Critical Views on the Prognostic Potential and Interpretation of Bone Marrow ^{18}F-FDG PET in Diffuse Large B-Cell Lymphoma

TO THE EDITOR: We read with interest the recent article by Cerci et al. (*1*), who performed a prospective multinational cohort study in 327 patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL) to determine the relative prognostic implications of blind bone marrow biopsy (BMB) and ^{18}F-FDG PET–based bone marrow status in this disease. We would like to share our views on the roles of BMB and ^{18}F-FDG PET in the prognostication of DLBCL and the interpretation of nonfocal diffusely increased bone marrow ^{18}F-FDG uptake in these patients.

Cerci et al. reported that neither BMB nor ^{18}F-FDG PET alone is a reliable indicator of poor-risk bone marrow disease. Only bone marrow involvement identified by both ^{18}F-FDG PET and histology was found to indicate a poor prognosis. The authors speculated that blind BMB is more likely to be tumor-positive in cases of more extensive marrow disease. That, rather than bone marrow involvement per se, was thought to be associated with a worse patient outcome. First, we do not agree with the authors' statement that BMB alone is not a reliable indicator of poor prognosis. Numerous large-scale studies have demonstrated that BMB-based bone marrow status is an independent predictor of outcome (*2–4*). Second, we believe bone marrow ^{18}F-FDG PET has not yet convincingly been shown to have prognostic value in DLBCL. Cerci et al. claimed the combination of both positive bone marrow ^{18}F-FDG PET and BMB findings to be of predictive value, but its incremental value over BMB-based bone marrow status alone was not assessed. In addition, the prognostic value of ^{18}F-FDG PET–based bone marrow status alone was not reported at all. Therefore, we believe Cerci et al. provided insufficient data to support their conclusion that bone marrow staging by ^{18}F-FDG PET is important for defining prognosis in DLBCL. On the contrary, our own recently published data indicate that, unlike BMB, ^{18}F-FDG PET–based bone marrow status has no value at all in predicting either progression-free survival or overall survival in newly diagnosed DLBCL (*5*). In our study, we also measured metabolic tumor volume and total lesion glycolysis of all ^{18}F-FDG–avid bone marrow lesions in each patient, but this did not have any prognostic value either (*5*). This finding contradicts the speculation of Cerci et al. that the amount of tumor burden in the bone marrow may be predictive of survival, at least when ^{18}F-FDG PET is used for this purpose. Furthermore, risk assessment by BMB may reach beyond that by dichotomizing into groups with and without marrow involvement (*6–8*). In the study by Cerci et al. the group of patients with positive BMB and negative bone marrow ^{18}F-FDG PET findings had a favorable outcome but consisted of 6 patients with large-cell low-volume tumor involvement, 2 with small-cell involvement, and only 2 with large-cell high-volume involvement, the last of which is known to have a major adverse impact on patient outcome (*6–8*). Unfortunately, Cerci et al. did not report how frequently large-cell high-volume involvement was observed in the group of patients who were positive for bone marrow involvement both on ^{18}F-FDG PET and BMB. However, it is not unlikely that the prevalence of large-cell high-volume bone marrow involvement was higher in this group, enabling an even more detailed risk assessment solely by BMB results and thus reducing the additional benefit of bone marrow ^{18}F-FDG PET.

Cerci et al. also reported that of their 18 patients who appeared to have nonfocal diffusely increased bone marrow ^{18}F-FDG uptake, only 4 had histologic evidence of marrow disease on iliac crest biopsy. Although this finding may suggest that this particular bone marrow appearance on ^{18}F-FDG PET is not associated with or due to lymphomatous bone marrow involvement in most cases, the finding should be interpreted cautiously. First, Cerci et al. did not indicate whether patients who were treated with hematopoietic growth factors (a well-known cause of diffusely increased bone marrow ^{18}F-FDG uptake (*9*)) were excluded. Second, the criterion that was used to define the presence of diffusely increased bone marrow ^{18}F-FDG uptake was not reported. This, in combination with ^{18}F-FDG interpretation by different observers, may have introduced considerable reader variability that may have affected their results (*9*). Our own unpublished results indicate that BMB is positive in most cases of treatment-naive non-Hodgkin lymphoma, including DLBCL, when nonfocal diffuse bone marrow ^{18}F-FDG uptake exceeds liver ^{18}F-FDG uptake.

