The JOURNAL of ONCOPATHOLOGY

Expert Perspective

[^{18}F]-FDG PET/CT Bests Gold Standard Bone Marrow Biopsy for Diagnosis and Prognosis of Lymphoma Patients

Louis Berthet, M.D

Lymphoma is classified into 3 major entities: Hodgkin lymphoma (HL), aggressive, and indolent non-Hodgkin lymphoma (NHL).

Accurate staging of lymphoma in adult and pediatric patients is necessary in selecting appropriate treatment and avoid unnecessary acute and long-term side effects of therapies.

Thus, assessment of bone marrow involvement (BMI) by lymphoma is important since it potentially changes staging.[1–4]

According to the most recent guidelines regarding lymphoma staging, bone marrow biopsy (BMB) is the standard procedure for assessment of bone marrow.[2]

Nevertheless, it is an invasive and painful procedure that explores a limited part of the bone marrow.[5] It would be an advancement to spare patients the distress of BMB with a noninvasive procedure that can evaluate more precisely BMI.

Despite actual guidelines stating that pretherapy [^{18}F]-FDG PET/CT is not obligatory to evaluate the response after treatment of patients with HL and aggressive NHL, this molecular imaging procedure is now widely used for staging and assessing response to therapy.

Guidelines state that clearly increased (multi)focal bone (marrow) uptake should be interpreted as positive for lymphoma but a negative [^{18}F]-FDG PET/CT in the bone marrow does not exclude mild or moderate BMI.[2] Indeed, [^{18}F]-FDG PET/CT is generally considered positive for BMI in cases of uni- or multifocal bone marrow [^{18}F]-FDG uptake that could not be explained by benign findings on the underlying CT image or history (eg fractures). Therefore, diffuse bone marrow [^{18}F]-FDG uptake is considered negative for BMI (diffuse intense uptake is related to anemia or inflammatory processes).[6]

Since those guidelines, the ability of [^{18}F]-FDG PET/CT to evaluate BMI in patients with lymphoma has been widely investigated.[6–16]

Consensus seems to have grown on HL and indolent NHL in totally different ways. I will not then detail the interest of [^{18}F]-FDG PET/CT to detect BMI in these two lymphoma subtypes.

Large data have been published in HL. In this lymphoma subtype, [^{18}F]-FDG PET/CT highly improves sensitivity for diagnosis of BMI compared to conventional staging. Furthermore, BMB adds limited useful clinical information and has no therapeutic consequences in newly diagnosed patients staged by [^{18}F]-FDG PET/CT. Therefore, BMB is considered obsolete in HL since it only detects extensive BMI that is always detected by pretherapy [^{18}F]-FDG PET/CT.[11,12,14–16]

By contrast, it has been demonstrated that indolent NHL has variable [^{18}F]-FDG avidity. Hence, in cases of negative [^{18}F]-FDG PET/CT, BMB cannot be avoided. Thus, BMB is still the gold standard to evaluate BMI in this type of lymphoma.[7,10,17]

Nevertheless, in cases of positive result, [^{18}F]-FDG PET/CT should not be ignored.

On the contrary, in aggressive NHL, consensus has not yet been found. Diffuse large B-cell lymphoma (DLBCL) is the preponderant subtype of this kind of lymphoma. It is in this specific lymphoma subtype that recent studies have shown promising results for [^{18}F]-FDG PET/CT.

It has been well documented that [^{18}F]-FDG PET/CT is at least complementary to BMB (guidance of the biopsy) in DLBCL.[2,6,7,10,13]

Recent studies have evaluated if, like in HL, BMB could be replaced by [^{18}F]-FDG PET/CT. It has been shown that noninvasive morphological procedures (MRI, [^{18}F]-FDG PET/CT) could be superior to BMB. Compared to BMB, [^{18}F]-FDG PET/CT has a better sensitivity (>95 vs. <60%), accuracy (>95 vs. <90%), and negative predictive value (>95 vs. <90%). On the contrary, BMB has a better specificity (100% vs. > 95%) and positive predictive value (100 vs. >90%).[6,8,10,13,17] Moreover, by [^{18}F]-FDG PET/CT, the false negative rate of BMI by DLBCL has been evaluated at <3%.[6]

But the most interesting findings concern the clinical values of the high sensitivity and high specificity. Indeed, it has been shown that [^{18}F]-FDG PET/CT bone marrow status is an independent predictor of progression-free survival (PFS) while BMB bone marrow status is not.[6] Then, [^{18}F]-FDG PET/CT should be employed as a first-line study, and is essential during the staging of DLBCL since BMI detected by [^{18}F]-FDG PET/CT is clinically relevant.

However, BMB could be useful to predict survival in patients already considered stage IV.[13]

It has also been proved that histology of BMI is important for staging. Concordant BMI (BMI by aggressive NHL) affects both overall survival (OS) and PFS, regardless of the International Prognosis Index (IPI) while discordant BMI (BMI by indolent NHL) impacts only PFS as the IPI.[18]

By changing prognostic scores, [^{18}F]-FDG PET/CT could enable hematologists to implement the best treatment for their patients. Moreover, since an examination procedure with perfect sensitivity and specificity does not exist, the best one should be chosen. I personally have no doubt that noninvasive morphological procedures will replace BMB as a first-line study, even if BMB may keep an interest in some situations. Prospective studies conducted by important institutions as the Eastern Cooperative Oncology Group (ECOG) and the Lymphoma Study Association (LYSA) could answer this question definitively. On the basis of these new insights, new guidelines should be proposed concerning usefulness of pretherapy [^{18}F]-FDG PET/CT and its role regarding BMI assessment in HL, indolent, and aggressive NHL.

