Original article

Bone marrow biopsy versus 18F-FDG PET/CT for the evaluation of Bone marrow in Lymphoma - A Single Institutional Study

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ABSTRACT

Background: Bone marrow involvement in lymphoma indicates stage IV disease and may affect both treatment and prognosis. **Aim and Objective**: The aim of the present study was to compare 18 F 2-fluoro-2-deoxy- glucose (FDG) positron emission tomography/ computered tomography (PET/CT) with bone marrow biopsy (BMB) in the initial evaluation of bone marrow (BM) involvement in lymphoma (HL&NHL) patients. **Material and Methods:** Patients with biopsy confirmed newly diagnosed lymphoma, during the period between May 2013 and December 2014 were included. The sensitivity, specificity, positive predictive value and negative predictive value of PET/CT was calculated and compared with bone marrow biopsy. **Results:** Out of the 60 patients 18 were diagnosed with Hodgkin's lymphoma and 42 with Non-Hodgkin's lymphoma. The sensitivity, specificity, positive predictive value and negative predictive value of PET/CT in Hodgkin lymphoma was 100%, 58.82%, 12.5%, 100% respectively. The sensitivity, specificity, positive predictive value and negative predictive value of PET/CT in Non-Hodgkin lymphoma was 90.91%, 77.42%,58.82%,96% respectively. **Conclusion:**18F FDG/PET had high sensitivity in detecting bone marrow involvement in Hodgkin's lymphoma than in non-Hodgkin's lymphoma. In Hodgkin's lymphoma it could replace blind iliac crest BMB. In Non-Hodgkin's lymphoma it plays a complimentary role with BMB in the staging.

KEYWORDS: Lymphoma, bone marrow biopsy, PET/CT.

INTRODUCTION

Bone marrow involvement in lymphoma indicates stage IV disease and may affect both treatment and prognosis [1]. Approximately 50 to 80% of patients with low grade Non-Hodgkin's lymphoma (NHL), 25 to 40 % of high grade NHL, and 5 to 14% of Hodgkin's lymphoma (HL) at diagnosis are found to have bone marrow involvement [2, 3]. Detection of bone marrow involvement is important not only for staging the disease but also for tailoring the treatment [4]. The International Prognostic Index (IPI) predicts prognosis in patients with aggressive NHL. Bone marrow involvement accounts for 1 point in the IPI score [5]. Accurate staging of bone marrow status is important to optimize the therapeutic strategy [6].

Unilateral or bilateral blind Bone Marrow Biopsy (BMB) of the iliac crest is the current gold standard method for diagnosing bone marrow involvement in lymphomas and in other hematological entities, like multiple myeloma [7].

However, it is a painful and invasive procedure. It is also associated with complications such as allergic reactions to local anaesthetic drug, excessive bleeding or infection of the sampling site. Sometimes a small sample can be obtained which may be inconclusive and makes this technique prone to sampling error. Bone marrow involvement in lymphoma is frequently patchy; there may be 10% to 50% discordance between unilateral and bilateral BMB [8, 9]. BMB is more prone to false-negative findings particularly in patients with focal bone marrow disease in sites other than the iliac crest.

Imaging the metabolic activity of tumor provides more sensitive and specific information about the extent of disease than anatomical imaging alone and thus, fluorodeoxyglucose positron emission tomography (FDG-PET) has become a standard imaging Procedure for staging many types of cancers including lymphomas. Hodgkin's and aggressive NHL show an intense glucose metabolism and

therefore a high FDG uptake. FDG PET/CT can be helpful in diagnosing both nodal and extra-nodal involvement of lymphoma, including the bone marrow assessment [10].A major advantage of FDG PET-CT over BMB is noninvasiveness.

