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High total metabolic tumor volume in PET/CT predicts worse prognosis in diffuse large B cell lymphoma patients with bone marrow involvement in rituximab era

Moo-Kon Song[a], Deok-Hwan Yang[b,*], Gyeong-Won Lee[c], Sung-Nam Lim[d], Seunghyeon Shin[e], Kyoung June Pak[e], Seong Young Kwon[f], Hye Kyung Shim[g], Bong-Hoi Choi[h], In-Suk Kim[i], Dong-Hoon Shin[j], Seong-Geun Kim[a], So-Yeon Oh[a]

[a] Department of Hematology-Oncology, Pusan National University Yangsan Hospital Medical Research Institute, Yangsan, Republic of Korea
[b] Department of Hematology, Chonnam National University Hwasun Hospital, Hwasun, Republic of Korea
[c] Department of Hematology, Gyeong-Sang National University Hospital, school of medicine, Gyeong-Sang National University Jinju, Republic of Korea
[d] Department of Hematology, Busan Haeundae Paik Hospital, Busan, Republic of Korea
[e] Department of Nuclear medicine, Pusan National University Hospital, Busan, Republic of Korea
[f] Department of Nuclear Medicine, Chonnam National University Hwasun Hospital, Hwasun, Republic of Korea
[g] Department of Nuclear Medicine, Busan Haeundae Paik Hospital, Busan, Republic of Korea
[h] Department of Nuclear Medicine, Gyeongsang National University Hospital, Jinju, Republic of Korea
[i] Department of Laboratory medicine, Pusan National University Yangsan Hospital, Yangsan, Republic of Korea
[j] Department of Pathology, Pusan National University Yangsan Hospital, Yangsan, Republic of Korea

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ABSTRACT

Bone marrow involvement (BMI) in diffuse large B cell lymphoma (DLBCL) was naively regarded as an adverse clinical factor. However, it has been unknown which factor would separate clinical outcomes in DLBCL patients with BMI. Recently, metabolic tumor volume (MTV) on positron emission tomography/computed tomography (PET/CT) was suggested to predict prognosis in several lymphoma types. Therefore, we investigated whether MTV would separate the outcomes in DLBCL patients with BMI.

MTV on PET/CT was defined as an initial tumor burden as target lesion ≥ standard uptake value, 2.5 in 107 patients with BMI. Intramedullary (IM) MTV was defined as extent of BMI and total MTV was as whole tumor burden.

260.5 cm^3 and 601.2 cm^3 were ideal cut-off values for dividing high and low MTV status in the IM and total lymphoma lesions in Receiver Operating Curve analysis. High risk NCCN-IPI ($p < 0.001$, $p < 0.001$), bulky disease ($p = 0.011$, $p = 0.005$), concordant subtype ($p = 0.025$, $p = 0.029$), high IM MTV status ($p < 0.001$, $p < 0.001$), high total MTV status ($p < 0.001$, $p < 0.001$), and ≥2CAs in BM ($p = 0.037$, $p = 0.033$) were significantly associated with progression-free survival (PFS) and overall survival (OS) than other groups. In multivariate analysis, high risk NCCN-IPI (PFS, $p = 0.006$; OS, $p = 0.013$), concordant subtype (PFS, $p = 0.005$; OS, $p = 0.007$), and high total MTV status (PFS, $p < 0.001$; OS, $p < 0.001$) had independent clinical impacts.

MTV had prognostic significances for survivals in DLBCL with BMI.

1. Introduction

Diffuse large B cell lymphoma (DLBCL) is a heterogeneous disease entity with a wide range of clinical outcomes [1,2]. Traditional International Prognostic Index (IPI) has been used as primary tool to predict prognosis in DLBCL [3–5].

Bone marrow involvement (BMI) in DLBCL has been categorized as an important extranodal (EN) site that adversely affects prognosis according to the traditional IPI [3]. Recently, after the introduction of rituximab, the enhanced National Comprehensive Cancer Network (NCCN) – IPI, which incorporates five clinical parameters including age (41–60 years, 61–75 years and >75 years), advanced Ann-Arbor stages (stage III and IV), Eastern Cooperative

* Corresponding author. Department of Hematology-Oncology, Chonnam National University Hwasun Hospital, 160 Ilsim-ri, Hwasun, Chonnam, 519–809 Republic of Korea. Fax: +82 61 379 7628.
E-mail address: drydh1685@hotmail.com (D.-H. Yang).

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Oncology Group (ECOG) performance status (PS) ≥ grade 2, elevated serum lactate dehydrogenase (LDH) level ratio (>1–3 and >3) important EN site involvement including BM, central nervous system (CNS), gastrointestinal tracts, liver and lung also emphasized the BMI as an adverse prognostic factor [6]. However, in other studies, clinical outcomes of BMI in DLBCL were suggested to be differentiated depending on histologic subtype and extent of BMI in DLBCL [7–10]. Histologically, the BMI is divided into concordant subtype with mostly large B cells and discordant subtype with BM infiltrated with mainly small sized lymphoma cells [7–9]. Concordant histologic subtype of BMI was suggested to be associated with poor outcome in DLBCL with BMI. Furthermore, other studies indicated that the degree of the lymphoma cell infiltration in BM tissues predicts survival in DLBCL with BMI [7,10].

