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Hepcidin and \(\beta\)-thalassemia major

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In this issue of *Blood*, Pasricha et al evaluated serum hepcidin and its putative pathological suppressor growth differentiation factor-15 (GDF-15) in patients with \(\beta\)-thalassemia major before and after transfusion, in the context of erythropoietic activity and iron loading. The study offers insight into dynamic regulation of hepcidin in this disease, reinforces the likely contribution of hepcidin to iron loading between transfusions, and highlights the potential clinical utility of hepcidin measurements in the management of patients with \(\beta\)-thalassemia major.1

Iron overload is the major cause of morbidity and mortality in patients with moderate to severe \(\beta\)-thalassemia. Iron overload is also seen in patients with other anemias with ineffective erythropoiesis, including patients with congenital dyserythropoietic anemias. Although erythrocyte transfusions are frequently the predominant source of iron (each milliliter of packed erythrocytes contains about 1 mg of iron), it is now widely appreciated that even non–transfusion-dependent thalassemia patients often develop lethal iron overload.2 The discovery of the pathological suppression of the iron-regulatory hormone hepcidin in \(\beta\)-thalassemia and other iron-loading anemias3-5 provided an explanation for these counterintuitive observations. Hepcidin deficiency allows increased intestinal iron absorption, often to rates similar to those in severe hereditary hemochromatosis.

In iron-loading anemias, hepcidin is thought to be regulated by the opposing influences of erythropoietic activity, which suppresses hepcidin, and iron loading, which increases hepcidin.6 Pasricha et al1 clearly demonstrated that even in \(\beta\)-thalassemia major patients, who are highly iron overloaded, serum hepcidin levels are lower than would be expected because of the exuberant erythropoiesis. The observed average doubling of serum hepcidin after transfusion is a mirror image of the average 50% reduction in serum erythropoietin and contrasts with the very minor posttransfusion changes in serum ferritin levels. Thus, the effect of transfusions on hepcidin is due to the correction of anemia and the associated decrease in erythropoietin concentrations (see figure) and is not related to the iron content of transfused erythrocytes.

The study also demonstrated that the posttransfusion suppression of erythropoiesis was less effective in men than women, and this was reflected by the lower posttransfusion hepcidin in men compared with women. The explanation for gender difference likely lies in men having a higher blood volume; thus, the male patients received a lower transfusion dose per unit blood volume. In addition, as men naturally have higher hemoglobin (Hb) levels than women, higher Hb concentrations may be required in men to suppress erythropoietic drive. The authors suggest that treatment guidelines may need to be adjusted to account for gender differences in blood volume, and hepcidin may be helpful in assessing the effectiveness of the transfusion regimen.

Why is hepcidin suppressed in ineffective erythropoiesis? Based on studies in patients with \(\beta\)-thalassemia and other iron-loading anemias, as well as related animal models and
In this issue of Blood, Khan and colleagues evaluated the clinical implications of marrow involvement identified by FDG–PET-CT (2-[18F]fluoro-2-deoxy-d-glucose–positron emission tomography combined with computed tomography) vs iliac crest biopsy in newly diagnosed patients with diffuse large B-cell lymphoma (DLBCL). They showed that FDG–PET-CT scanning had a higher level of accuracy for identifying marrow disease than bone marrow (BM) biopsy (BMB). Nevertheless, the identification of BM involvement by histology per se still had a prognostic impact in terms of overall survival (OS) and progression-free survival (PFS).

In recent years, FDG–PET-CT scanning has been used as a powerful tool in staging most patients with a variety of subtypes of lymphoma before starting and after completing chemotherapy. Recently, El-Galaly et al demonstrated that routine BMB added limited useful clinical information and had no therapeutic consequences in newly diagnosed patients with Hodgkin lymphoma (HL) staged by FDG–PET-CT scan. Consequently, it appears that the value of routine BMB in treatment-naive patients with HL undergoing FDG–PET-CT staging is now obsolete. Furthermore, the prognostic significance of early interim-PET activity in patients with HL has also been established recently. In this regard, the ongoing large multicenter studies, incorporating risk-adapted strategies based on PET activity, will hopefully provide guidance in how to spare these patients from developing both the acute and long-term toxicities of these highly efficient therapies developed for HL over the last 40 years. Unfortunately, this is not the case for DLBCL, where the prognostic significance of early interim-PET results is still debatable and remains an open issue because of the inconsistent and conflicting results obtained in the different clinical studies.

The main objective of the present study by Khan et al was to determine whether routine BMB could also be omitted at diagnosis in patients with DLBCL staged by FDG–PET-CT scan, as shown in newly diagnosed patients with HL. This retrospective study provides valuable data on the power of FDG–PET-CT scanning in detecting focal BM involvement with DLBCL. Indeed, PET scanning identified all the clinically important marrow involvement by lymphoma while BMB did not upstage any patient. The sensitivity and specificity for identifying marrow involvement were as high as 94% and 100% for PET-CT scan and only 40% and 100% for BMB, respectively. Furthermore, the overall accuracy was 98.5% for PET-CT scan and 84% for BMB. These data are very convincing indeed and may well lead to omission of routine BMB in patients staged by PET-CT scan who have focal marrow involvement by DLBCL. Only patients with
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