Furthermore it has the ability to study the entire bone marrow which overcomes the false-negative findings of BMB in case of sampling error and focal disease. This can also be used as a substitute for BMB or as a guide to perform a targeted biopsy in sites showing focal uptake of FDG [10] .In the PET era the value of bone marrow biopsy in staging has come into question as evidenced by an increasing number of studies and meta-analyses comparing the sensitivity of FDG-PET-CT with that of the trephine sample [11-15].

The aim of the present study is to compare 18 F FDG-PET/CT with bone marrow biopsy to detect bone marrow involvement in patients of HL and NHL.

MATERIAL AND METHODS

Patients with biopsy confirmed newly diagnosed lymphoma presenting to the medical oncology Department, during the period between May 2013 and December 2014 were included in this prospective study. The study was cleared by the Institutional Research Approval Committee and Ethical Committee (IEC NO: 325/10-06-2013).All patients with age between 10yrs to 80 yrs with histopathologically confirmed both nodal and extra nodal lymphoma and patients who underwent both bone marrow biopsy and PET/CT were included. Relapsed and cutaneous lymphomas were excluded. Histological diagnosis was established by excision biopsy of a node or guided trucut biopsy (for deep seated nodes).

Histological samples were classified according to WHO recommendations. Clinical stage of the disease was assigned by Ann Arbor classification. After taking written informed consent all the patients were subjected to a clinical evaluation which included detailed history and a thorough physical examination. Diagnostic work up included; complete hemogram including total blood counts and differential, renal and hepatic function tests, serum Lactate dehydrogenase (LDH), echo cardiography to assess left ventricular function, whole body 18 F FDG/PET-CT, unilateral blind posterior iliac crest bone marrow biopsy. In all patients 18 F FDG PET/CT was performed prior to bone marrow biopsy.The PET/CT results were correlated with BMB reports.

Bone marrow assessment: Marrow aspirates were stained with leishman stain. Trephine biopsy samples were decalcified and stained with hematoxylin and eosin. Infiltration of bone marrow was assessed by pathologist blinded to the PET/CT results.

PET scan:

Patient preparation:

Patients were advised to fast for at least 6 hours before scanning to minimize blood insulin levels and glucose utilization of normal tissue. Blood glucose levels were checked in all patients prior to 18F-FDG (18-Fluoro-2-deoxyglucose) injection and blood glucose levels should be below 160 mg/dl. Patients were withheld from short-acting insulin for 2 hours and long-acting insulin for 6 to 8 hours prior to scan. Intravenous fluid containing dextrose or parenteral feeding was withheld for 4 – 6 hours. Patients with renal impairment were excluded from contrast enhanced CT study. An intravenous access was placed at least 10 minutes prior to injection.

Imaging protocol:

All adult patients were injected 259 - 370 MBq (8-10 mCi) of 18F-FDG intravenously. Imaging was performed 60 min after FDG injection using Biograph-6, LSO, PET/CT scanner by SIEMENS. Patients were positioned comfortably in a quiet room at least 20 min before FDG administration and also during the uptake phase of FDG (i.e. up to 60 min post injection).They were instructed not to speak, read and to avoid major movements. Patients were advised to void before and after the scanning session to minimize radiation exposure. Water soluble iodinated oral contrast medium (Diatrizoate sodium solution, 25%, iodine content 149 mg/ml) approximately 30 ml diluted in 1000 ml of water were given to each patient orally over 1hour prior to scan.

Data acquisition:

Whole-body PET/CT scan was performed in cranio-caudal orientation from the skull to mid-thigh. First CT was performed for attenuation correction and localization of PET lesions from head to mid-thigh. Additionally a full diagnostic CT with intravenous non-ionic contrast agent (Omnipaque^{TM} Iohexol-350 mg of iodine /ml) if indicated, was performed. The CT component was operated at Effective X Ray tube current, 120-160 mAs; tube voltage of, 80-130 keV; slice width, 5.0 mm; collimation, 05 mm; in craniocaudal table feed, for Biograph 6 LSO PET/CT scanner.

