Journal of Bone Marrow Research

Caldarella et al., J Bone Marrow Res 2014, 2:1
http://dx.doi.org/10.4172/2329-8820.1000e111

Editorial Open Access

Bone Marrow Involvement in Hodgkin and Non-Hodgkin Lymphomas: The Role of Fluorine-18-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography

Carmelo Caldarella[1], Maria Antonietta Isgrò[2] and Giorgio Treglia[3]*

[1]*Institute of Nuclear Medicine, Catholic University of the Sacred Heart, 00168, Rome, Italy*
[2]*Institute of Biochemistry and Clinical Biochemistry, Catholic University of the Sacred Heart, 00168, Rome, Italy*
[3]*Department of Nuclear Medicine and PET/CT Center, Oncology Institute of Southern Switzerland, 6500, Bellinzona, Switzerland*

Lymphomas are the most common haematological malignancies, accounting for the 5% of all cancers in both genders. Incidence of Hodgkin lymphoma is about 2.8 new cases per 100,000 people per year; overall incidence of non-Hodgkin lymphomas is about 19.7 new cases per 100,000 people per year [1,2]. Estimated 5-year survival rate depends on several factors: age at diagnosis (co-morbidity in older patients negatively affects prognosis), blood haemoglobin and serum LDH levels, presence of extra-nodal disease, and above all the initial stage of disease: about 90% in patients with stage I Hodgkin lymphoma; about 65% in patients with stage IV Hodgkin lymphoma. In non-Hodgkin lymphomas, survival rates may vary widely depending on the lymphoma type (aggressive or indolent) and the presence of the aforementioned risk factors: from 91% in low-risk patients to 53% in high-risk ones [2]. However, in both Hodgkin and non-Hodgkin lymphomas, the evidence of bone marrow involvement indicates the highest Ann Arbor stage (stage IV) by itself, with several therapeutic implications [3,4]. Therefore, the assessment of eventual bone marrow involvement is recommended in all patients with aggressive non-Hodgkin lymphoma, such as diffuse large B-cell lymphoma (DLBCL), that could benefit from curative treatment and in Hodgkin lymphoma, especially with stage III-IV disease or stage II disease with adverse risk factors, when a change in therapy planning is expected depending on the presence/absence of bone marrow disease [5-7].

Blind Bone Marrow Biopsy (BMB) of the iliac crest, either performed unilaterally or bilaterally, is the gold standard method for diagnosing bone marrow involvement in lymphomas and in other haematological entities, like multiple myeloma [8]. However, it is a painful and invasive procedure which can cause long-lasting discomfort in most patients and it is not free from complications, such as allergic reactions to local anaesthesia, excessive bleeding or infection of the sampling site. Moreover, BMB is prone to false-negative findings deriving from the fact that a very small portion of bone marrow is sampled and analyzed, thus leading to misdiagnosis in patients with bone marrow disease in sites other than the iliac crest.

Positron emission tomography/computed tomography using fluorine-18-fluorodeoxyglucose (FDG PET/CT) is a diagnostic technique which is currently used in a variety of oncological settings [9]. Since Hodgkin and aggressive non-Hodgkin lymphomas show an intense glucose metabolism and therefore a high FDG uptake [9], FDG PET/CT can be helpful in both nodal and extra-nodal staging of lymphoma, including the bone marrow assessment. A major advantage of FDG PET/CT is its non-invasiveness, with respect to BMB; furthermore, its ability to study the entire bone marrow overcomes the false-negative findings of BMB in case of sampling error, rather being used as a possible substitute for BMB or as a guide to perform a targeted biopsy in sites showing intramedullary focal uptake of FDG.

In this regard, a recently published paper from Khan et al. [10] has investigated whether FDG PET/CT identifies clinically relevant bone marrow involvement in patients with DLBCL with a sufficient accuracy to replace routine staging BMB. In their cohort of patients, FDG PET/CT identified all clinically important bone marrow involvement, with sensitivity and specificity values of 94% and 100%, respectively; on the contrary, sensitivity and specificity values for BMB were 40% and 100%, respectively, and BMB did not upstage any patient. Indeed, patients with both FDG PET/CT and BMB positive findings showed a lower progression-free survival than those not confirmed on BMB. Similarly, Berthet et al. [11] have demonstrated that the FDG PET/CT bone marrow status is an independent predictor of progression-free survival in patients with DLBCL; conversely, Hong et al. [12] found no significant differences in progression-free and overall survival in patients with positive or negative findings on FDG PET/CT.