In conclusion, it is our opinion that, unlike BMB, the prognostic potential of bone marrow ^{18}F-FDG PET in DLBCL has not been proven yet. Furthermore, we believe that the phenomenon of nonfocal diffusely increased bone marrow ^{18}F-FDG uptake in DLBCL should be interpreted within the appropriate clinical context (particularly considering recently administered therapies) and using standardized criteria, to predict the most likely histologic correlate.

DISCLOSURE

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REPLY: We thank Adams and Kwee for their critical review of our paper (*1*). We clarify that, as implied by the title, the paper reports marrow involvement by large B-cell lymphoma in cases presenting with diffuse large B-cell lymphoma (DLBCL). Only 2% (2/87) of cases with positive marrow histology had small cell lymphoproliferative disease identified as the sole infiltrate. We also clarify that as marrow was assessed on the staging PET examination, this was before any steroid, chemotherapy, or growth factor was given.

The authors are incorrect in stating that we report neither the prognostic significance of ^{18}F-FDG PET–positive marrow disease alone nor the incremental value of PET-positive together with bone marrow biopsy (BMB)–positive involvement over BMB-positive involvement alone. Our cohort of 327 cases was large enough to explore, in a multivariate model including the International Prognostic Index components, the prognosis of marrow disease identified by PET alone, BMB alone, and PET and BMB together. We report, in Table 4, that compared with cases with no marrow involvement, PET-positive marrow disease alone has no significant effect on survival ($P = 0.46$), nor does BMB-positive marrow disease alone ($P = 0.49$). In contrast, marrow disease identified by both PET and BMB does have a significant impact on survival ($P = 0.05$) (*1*).

In their own research, Adams and Kwee focus on the argument as to whether either BMB or ^{18}F-FDG PET is best at assessing for marrow involvement, for the clinical purpose of predicting prognosis and guiding treatment. Their recent publications present conflicting views; on the one hand they "support the omission of BMB for routine staging of newly diagnosed DLBCL," and on the other hand they state that "visual 18-FDG PET/CT bone marrow status has no prognostic value. . .and cannot replace BMB in newly diagnosed DLBCL" (*2,3*).

Their dichotomous focus leads them to overlook the clinical relevance of our report, which, with the benefit of 327 prospectively collected cases, examines this conundrum from the perspective of the treating clinician's decision making and the patient's overall benefit.

The message of our paper is both practical and simple. All centers having this debate will be doing staging PET or PET/CT scans on all DLBCL patients; hence, assessment of abnormal ^{18}F-FDG uptake in marrow is routinely available for all cases. The data from our large cohort demonstrate that those with PET-negative marrow gain no clinical benefit, in terms of altered prognosis, from a routine iliac crest biopsy. These patients, 74% of the cohort, can therefore omit and avoid the pain and distress of this procedure. However, those with PET-positive marrow do gain clinically important additional information from a biopsy, whether ^{18}F-FDG uptake is focal or diffuse.

Diffuse ^{18}F-FDG uptake was quite clearly defined in the methods, contrary to Adams' and Kwee's statement, and the definition was based on previously reported criteria, namely diffuse homogeneous ^{18}F-FDG uptake throughout the marrow space, with intensity greater than uptake in normal liver and with no anatomic changes to suggest alternative benign bone pathology or spread from a contiguous nonskeletal site (*1,4*). We agree that diffuse ^{18}F-FDG uptake in marrow is difficult to assess (though assessment improves with experience) and that, consequently, marrow showing diffuse uptake should always undergo biopsy (*1,5,6*).

Focal marrow involvement identified by PET together with marrow biopsy histology showing large cell lymphoma does confer a worse prognosis than PET-positive/marrow histology–negative marrow disease, as shown in Figure 3 (*1*). Hence derives our statement that both biopsy and PET together have a role to play in the staging of DLBCL but that the addition of a marrow biopsy when PET data are already available is useful in only a minority of patients.

Although Adams and Kwee conclude that the prognostic potential of marrow assessment in DLBCL by PET has not yet been proven, our study does clarify the distinct and separate roles of PET and marrow biopsy for predicting outcome and hence influencing treatment decisions.

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