Immediately after the CT examination, the process was continued with a full ring, dedicated PET System using three-dimensional PET acquisition protocol, in seven bed positions (2 min/bed position) caudocranially of the same axial length. Both CT and PET scan were obtained in normal tidal breathing. PET images were reconstructed with CT derived attenuation correction and using Ordered Subset Expectation Maximization (OSEM) software, then attenuation corrected PET images, CT images and fused PET/CT images were viewed in axial, sagittal, coronal planes and a cine display of maximum intensity projection (MIP) of PET data using manufacturers review station (SYNGO, SIEMENS).

Identification of marrow involvement by PET:

Intensity and distribution of FDG uptake was visually assessed by Nuclear medicine physician. The marrow was presumed to be involved when the uptake was greater than the liver uptake, taking in to account that the liver uptake was more than the back ground. The PET/CT scan was reported as positive if there was focal or diffuse tracer uptake in the bone marrow. The number and location of FDG-avid lesions in the bone marrow were also noted. No abnormal FDG uptake in bone marrow was considered as negative PET/CT. Uni focal involvement was defined as only one FDG uptake lesion in bone marrow. Two or more FDG uptake lesions in bone marrow were considered as multifocal bone marrow involvement. Intense homogeneous FDG uptake in the axial and proximal appendicular skeletons was considered as diffuse marrow involvement.

Identification of marrow involvement by BMB:

Infiltration of neoplastic lymphoid cells by bone marrow was reported as positive bone marrow biopsy. The BMB was taken as the gold standard in calculating the sensitivity of 18F-FDG PET/CT in detecting bone marrow involvement by lymphoma. True-positives were patients with a positive BMB and PET/CT scan. True-negatives were patients with a negative BMB and PET/CT scan. False-positive cases were those with positive PET/CT and negative BMB. False-negative cases were those with negative PET/CT and positive BMB.

Statistical analysis:

Data were recorded on a pre-designed proforma and managed using statistical packages for social sciences (SPSS) version 22. Data were expressed in terms of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV). These parameters were calculated using MedCalc trial version 18.

RESULTS

A total of 65 patients were diagnosed to have Lymphoma (HL & NHL) during the study period. Five patients were excluded from the study as PET/CT results were not available. Of the 60 patients 18 were diagnosed with Hodgkin's lymphoma and 42 with Non-Hodgkin's lymphoma. The age range was from 12 to 77 years (mean 46.28 years) .Males were 58.3% (35) and females were 41.7% (25). Of 60 patients, comparison of FDG-PET/CT and BMB results revealed concordant negative(true negative) findings in 34 patients (56.6%) and concordant positive(true positive) findings in 11 patients (18.3%). Fifteen patients (25%) showed discordant results. Among them 14 patients (23.3%) showed FDG uptake in PET/CT in whom BMB revealed no lymphomatous infiltration (false positive).

One patient (1.66%) showed lymphomatous infiltration in bone marrow by BMB, but PET showed no FDG uptake in marrow (false negative). Twenty five patients in whom PET/CT findings were positive, focally increased FDG uptake was observed in 5 patients (thoracic vertebrae in 2 patients, sacrum, left sacroiliac joint, lumbar vertebrae in 1patient each). Multi focal and diffuse FDG uptake was observed in 6 and 14 patients respectively. The sensitivity, specificity, positive predictive value and negative predictive of PET/CT in all lymphoma (HL & NHL) patients are 91.67%, 70.83%, 44%, 97.14%.respectively. In HL (18patients) comparison of PET/CT and BMB results depicted in Table1.