ACKNOWLEDGMENTS

The author thanks Orland Angoue for his assistance in the revision of the manuscript.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author indicated no potential conflicts of interest.

From the Nuclear Medicine Department, University Hospital of Besançon, Besancon, France (L.B.). Correspondence: Louis Berthet, M.D., Nuclear Medicine Department, University Hospital of Besançon, 3 bd Fleming, Besancon 25000, France (berthet.louis@free.fr).

Conception and design: LB
Collection and assembly of data: LB
Data analysis and interpretation: LB
Manuscript writing: LB
Final approval of manuscript: LB

Submitted September 25, 2013; revised September 8, 2013; accepted October 20, 2013

TJOP 2013:00:1–6
DOI: 10.13032/tjop.2052100073.

REFERENCES

1. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol.* 2007;25:579–586.
2. Juweid ME, Stroobants S, Hoekstra OS, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. *J Clin Oncol.* 2007;25:571–578.
3. Rosenberg SA. Validity of the Ann Arbor staging classification for the non-Hodgkin's lymphomas. *Cancer Treat Rep.* 1977;61:1023–1027.
4. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med.* 1993;329:987–994.
5. Bain BJ. Bone marrow biopsy morbidity and mortality. *Br J Haematol.* 2003;121:949–951.
6. Berthet L, Cochet A, Kanoun S, et al. In newly diagnosed diffuse large B-cell lymphoma, determination of bone marrow involvement with 18F-FDG PET/CT provides better diagnostic performance and prognostic stratification than does biopsy. *J Nucl Med.* 2013;54:1244–1250.

7. Pakos EE, Fotopoulos AD, Ioannidis JP. 18F-FDG PET for evaluation of bone marrow infiltration in staging of lymphoma: a meta-analysis. *J Nucl Med.* 2005; 46:958–963.
8. Ribrag V, Vanel D, Leboulleux S, et al. Prospective study of bone marrow infiltration in aggressive lymphoma by three independent methods: whole-body MRI, PET/CT and bone marrow biopsy. *Eur J Radiol.* 2008;66(2):325–331.
9. Cheng G, Chen W, Chamroonrat W, Torigian DA, Zhuang H, Alavi A. Biopsy versus FDG PET/CT in the initial evaluation of bone marrow involvement in pediatric lymphoma patients. *Eur J Nucl Med Mol Imaging.* 2011;38(8):1469–1476.
10. Pelosi E, Penna D, Douroukas A, et al. Bone marrow disease detection with FDG-PET/CT and bone marrow biopsy during the staging of malignant lymphoma: results from a large multicentre study. *Q J Nucl Med Mol Imaging.* 2011;55:469–475.
11. Agrawal K, Mittal BR, Bansal D, et al. Role of F-18 FDG PET/CT in assessing bone marrow involvement in pediatric Hodgkin's lymphoma. *Ann Nucl Med.* 2013;27(2):146–151.
12. Hamilton R, Andrews I, McKay P, Leach M. Loss of utility of bone marrow biopsy as a staging evaluation for Hodgkin lymphoma in the positron emission tomography-computed tomography era: a West of Scotland study. *Leuk Lymphoma.* 2013 (press).
13. Khan AB, Barrington SF, Mikhaeel NG, et al. PET-CT staging of DLBCL accurately identifies and provides new insight into the clinical significance of bone marrow involvement. *Blood.* 2013; 122(1):61–67.
14. Moulin-Romsee G, Hindié E, Cuenca X, et al. (18)F-FDG PET/CT bone/bone marrow findings in Hodgkin's lymphoma may circumvent the use of bone marrow trephine biopsy at diagnosis staging. *Eur J Nucl Med Mol Imaging.* 2010;37(6): 1095–1105.
15. El-Galaly TC, d' Amore F, Mylam KJ, et al. Routine bone marrow biopsy has little or no therapeutic consequence for positron emission tomography/computed tomography-staged treatment-naive patients with Hodgkin lymphoma. *J Clin Oncol.* 2012;30(36):4508–4514.
16. Cheng G, Alavi A. Value of 18F-FDG PET versus iliac biopsy in the initial evaluation of bone marrow infiltration in the case of Hodgkin's disease: a meta-analysis. *Nucl Med Commun.* 2013;34: 25–31.
17. Adams HJA, Kwee TC, Vermoolen MA, et al. Whole-body MRI for the detection of bone marrow involvement in lymphoma: prospective study in 116 patients and comparison with FDG-PET. *Eur Radiol.* 2013.
18. Sehn LH, Scott DW, Chhanabhai M, et al. Impact of concordant and discordant bone marrow involvement on outcome in diffuse large B-cell lymphoma treated with R-CHOP. *J Clin Oncol.* 2011; 29:1452–1457.