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Tumor necrosis at FDG-PET is an independent predictor of outcome in diffuse large B-cell lymphoma

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ABSTRACT

Purpose: To determine the prognostic performance of tumor necrosis at FDG-PET in patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL) who are treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) therapy.
Materials and methods: 108 patients with newly diagnosed DLBCL who underwent FDG-PET before R-CHOP therapy were retrospectively included. Lymphomatous sites at FDG-PET were assessed for the presence of a photopenic area, in keeping with tumor necrosis. Univariate and multivariate Cox regression analyses were performed to determine the associations of tumor necrosis and National Comprehensive Cancer Network International Prognostic Index (NCCN-IPI) with progression-free survival (PFS) and overall survival (OS).
Results: On univariate Cox regression analysis, both tumor necrosis and higher NCCN-IPI risk groups were significantly associated with PFS ($P = 0.024$ and $P < 0.001$, respectively) and OS ($P = 0.034$ and $P < 0.001$, respectively). On multivariate Cox regression analysis, both tumor necrosis and the NCCN-IPI were independent significant predictors for PFS ($P = 0.007$, hazard ratio: 2.723 [95% confidence interval: 1.324–5.597] and $P < 0.001$, hazard ratio: 2.952 [95% confidence interval: 1.876–4.646], respectively) and OS ($P = 0.009$, hazard ratio: 2.794 [95% confidence interval: 1.305–5.985] and $P < 0.001$, hazard ratio: 2.813 [95% confidence interval: 1.724–4.587], respectively).
Conclusion: Tumor necrosis at FDG-PET is an NCCN-IPI-independent predictor of outcome in DLBCL.

1. Introduction

Diffuse large B-cell lymphoma is the most common non-Hodgkin lymphoma subtype [1]. Despite improvement in survival thanks to the addition of rituximab (R) to conventional cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy, nearly 40% of DLBCL patients still die of relapsed/refractory disease [2]. Early identification of non-responders to R-CHOP therapy is of crucial importance to prevent unnecessary toxicity and costs, and to offer these patients alternative therapies in a timely manner. The National Comprehensive Cancer Network International Prognostic Index (NCCN-IPI) is currently the most powerful risk stratification model for R-CHOP-treated DLBCL [3], but is still insufficiently accurate to identify non-responders. Therefore, new prognostic markers are needed. In a recent feasibility study in 51 patients with newly diagnosed DLBCL who were treated with R-CHOP, it was demonstrated that tumor necrosis at CT may be predictive of both progression-free survival (PFS) and overall survival (OS) [4]. However, the sample size of that study was too small to draw any definitive conclusion [4]. ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) is another imaging method that is routinely performed in patients with DLBCL [5,6]. FDG-PET may show tumor necrosis as photopenic defects. However, it is still unknown whether this has any prognostic value beyond that of the established NCCN-IPI. The purpose of this study was therefore to determine the prognostic performance of tumor necrosis at FDG-PET in patients with

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newly diagnosed DLBCL who are treated with R-CHOP therapy, and to compare its value to that of the NCCN-IPI.

2. Materials and methods

2.1. Patients

This retrospective study was approved by the local institutional review board and the requirement for written informed consent was waived. All patients who are newly diagnosed with DLBCL routinely undergo FDG-PET for staging purposes at our center. The database of the hospital was searched for all patients who were newly diagnosed with DLBCL between January 2004 and June 2014. Study inclusion criteria were: newly diagnosed (histologically proven) DLBCL, availability of pretreatment FDG-PET (either stand-alone PET [before September 2007] or integrated PET/CT [after September 2007]), availability of bone marrow biopsy and serum lactate dehydrogenase (LDH) measurement (which are necessary to calculate the NCCN-IPI score), and front-line therapy with R-CHOP. Study exclusion criteria were: primary mediastinal DLBCL (which is a separate disease entity), previously treated lymphoma, transformed lymphoma, coexistence of another lymphoma subtype in the diagnostic biopsy, diagnosis of another cancer within the past five years (except for non-melanoma skin cancer), lack of BMB or serum LDH measurement, start of therapy before FDG-PET, and other treatment than R-CHOP. The local institutional review board approved this study and the need for written informed consent was waived because of its retrospective design.

