy, J.K. Olynyk
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.K. Olynyk

Received September 25, 2012; accepted September 28, 2012; published OnlineFirst October 10, 2012.

References
Assessing Iron Overload: Are We There Yet?
Paul C. Kruger, Michael F. Leahy and John K. Olynyk


Updated version
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-12-2881

Cited articles
This article cites 12 articles, 5 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/18/23/6395.full#ref-list-1

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, use this link
http://clincancerres.aacrjournals.org/content/18/23/6395.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.