Ann-Arbor staging system is currently used to determine the stage in non-Hodgkin's lymphoma (NHL) including DLBCL, although it has been originally developed for Hodgkin's lymphoma (HL), However, our recent study was demonstrated that metabolic tumor volume (MTV) on 18 F-fluorodeoxyglucose (18 F-FDG) positron emission tomography/computed tomography (PET/CT) could have superior predictive value for survivals compared with the staging system of DLBCL in rituximab era [11]. It is not surprising that the Ann-Arbor staging system is less accurate to determine due to disseminated spread pattern of NHL, which is different to that of HL. Moreover, in other clinical studies, the MTV was a useful marker to predict prognosis in NHL including DLBCL [12–14]. However, it is unclear whether high MTV status would predict worse prognosis in DLBCL patients with BMI.

The present study was investigated whether MTV on PET/CT as active tumor burden measured by PET/CT would be a valuable predictive factor for survivals compared with histologic subtype of BMI, recently enhanced NCCN-IPI score and other prognostic factors in DLBCL patients with BMI in rituximab era.

1.1. Patients and methods

The patients with DLBCL initially diagnosed from 2006 to 2014 at 4 medical centers (Pusan National University Yangsan Hospital, Chonnam National University Hwasun Hospital, Gyeong-Sang National University Hospital and Busan Haeundae Paik Hospital) were reviewed. Approval for retrospective review of the records was obtained from the Institutional Review Boards of all participating medical centers.

Patients with de novo DLBCL were included. Patients with transformed DLBCL from low grade B cell lymphoma and primary CNS lymphoma were excluded. Patients with HIV, hepatitis B virus or C virus at diagnosis were also excluded.

18 F-FDG PET/CT were performed for assessment of initial stage and response after R-CHOP therapy. Baseline clinical and laboratory characteristics based on NCCN-IPI included gender, age (<41 years, 41–60 years, 61–75 years or > 75 years), LDH level ratio (>1–≤3 or >3), Eastern Cooperative Oncology Group performance status (<grade 2 or ≥grade 2), Ann-Arbor stage (stage II/II or III/IV), EN sites involvement such as BM, CNS, liver, gastrointestinal tract or lung, bulky mass (≥10 cm), and B symptoms.

1.2. Histologic types of BMI

Bone marrow biopsy (BMB) was performed to confirm BMI of the lymphoma cells at the time of diagnosis and residual BMI after final cycle of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone therapy (R-CHOP) therapy. The presence or absence of BMI by the neoplastic cells and the histologic type (concordant or discordant BMI) were evaluated by BMB. Concordant BMI was defined when the involved area consisted mostly of large cells with prominent nucleoli and cytoplasm. Meanwhile, discordant BMI was defined when the involved area consisted mostly of small lymphoma cells forming lymphoid cell aggregates referred to in a recent study [9].

1.3. Cytogenetic analysis of BMI

Conventional cytogenetic analysis using G-banding technique was performed on BM aspirated sample at the time of initial diagnosis from the patients with BMI. Cytogenetic abnormalities (CAs) were classified according to the international system for human cytogenetic nomenclature criteria. Two laboratory medicine experts reviewed and confirmed the reports of chromosome studies. ≥2CAs were defined as two or more numerical or structural cytogenetic abnormalities.

1.4. Measurement of metabolic tumor burden on 18F-FDG PET/CT

Dual-modality PET/CT tomography was performed on a biograph (Siemens Medical Solution, Hoffman Estates, IL) according to a major guideline for standard oncological PET imaging [15] and based on a dual-slice helical CT and a full-ring PET tomography to measure MTV in patients with DLBCL with BMI confirmed by BMB.

Three-dimensional FDG-PET images were evaluated for lesions of focally increased tracer uptake. In target lesions showing an SUV ≥2.5, MTV was calculated from PET/CT data with defined contouring border that represents lymphoma involved lesions, as suggested by Freudenberg et al. [16]. Intramedullary (IM) MTV was defined as a volume of the active metabolic lesion on PET/CT within BM. Total MTV was defined as the sum of MTV of all focal lesions. Intravenous or oral contrast agents were used in all patients and a standardized breathing protocol was applied. CT images were acquired with 130 mAs, 130 kV and slice width (or 5 min and Table feed) of 8 mm per rotation.

1.5. Statistical analysis

Receiver operating characteristic (ROC) curve was performed to measure the ideal cut-off values of IM and EM MTV. Determinations of sensitivity and specificity were according to the cut-off values of the MTVs. Progression-free survival (PFS) was calculated from the date of diagnosis to disease progression. Overall survival (OS) was calculated from the date of diagnosis until death of any cause or the last date known to be alive. PFS and OS were estimated by the Kaplan–Meier method and the differences were compared by the log-rank test. A Cox proportional hazard model was used to analyze various prognostic factors for PFS and OS in multivariate analyses. Hazard ratios (HRs) and 95% confidence intervals (CIs) were determined for all survival endpoints.

Statistical analysis was carried out with SPSS software for Macintosh version 18.0 (SPSS Inc., Chicago, IL). A probability value <0.05 was considered as statistically significant.

2. Results

In enrolled 801 patients with DLBCL received R-CHOP therapy, one hundred and seven patients had BMI (13.4%), while the other 694 patients (86.6%) did not have BMI. The median follow up time was 40.8 months (range, 11.9–90.8 months). Baseline characteristics of the patients are summarized in Table 1.

In total patients, the male and female ratio was 1.83: 1 and the median age was 63 years (range, 27–75 years). In patients with BMI ($n = 107$), the median age was 64 years (range, 27–75 years), while the median age in those without BMI was 62 years (range, 30–74 years). Elevated Lactate dehydrogenase levels (LDH ratio ≤1, $p = 0.021$; LDH ratio, 1–3, $p = 0.005$; LDH ratio >3,