Performance of FDG PET/CT in detecting bone marrow involvement was compared to contrast enhanced CT scan (CE-CT) in a prospective study by Omür et al. [13], on a cohort of 110 patients with lymphoma (35 Hodgkin; 75 non-Hodgkin): they showed that CE-CT was falsely negative in 6 Hodgkin and 11 non-Hodgkin patients with bone marrow involvement on FDG PET/CT. All 17 cases were confirmed on BMB and successfully treated, with evidence of complete metabolic response on post-treatment PET/CT scans.

A more extensive evaluation concerning the role of FDG PET/CT to assess bone marrow involvement in patients with newly diagnosed Hodgkin lymphoma was performed in a systematic review and meta-analysis by Adams et al. [14]: despite different methodological aspects among the selected studies, pooled sensitivity and specificity of FDG PET/CT in assessing bone marrow involvement, with respect to BMB and follow FDG PET/CT scans used as reference standard, were 96.9% and 99.7%, respectively. Overall accuracy was 98.6%. In addition, the chance of having a positive BMB in a patient with negative findings on FDG PET/CT is very low. Criteria to assess positivity for bone marrow involvement on FDG PET/CT in patients with Hodgkin lymphoma may vary from one study to another: bone marrow FDG uptake higher than the liver, focal, multi-focal or abnormally increased FDG uptake, or bone marrow FDG uptake higher than the mediastinal blood pool as reference.

***Corresponding author:** Giorgio Treglia, Nuclear Medicine and PET/CT Center, Oncology Institute of Southern Switzerland, Via Ospedale, 12 CH-6500, Bellinzona, Switzerland, Tel: +41918118919; E-mail: giorgiomednuc@libero.it

Received February 21, 2014; **Accepted** February 24, 2014; **Published** February 27, 2014

Citation: Caldarella C, Isgrò MA, Treglia G (2014) Bone Marrow Involvement in Hodgkin and Non-Hodgkin Lymphomas: The Role of Fluorine-18-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography. J Bone Marrow Res 2: e111. doi:10.4172/2329-8820.1000e111

The same authors also have systematically reviewed and meta-analyzed the role of FDG PET/CT for assessing bone marrow involvement in patients with DLBCL [15], which represents the 30-35% of all non-Hodgkin lymphomas by itself. Pooled sensitivity and specificity of FDG PET/CT were 88.7% and 99.8%, respectively, with an overall accuracy of 99.8%. The proportion of patients with negative FDG PET/CT and positive BMB finding was low (about 3.1%), while FDG PET/CT was able to detect bone marrow involvement when missed by BMB in 12.5% of patients. Thus, bone marrow involvement is almost certain when FDG PET/CT is positive, and BMB could be omitted in these patients. Criteria to assess positivity for bone marrow involvement on FDG PET/CT were either FDG uptake in the bone marrow higher than in the liver or focal (single focus or multiple foci) bone marrow uptake that could not be explained by benign findings on the underlying CT image or history.

However, it is not clear whether a diffuse bone marrow FDG uptake should be regarded as positive for bone marrow involvement, although the aforementioned meta-analysis [15] demonstrates that 12 out of 14 patients (85.7%) with diffuse bone marrow uptake on FDG PET/CT had positive BMB findings.

A recent study by El-Galaly et al. [16] has compared retrospectively the staging results in a large cohort of patients with Hodgkin lymphoma diagnosed before and after the introduction of FDG PET/CT: advanced stage disease (stage IV) was more frequently diagnosed after the introduction of PET/CT than before, while early stage disease (stage I) was less frequent. Besides, the presence of focal FDG bone marrow uptake was associated with a higher risk of progression.

Despite excellent performance in bone marrow staging in both Hodgkin and non-Hodgkin lymphomas, FDG PET/CT false-positive findings may occur, especially when diffuse bone marrow and splenic uptake are observed at the initial imaging. As demonstrated by Salaun et al. [17], diffuse bone marrow uptake is more likely to be due to inflammatory changes than bone marrow involvement, while splenic uptake more frequently reflects disease involvement. Similarly, reduction in FDG uptake after treatment could be attributed either to response in sites of lymphomatous infiltration or to the resolution of benign inflammatory involvement.