Table: 1 Evaluation of bone marrow in Hodgkin's lymphoma by PET/CT and Bone marrow biopsy

		Bone marrow biopsy		Total
		Negative	Positive	
PET/CT	Negative	10 (55.5%)	0	10
	Positive	7 (38.8%)	1 (5.5%)	8
Total		17	1	18

In 8 patients whom PET showed FDG uptake, focal uptake was noted in 2 patients, multifocal uptake in 2 patients and diffuse uptake in 4 patients. The sensitivity, specificity, positive and negative predictive value of PET/CT compared to BMB in HL is depicted in Table 2. In NHL (42 patients) comparison of PET/CT and BMB results were showed in Table 3.Seventeen patients in whom PET/CT showed FDG uptake, focal uptake was noted in 3 patients, multifocal uptake noted in 4 patients and diffuse uptake was noted in 10 patients. The sensitivity, specificity, positive and negative predictive value of PET/CT compared to BMB in NHL is depicted in table 4.

Table: 2 Comparison of sensitivity, specificity, positive predictive and negative predictive value of PET/CT with Bone marrow biopsy in Hodgkin's lymphoma

	PET/CT
Sensitivity	100%
Specificity	**58.82%**
Positive Predictive Value	**12.50%**
Negative Predictive Value	**100%**

Table:3 Evaluation of bone marrow in Non-Hodgkin's lymphoma by PET/CT and Bone marrow biopsy

		Bone marrow biopsy		Total
		Negative	Positive	
PET/CT	Negative	24(57.1%)	1(2.385%)	25
	Positive	7 (16.6%)	10(23.8%)	17
Total		31	11	42

Table:4 Comparison of sensitivity, specificity, positive predictive and negative predictive value of PET/CT with Bone marrow biopsy in Non-Hodgkin's lymphoma

	PET/CT
Sensitivity	90.91%
Specificity	**77.42%**
Positive Predictive Value	**58.82%**
Negative Predictive Value	**96%**

DISCUSSION

PET/CT is exclusively used in lymphomas for baseline staging workup and response evaluation. PET has an established role in the staging and restaging of patients with HL and aggressive NHL [16, 17].Presence or absence of bone marrow involvement plays a crucial role in staging. The current gold standard method for detecting bone marrow involvement is the trephine BMB. In a study by Cheng et al [18], the role of FDG-PET/CT versus bone marrow biopsy (BMB) in the initial evaluation of bone marrow involvement in pediatric lymphoma patients was assessed. This study included 31 HL patients and 23 NHL patients. They found that the overall sensitivity of detecting bone marrow involvement by PET/CT was 92% and BMB was 54%.

Another study by Cortes Romero et al [19] compared PET/CT and BMB for bone marrow involvement in the initial staging of lymphomas. One hundred and forty seven patients with DLBCL (84) and HL (63) were included. The sensitivity, specificity, positive and negative predictive value was 95%, 86%, 54% and 99% respectively. In the present study the sensitivity of FDG-PET/CT in detecting bone marrow infiltration in all lymphoma patients (both HL and NHL) was 91.67% and specificity was 70.83% with a negative predictive value of 97.14% and positive predictive value of 44%. The results of the present study were consistent with previous studies.

Stratification of PET /CT findings by lymphoma subtypes showed high sensitivity in HL than NHL. In HL the sensitivity, specificity, positive and negative predictive value of PET/CT in identifying bone marrow involvement was 100%, 58.82%, 12.5% and 100%, while in NHL it was 90.91%, 77.42%, 58.82% and 96% respectively. In a study done by Muzahir et al [20] in HL, the sensitivity, specificity, positive and negative predictive value of PET/CT was 100%, 76.57%, 29.72% and 76.57% respectively. A meta-analysis done by Adams et al [21] in DLBCL found the sensitivity and specificity of FDG PET/CT for detecting bone marrow involvement ranged from 70.8 % to 95.8 % and from 99 % to 100 % respectively. In the present study we found high negative predictive value of 100%.This could be due to absence of false negative results.

In the present study 34(56.7%) patients had no bone marrow involvement by either PET/CT scan or BMB. Of a total of 35 patients who had no bone marrow uptake on PET/CT only one patient (2.8%) had positive iliac crest BMB. This finding suggests that routine BMB might be unnecessary if PET/CT is negative.

