cellular studies, it has been proposed that erythropoietin-stimulated erythroblasts produce secreted mediators that act on the liver to suppress hepcidin production. Dying erythroblasts or erythroblasts that fail to mature appropriately may further contribute to secretion of hepcidin suppressors, perhaps explaining the paradoxical lack of iron overload in patients with expanded erythroblasts but normal maturation, such as in untransfused chronic hemolytic anemias.

GDF-15 has been proposed as a hepcidin suppressor in β-thalassemia. GDF-15 is secreted by late and apoptotic erythroblasts, and its levels are greatly elevated in human β-thalassemia patients, although not in a thalassemia mouse model. A definitive demonstration of the role of GDF-15 in hepcidin suppression in thalassemia is still missing, and it seems that GDF-15 does not play a role in physiological hepcidin suppression after hemorrhage. In the current study, GDF-15 levels were greatly elevated before transfusion, as expected. After transfusion, GDF-15 decreased by 25% to 35%, but still remained extremely high compared with normal levels. Although the current study does not provide evidence for a specific hepcidin suppressor, it highlights the importance of this regulation in β-thalassemia. The nature of the hepcidin-suppressive erythroblast-derived mediators (erythrokines) is an active area of research, with important implications for the diagnosis and treatment of iron-loading anemias.

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 Comment on Khan et al, page 61

**Staging DLBCL: bone marrow biopsy or PET-CT?**

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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).1

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 al2 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.3 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.4

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
the rare pattern of diffuse FDG uptake throughout the skeleton may still need marrow biopsy to determine pathology other than DLBCL, such as reactive myelopoiesis.

Detection of marrow involvement by either FDG–PET–CT scan or biopsy was, however, associated with different outcomes. In this cohort, patients with marrow involvement detected by PET had similar PFS and OS to those individuals with stage IV disease without an involved marrow, while narrow involvement identified by biopsy was associated with worse outcome (see figure).

The possible explanation for this difference could relate to the limitations of BMB in detecting only extensive BM involvement (which is probably an important surrogate along with other clinical parameters for poor-risk disease), while FDG–PET–CT scanning is more sensitive in identifying limited BM involvement. This explanation remains speculative due to the low number of cases with a positive BMB in this cohort of patients. Because of this, the authors were unable to demonstrate whether BM histology was an independent predictor of poor outcome, using a multivariate analysis.1

The decision to spare patients with DLBCL the distress of marrow biopsy is even more problematic in the light of the data provided by Sehn et al,5 who studied the prognostic impact of concordant vs discordant marrow involvement in a large cohort of patients with DLBCL treated with R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone). The results of their study showed that concordant BM involvement negatively affects both OS and PFS independently of the International Prognostic Index (IPI), while discordant involvement negatively impacts only on PFS and is adequately reflected in the IPI score. The latter study emphasizes the need for accurate assessment of the nature of marrow involvement before commencing treatment in previously untreated patients with DLBCL.

Considering all the data together, it appears that in contrast to HL, there is no clear-cut answer to the question posed in the title of this commentary. I tend to agree with the authors’ claim that in clinical practice routine BMB is no longer necessary for all patients with DLBCL who are staged in experienced PET centers, unless the results would change both staging and therapy. The decision to omit BMB in this group of patients will definitely relieve the distress and “agony” which accompany the procedure. However, given the significant impact of BM histopathology on survival and outcome in DLBCL, as reported in this1 and other studies,2,3 the exclusion of BMB from staging procedures in DLBCL does not as yet appear justified in the context of clinical trials. In the light of these data, the role of BMB in DLBCL will probably be one of the major debatable issues in the upcoming workshops dealing with the new proposals to change staging criteria and response assessment for lymphoma.

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