Hematol Oncol Stem Cell Ther (2017) xxx, xxx–xxx

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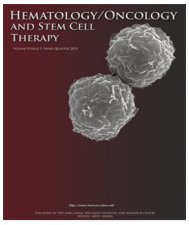

LETTER TO EDITOR

Limited role of bone marrow biopsy for detection of marrow involvement in patients with Hodgkin lymphoma from the Middle East and North Africa region

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Received 3 June 2017; received in revised form 24 July 2017; accepted 7 August 2017

Introduction

Routine bone marrow biopsy (BMB) for the initial staging of Hodgkin Lymphoma (HL) is not recommended in the era of positron emission tomography–computed tomography (PET/CT) staging [1]. However, patients from the Middle East and North Africa (MENA) region have different epidemiologic features of lymphoma compared with those from other ethnicities [2,3]. Furthermore, PET/CT marrow uptake can be focal or diffuse, with unknown significance of the latter. Our aim for this study was twofold-first, to investigate whether BMB is essential for staging in HL where PET/CT is utilized in patients from the MENA region and second, to examine the significance of diffuse marrow signal on PET/CT.

After due Institutional Review Board approval, patients with newly diagnosed HL between 2010 and 2015 who had BMB and PET/CT as initial staging were retrospectively identified. Pathology reports of BMBs were reviewed by two hematologists. All PET/CT reports were carefully reviewed, and cases with positive skeletal uptake were re-interpreted by an experienced radiologist. Pattern of skeletal PET/CT uptake was classified as unifocal, multifocal, or diffuse. Variables were compared using Pearson's chi-square and Wilcoxon/Kruskal–Wallis tests, as appropriate. Sensitivity and negative predictive values (NPVs) were calculated while defining marrow disease as positive BMB and/or focal skeletal uptake on PET/CT.

In total, 92 patients were included for the analysis. All patients were from the MENA region, and >90% patients were from the Arabian Peninsula. The presenting characteristics

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https://doi.org/10.1016/j.hemonc.2017.08.002

are shown in Table 1. From this cohort, BMB was positive in 7 (7.6%) patients, whereas 17 (18.5%) patients had focal marrow uptake on PET/CT, deemed pathologic. Abnormal skeletal uptake was unifocal in 11 (65%) patients and multifocal in 6 (35%) patients. Furthermore, 22 (24%) patients had a diffuse homogeneous uptake which was not considered pathologic. The remaining 53 (58%) patients did not have any marrow uptake.

Involvement by BMB upstaged three patients from stage III (CT-based) to stage IV without altering the initial therapeutic plan. However, PET/CT upstaged 24 (26%) patients; 9 patients from stage III to stage IV, and 14 patients from early to advanced stage, resulting in treatment alteration. BMB identified one patient with histologic marrow involvement yet with negative uptake on PET/CT. Focal skeletal PET/CT lesions identified positive marrow disease with a sensitivity and NPV of 94.4% (72.7—99.9) and 95.7% (76.2—99.3), respectively. Sensitivity and NPV of BMB was 41.2% (18.4—67) and 88.4% (83.6—91.9), respectively. Patients with involved BMB compared to those with involved marrow PET/CT but negative BMB were more likely to be male (100% vs. 36.5% $p = .0019$), have B-symptoms (100% vs. 70% $p = .05$), with extranodal disease outside the marrow (85.7% vs. 27.3% $p = .012$), have stage IV disease by CT (100% vs. 45.5% $p = .02$), and with multifocal pattern on PET/CT (60% vs. 9% $p = .03$).

Patients were subsequently stratified into three cohorts according to marrow uptake: unifocal/multifocal uptake, diffuse homogeneous uptake, or negative uptake. Compared to patients with focal signal, patients with diffuse marrow uptake had a trend toward higher median white blood cell count of 15×10^9/L versus 8.6×10^9/L ($p = .06$), white blood cell count >15×10^9/L at 48% versus 25% ($p = .002$), higher platelet count of 519×10^9/L versus 322×10^9/L ($p = .01$), higher hemoglobin of 105 g/L versus 95 g/L ($p = .005$), and lower stage disease ($p = .0004$). Interestingly, the inflammatory markers erythrocyte sedimentation rate and albumin were not significantly different. Furthermore, all patients with diffuse marrow PET/CT signal had a negative BMB. These results are shown in Table 2.

Prognosis of HL is excellent overall but remains dependent on accurate pre-therapeutic staging and presence of risk factors. The Ann Arbor system is the main staging method which requires a BMB [4]. Numerous retrospective studies in pediatric and adult patients indicated that routine BMB has little therapeutic consequence in patients staged with PET/CT [5—7]. Considering that higher number of patients in the MENA region present with advanced or early unfavorable disease, we examined whether BMB is still warranted in the era of PET/CT staging.

We validated in this ethnically homogeneous group that PET/CT has higher sensitivity and NPV than BMB in detecting marrow involvement with HL. These results suggest reserving BMB for patients for whom there is a high suspicion of marrow disease. In our analysis, we noted that patients with evidence of histologic marrow involvement were more likely to be male with B-symptoms and extranodal disease. Thus, it is perhaps reasonable to perform staging BMB to patients with these presentations.

Our secondary aim was to examine the significance of diffuse marrow uptake on PET/CT. Therefore, we classified the pattern of uptake on PET/CT to patchy disease (unifocal to multifocal), diffuse homogeneous uptake, or absent uptake. Diffuse uptake is an intriguing phenomenon that possibly represents para-neoplastic activation of the bone marrow, cytokine stimulation, or chemotherapy effects [8—10]. Adams et al. [11] showed that diffuse uptake is an infrequent finding in HL with an incidence of approximately 10%, and no evidence of disease was found in the 75 patients examined. This was in contrast to non-Hodgkin lymphoma where the incidence of pathologic disease confirmation was virtually universal. El-Galaly et al. [5] indicated that

Table 1 Baseline characteristics of the study cohort.

Characteristic	No. of Patients (%)
Number of patients	92
Male/Female	54/38
Age at Diagnosis, median (range)	27 (6—83)
Lymphoma Subtype	
Nodular Sclerosing (NS)	56 (61)
Mixed Cellularity (MC)	10 (11)
Lymphocyte Rich (LR)	1 (1)
Lymphocyte Deplete (LD)	1 (1)
Nodular Lymphocyte Predominant (NLP)	5 (5)
Classical Hodgkin Lymphoma NOS	19 (21)
Ann Arbor Stage	
I	3 (3)
II	35 (38)
III	26 (28)
IV	28 (31)
Early Unfavorable (NCCN) Early Stage	34/41 (83)
Bulky Disease	29 (32)
B symptoms	46 (50)
IPS, median (range) Advanced Disease	2 (0—6)

Abbreviations: NOS, not otherwise specified; NCCN, national comprehensive cancer network; IPS, international prognostic score.

Please cite this article in press as: Damlaj M et al., Limited role of bone marrow biopsy for detection of marrow involvement in patients with Hodgkin lymphoma from the Middle East and North Africa region ..., *Hematol Oncol Stem Cell Ther* (2017), https://doi.org/10.1016/j.