Original Investigation

Bone Marrow Involvement in Malignant Lymphoma: Evaluation of Quantitative PET and MRI Biomarkers

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Abbreviations and Acronyms

ADC apparent diffusion coefficient

BMB bone marrow biopsy

DLBCL diffuse large B-cell lymphoma

DWI diffusion-weighted imaging

HL Hodgkin lymphoma

SUV standardized uptake value

VOI volume of interest

WB-DWI whole-body diffusion-weighted imaging

Rationale and Objectives: This study aimed to determine the diagnostic utility of standardized uptake values (SUV) and apparent diffusion coefficients (ADC) for assessment of focal and diffuse bone marrow involvement in patients with malignant lymphoma.

Materials and Methods: Sixty treatment-naive patients (28 males; mean age 51.2 ± 16.7 years) with histologically proven lymphoma, who underwent fludeoxyglucose (^{18}F) positron emission tomography-computed tomography ([F18]-FDG-PET/CT) and whole-body diffusion-weighted imaging (WB-DWI) within 7 days, and also routine bone marrow biopsy, were included in this institutional review board-approved, retrospective study. The maximum SUV (SUVmax) on [F18]-FDG-PET/CT, and the mean ADC (ADCmean, $\times 10^{-3}$ mm^2/s) on whole-body-DWI, were extracted from focal lesions, or, in their absence, from the thoracic (Th8) and lumbar vertebral bodies (L4), the sacral bone (S1), and the iliac crest. Lesion-to-liver-ratios (SUVmax-ratio) were calculated. Pearson correlation coefficients were used to assess the correlation between SUVmax-ratios and ADCmean values.

Results: Bone marrow involvement was observed in 16 of 60 patients (8 of 16 with diffuse infiltration). The SUVmax-ratio cutoff value was 95.25% for focal and 70.2% for diffuse bone marrow involvement (sensitivity/specificity of 87.5%/86.4% and 100%/43.2%, respectively). The ADCmean cutoff value was 0.498 for focal and 0.401 for diffuse bone marrow involvement (sensitivity/specificity of 100%/90.9% and 87.5%/56.8%, respectively). No significant correlations were found between SUVmax-ratios and ADCmean values in the different groups.

Conclusion: With the liver as reference tissue, quantitative [F18]-FDG-PET/CT may be useful to differentiate bone marrow involvement from normal bone marrow in patients with lymphoma, even though the specificity for diffuse marrow involvement is rather low. Quantitative DWI can be used only to distinguish focal bone marrow lesions from normal bone marrow.

Key Words: Bone marrow involvement; lymphoma; ADC; SUV; DWI; [18F]-FDG-PET/CT; MRI.

INTRODUCTION

Bone marrow is defined as an extranodal site of disease in patients with malignant lymphoma (1). Therefore, patients with multifocal or diffuse bone marrow involvement are assigned to the highest stage (IV) of the Ann Arbor system, which affects prognosis and treatment. Blind, unilateral bone marrow trephine biopsy (BMB) of the iliac crest is the standard method for the diagnosis of bone marrow involvement (2).

Fludeoxyglucose (^{18}F) positron emission tomography-computed tomography ([18F]-FDG-PET/CT) is increasingly used as a staging and response assessment tool in malignant lymphomas (3). In clinical PET imaging, the glucose uptake of cancer cells is measured semiquantitatively by the maximum standardized uptake value (SUVmax). Because the degree of FDG avidity depends on the histologic lymphoma subtypes, [18F]-FDG-PET/CT has a varying sensitivity for the detection of bone marrow involvement (4–6), which can show either

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a focal or a diffuse uptake pattern (7). The present consensus is that, for patients with Hodgkin lymphoma (HL), [18F]-FDG-PET can completely replace BMB, whereas for patients with diffuse large B-cell Lymphoma (DLBCL), BMB is necessary only if there is a negative [18F]-FDG-PET result (3). For all other lymphoma subtypes, and particularly for the indolent types, BMB cannot be replaced by [18F]-FDG-PET as yet (3).

The diagnosis of diffuse bone marrow involvement on [18F]-FDG-PET/CT remains particularly challenging, because the FDG uptake is often just slightly elevated, resembling the appearance of activated hematopoietic marrow or inflammatory conditions on PET (8,9). Although visual assessment of [18F]-FDG-PET is the current standard, one previous study reported a higher sensitivity for the detection of bone marrow involvement through the use of semiquantitative PET data, using the mediastinal blood pool as the reference tissue for diffuse bone marrow involvement (10).