2.2. FDG-PET imaging

Patients presenting before September 2007 underwent FDG-PET using a stand-alone PET system (ECAT-ACCEL, Siemens-CTI, Knoxville, TN, USA). Patients presenting after September 2007 underwent FDG-PET using an integrated PET/CT system (Biograph 40 TruePoint system, Siemens Healthcare, Erlangen, Germany). Patients fasted for 6 h and blood glucose levels were checked to be less than 11 mmol/L before intravenous injection of FDG (5 MBq/kg for stand-alone PET and 3 MBq/kg for integrated PET/CT). Approximately 60 min after FDG administration, PET scanning was initiated from mid thigh to skull base, in 5–7 bed positions (2D acquisition and 5 min per bed position for stand-alone PET, and 3D acquisition and 3 min per bed position for integrated PET/CT). Transmission scanning was performed using either an external ^{68}Ge–^{68}Ga rod source (stand-alone PET) or low-dose CT (integrated PET/CT). PET images were reconstructed using a weighted iterative ordered-subsets expectation maximization algorithm (8 subsets and 2 iterations for stand-alone PET, and 14 subsets and 4 iterations for integrated PET/CT), after which they were smoothed using a 3D isotropic Gaussian filter with a full width at half maximum of 8–9 mm (stand-alone PET) or 6 mm (integrated PET/CT).

2.3. FDG-PET review

An experienced reader (T.C.K.) who was blinded to clinical, laboratory, bone marrow biopsy, and follow-up findings, reviewed all FDG-PET images. Any site with FDG uptake exceeding background FDG uptake in a location incompatible with normal anatomic and physiologic conditions was considered positive for lymphomatous involvement. Nodal and extranodal lymphomatous sites were assessed for the presence of a photopenic area, in keeping with tumor necrosis (Fig. 1).

2.4. NCCN-IPI

Age, serum LDH level, presence of extranodal disease in major organs (either bone marrow [histologically proven], central nervous system, liver/gastrointestinal tract or lung involvement), presence of Ann Arbor stage III/IV disease, and Eastern Cooperative Oncology Group (ECOG) performance status score were recorded before start of therapy. The NCCN-IPI uses a maximum of 8 scoring points for categorized age >40–60 (1 point), >60–75 (2 points) and >75 years (3 points), LDH ratio >1 (1 point) and >3 (2 points) times the upper limit of normal in addition to extranodal disease in major organs, Ann Arbor stage III/IV and ECOG performance status ($\geq$2), each having a score of 1 [3]. The NCCN-IPI score categorizes each patient into one of the four NCCN-IPI risk groups (low risk [scores 0–1], low-intermediate risk [scores 2–3], high-intermediate risk [scores 4–5] and high risk [scores 6–8]) [3].

2.5. Patient follow-up

Patients were followed up clinically and with imaging (FDG-PET and CT) studies. The recently revised criteria for response assessment in malignant lymphoma were used to determine if and when progressive or relapsed disease occurred [5,6]. PFS was defined as the time from the date of diagnosis to the identification date of progressive disease or death, whichever occurred first. When no event occurred, the patient was censored at the last date of follow-up. OS was defined as the time from the data of diagnosis to the date of death of any cause, or, in surviving patients, censored at the last date of follow-up.

2.6. Statistical analysis

Associations between tumor necrosis at FDG-PET (absence vs. presence of tumor necrosis at FDG-PET) and the NCCN-IPI factors categorized age ($\leq$40, 40–60, 60–75, and >75 years), categorized LDH ratio ($\leq$1, 1–3 or >3 upper limit of normal), presence of extranodal disease in major organs (bone marrow, central nervous system, liver/gastrointestinal tract or lung), presence of Ann Arbor stage III/IV disease, and ECOG performance status ($\geq$2) were tested using Spearman (ρ) or Pearson (r) correlation coefficient analyses (for ordinal and binary NCCN-IPI factors, respectively). Very weak, weak, moderate, strong, and very strong correlations were defined as ρ or r between 0–0.19, 0.20–0.39, 0.40–0.59, 0.60–0.79, and 0.80–1.00, respectively.

PFS and OS were assessed using the Kaplan–Meier method with log-rank test for comparison of differences [7], according to tumor necrosis at FDG-PET (present vs. absent) and dichotomized NCCN-IPI risk groups (low risk [including low and low-intermediate risk] vs. high risk [including high-intermediate and high risk]). Univariate and multivariate Cox regression analyses were then performed to determine the influence of tumor necrosis at FDG-PET (present vs. absent) and categorized NCCN-IPI risk groups (low, low-intermediate, high-intermediate and high risk) on PFS and OS. P-values less than 0.05 (two-sided) were regarded statistically significant difference. Statistical analyses were executed using MedCalc statistical software version 12.6.0 (Ostend, Belgium).

3. Results

3.1. Patients

A total of 215 patients were newly diagnosed with DLBCL between January 2004 and June 2014. Of these 215 patients, 4 were excluded because of primary mediastinal DLBCL, 15 were excluded because of transformed lymphoma, 18 were excluded because of coexistence of another lymphoma subtype in the diagnostic biopsy,