In conclusion, FDG PET/CT is a reliable and accurate diagnostic tool for the assessment of bone marrow disease and correct staging of patients with Hodgkin or non-Hodgkin lymphomas, with a greater sensitivity than BMB in detecting focal involvement non-invasively; however, because of the risk of possible false-positive inflammatory findings, the use of both BMB and FDG PET/CT in the pre-treatment setting can be considered acceptable in clinical practice.

References

1. SEER fact stat sheets. Hodgkin Lymphoma.
2. SEER fact stat sheets: Non-Hodgkin Lymphoma.
3. Flowers CR, Sinha R, Vose JM (2010) Improving outcomes for patients with diffuse large B-cell lymphoma. CA Cancer J Clin 60: 393-408.
4. Connors JM (2005) State-of-the-art therapeutics: Hodgkin's lymphoma. J Clin Oncol 23: 6400-6408.
5. Tilly H, Vitolo U, Walewski J, da Silva MG, Shpilberg O, et al. (2012) Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 23 Suppl 7: vii78-vii82.
6. Eichenauer DA, Engert A, Dreyling M (2011) Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 22 Suppl 6: V55-V58.
7. Lister TA, Crowther D, Sutcliffe SB, Glatstein E, Canellos GP, et al. (1989) Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol 7: 1630-1636.
8. Caldarella C, Isgrò MA, Treglia I, Treglia G (2012) Is fluorine-18-fluorodeoxyglucose positron emission tomography useful in monitoring the response to treatment in patients with multiple myeloma? Int J Hematol 96: 685-691.
9. Treglia G, Cason E, Fagioli G (2010) Recent applications of nuclear medicine in diagnostics (1 part). Ital J Med 4: 84-91.
10. Khan AB, Barrington SF, Mikhaeel NG, Hunt AA, Cameron L, et al. (2013) PET-CT staging of DLBCL accurately identifies and provides new insight into the clinical significance of bone marrow involvement. Blood 122: 61-67.
11. Berthet L, Cochet A, Kanoun S, Berriolo-Riedinger A, Humbert O, et al. (2013) 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 54: 1244-1250.
12. Hong J, Lee Y, Park Y, Kim SG, Hwang KH, et al. (2012) Role of FDG-PET/CT in detecting lymphomatous bone marrow involvement in patients with newly diagnosed diffuse large B-cell lymphoma. Ann Hematol 91: 687-695.
13. Omür O, Baran Y, Oral A, Ceylan Y (2014) Fluorine-18 fluorodeoxyglucose PET-CT for extranodal staging of non-Hodgkin and Hodgkin lymphoma. Diagn Interv Radiol.
14. Adams HJ, Kwee TC, de Keizer B, Fijnheer R, de Klerk JM, et al. (2013) Systematic review and meta-analysis on the diagnostic performance of FDG-PET/CT in detecting bone marrow involvement in newly diagnosed Hodgkin lymphoma: is bone marrow biopsy still necessary? Ann Oncol.
15. Adams HJ, Kwee TC, de Keizer B, Fijnheer R, de Klerk JM, et al. (2014) FDG PET/CT for the detection of bone marrow involvement in diffuse large B-cell lymphoma: systematic review and meta-analysis. Eur J Nucl Med Mol Imaging 41: 565-574.
16. El-Galaly TC, Hutchings M, Mylam KJ, Brown PD, Bukh A, et al. (2014) Impact of 18F-FDG PET/CT Staging in Newly Diagnosed Classical Hodgkin Lymphoma: Less Cases with Stage I Disease and More with Skeletal Involvement. Leuk Lymphoma.
17. Salaun PY, Gastinne T, Bodet-Milin C, Campion L, Cambefort P, et al. (2009) Analysis of 18F-FDG PET diffuse bone marrow uptake and splenic uptake in staging of Hodgkin's lymphoma: a reflection of disease infiltration or just inflammation? Eur J Nucl Med Mol Imaging 36: 1813-1821.

Citation: Caldarella C, Isgrò MA, Treglia G (2014) Bone Marrow Involvement in Hodgkin and Non-Hodgkin Lymphomas: The Role of Fluorine-18-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography. J Bone Marrow Res 2: e111. doi:10.4172/2329-8820.1000e111