Diffusion-weighted imaging (DWI) is a functional magnetic resonance imaging (MRI) technique, which assesses the diffusion of water molecules in biologic tissue and therefore enables indirect assessment of cell density. It was already shown to be a valuable tool and a radiation-free alternative to [18F]-FDG-PET/CT in pretherapeutic staging and follow-up in patients with lymphoma. Diffusion restriction is quantified by the apparent diffusion coefficient (ADC) (11). Focal metastatic bone marrow lesions and tumor-related hypercellular marrow in various cancer types are known to have different ADC values from that of normal adult marrow (12,13). DWI may potentially be useful for the quantitative assessment of bone marrow involvement in patients with lymphoma as well (14).

Therefore, the aim of this study was to determine the diagnostic values of SUV and ADC measurements for the assessment of bone marrow involvement in patients with lymphoma, and to determine the correlation between these two quantitative parameters.

MATERIALS AND METHODS

Study Design and Patients

This was a retrospective, single-center study of treatment-naive patients with histologically proven lymphoma based on the current classification of the World Health Organization of hematologic and lymphoid malignancies (15). This patient population has been previously reported (16). Patients who had undergone [18F]-FDG-PET/CT and whole-body DWI (WB-DWI) within 7 days (for clinical purposes, or as part of a previous prospective studies), as well as routine unilateral bone marrow biopsy within 30 days of the first imaging examination, were eligible for inclusion. Exclusion criteria were a record of therapeutic interventions between [18F]-FDG-PET/CT and WB-DWI, the presence of severe MRI artifacts, or an incomplete MR examination. The local ethics committee approved the study protocol, and waived written informed consent.

Imaging Protocols

Whole-body (WB) [18F]-FDG-PET/CT was performed for routine diagnostic purposes using a 64-row multidetector PET/CT scanner (Biograph TruePoint64; Siemens, Erlangen, GER). Glucose levels were measured before the examination, with a cutoff limit of 8 mmol/L (150 mg/dL). Imaging was performed 50–60 minutes following the intravenous administration of 300 MBq of [18F]-FDG. First, CT was performed after an intravenous injection of 100 mL of Iomeprol, a tri-iodinated, non-ionic contrast medium (Iomeron 300; Bracco, Milan, ITA) at a rate of 2 mL/s, followed by a 50-mL saline flush. The following acquisition parameters were used: a tube voltage of 230 kV; a tube current of 120 mA; a collimation of 64×0.6 mm; a slice thickness of 3 mm with 2-mm increments; and a matrix of 512×512. CT was acquired in a breath-hold during (non-forced) expiration. Then, without changing the patient's position, WB PET was acquired over five to six bed positions with 3 minutes per bed position. Depending on the patient's constitution and the consecutive PET positions, the total scan time was between 18 and 25 minutes. PET images were reconstructed using the iterative TrueX algorithm (Siemens, Erlangen, Germany), which incorporates a specific correction for the point-spread function in addition to commonly used correction factors. Four iterations per 21 subsets were used, with a matrix size of 168×168, a transaxial field of view of 605 mm (pixel size 3.6 mm), and a section thickness of 5 mm. The attenuation correction was based on the CT maps. CT and PET data were co-registered, and image fusion was performed to generate color-coded images.

WB-DWI was performed on a 3-Tesla MR scanner (TrioTim; Siemens, Erlangen, Germany). A single-shot, echo planar imaging-based spectral, adiabatic, inversion recovery DWI sequence was obtained, with b-values of 50 and 1000, a repetition time/echo time of 5100/73 ms, five averages, 86-phase encoding steps, a 192×115 matrix, and a slice thickness of 5 mm with no gap. Axial images of the head and neck, chest, abdomen, and pelvis were sequentially obtained using a WB, phased-array surface coil for signal reception. DWI was performed during free breathing (with a scan time of 4 minutes and 5 seconds per body region), except for the lower neck and chest, where respiratory gating was used (with a prolonged scan time of 5 minutes and 2 seconds). Depending on the patients' body height, four to five image stacks were necessary, with a total scan time of 20–25 minutes. ADC maps were generated automatically by the operational software supplied by the scanner manufacturer of the abovementioned MR scanner. For better anatomic correlation, axial T1-weighted, turbo spin-echo or gradient echo sequences were also obtained, and based on that, fused, color-coded DWI-MRI images. The T1-weighted, turbo spin-echo sequence was performed with a scan time of 1 minute 5 seconds; or alternatively,