Focal mono or polyostotic bone marrow disease may produce abnormal PET results, but if the disease does not extend to the dorsal iliac crest then bone marrow sampling would be negative[22]. In the present study uni focal FDG uptake was noted in 8.4% patients. (11.1% in HL and 7.1% in NHL). None of the patients with focal bone marrow uptake on PET/CT scan had positive BMB. These findings suggest that the possibility of obtaining a positive result on BMB is low with focal uptake on PET/CT. Therefore even in the presence of focal FDG uptake on PET/CT scan and negative BMB the probability of bone marrow involvement is high, suggesting PET/CT can be used to guide biopsy of sites with increased FDG uptake [23].

Multifocal FDG bone marrow uptake was observed in 18.4% patients (11.1% patients in HL, 9.5% patients in NHL). Three out of 6 patients (50%) (1 patient in HL, 2 patients in NHL) with multi focal FDG bone marrow uptake had positive BMB. Multi focal FDG abnormalities have greater probability of yielding a positive BMB. It is reported that in HL there is also very high reporter agreement for the identification of marrow involvement with PET, attributable to the high lesion-to background contrast [24]. Thus, routine biopsy confirmation of multifocal FDG-avid marrow abnormality is unwarranted, especially if the intensity of metabolic abnormality within marrow mirrors the intensity at other sites of known disease.

It is reported in literature that diffuse homogeneous FDG uptake in the HL is more likely reactive due to reactive or

inflammatory changes driven by cytokine release [25, 26]. In the present study we found 4 (22.3%) HL patients with diffuse FDG uptake, but none of the patients had positive BMB. These findings suggest that diffuse FDG uptake should not be interpreted as bone marrow involvement in HL. In NHL diffuse FDG uptake was noted in 10(23.8%) patients of whom 8(80%) patients had positive BMB. Diffuse FDG uptake in NHL should be regarded as bone marrow involvement.

Anemia is one of the contributing factors for diffuse FDG uptake in PET/CT [27]. Other causes include coexisting myelodysplastic syndrome, beta thalassemia, chronic myeloid leukemia (CML), interleukins in pyrexic states and cytokine release. In the present study 13(22%) patients had anemia (hemoglobin ≤10g/dL). Among them diffuse marrow uptake was noted in 6(46%) patients, unifocal uptake was noted in 2 (15%)patients, multi focal uptake was noted in 1(7.6%) patient and no FDG uptake was seen in 4(30.7%) patients. Four patients out of six with diffuse marrow uptake had negative bone marrow biopsy.

Mean SUV of these patients were 3.5. Two patients showed positive bone marrow biopsy with diffuse FDG uptake. Mean SUV value was 7. In the current study we observed anemic patients had high SVU with positive bone marrow biopsy than negative biopsy. A possible explanation is anemic patients had increased FDG metabolism in their bone marrow. This finding is comparable with previous study [27]. Interestingly patients with hemoglobin >10 g/dL also showed diffuse FDG marrow uptake (8 patients). This could be due reactive or inflammatory change driven by cytokine release [26].

FDG-PET/CT has the ability to detect additional areas of involvement which results in change in the stage Change in the stage range from 18% to 45% [28]. In the present study PET/CT upstaged disease in 14 patients (23.3%), (7 patients in HL, 7 patients in NHL patients).

CONCLUSION

18F FDG/PET-CT outperforms Bone Marrow Biopsy in staging lymphomas and had high sensitivity in detecting bone marrow involvement in Hodgkin's lymphoma than in non-Hodgkin's lymphoma. In Hodgkin's lymphoma 18F FDG/PET-CT could replace blind iliac crest Bone Marrow Biopsy with negative PET/CT result because of high negative predictive value (100%). PET/CT can replace BMB for diffuse marrow FDG uptake. For focal lesions PET/CT guided biopsy is a valuable option. In Non-Hodgkin's lymphoma PET/CT cannot substitute BMB. It plays a complimentary role with BMB in the staging.

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