Comparing radioactive tracers ^{18}F-FDG and ^{18}F-FLT in the staging of diffuse large B-cell lymphoma by PET/CT examination: A single-center prospective study

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Abstract

Background. Positron emission tomography in combination with computer tomography (PET/CT) is a very important method of imaging patients with non-Hodgkin lymphomas (NHLs). It is used to define the initial grade of the disease and to assess early response to treatment and after chemotherapy. The most commonly used radioactive tracer is ^{18}F-FDG, but ^{18}F-FLT seems to be more specific.

Objectives. The aim of our study was to compare the staging of diffuse large B-cell lymphoma (DLBCL) with PET/CT examination using ^{18}F-FLT and ^{18}F-FDG.

Material and methods. The study included 33 patients with newly diagnosed DLBCL (17 women and 16 men). The median age of the patients was 57 years. In each patient, 2 PET/CT examinations were performed before treatment, one using ^{18}F-FLT and the second using ^{18}F-FDG.

Results. The average maximum ^{18}F-FDG uptake in the whole group of patients was higher than the average maximum of ^{18}F-FLT. This was also true of individual patients; however, 3 patients with an aggressive disease course had greater FLT uptake than the other patients.

Conclusions. Our analysis suggests that PET/CT exams using ^{18}F-FLT may be a useful diagnostic tool in patients with DLBCL.

Key words: diffuse large B-cell lymphoma, positron emission tomography, ^{18}F-FLT

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Introduction

Positron emission tomography in combination with computer tomography (PET/CT) is a very important method of imaging patients with lymphomas. It is used to define the initial grade of the disease and to assess early response to treatment and after chemotherapy.[1,2] The most commonly used radiopharmaceutical is 2-deoxy-2-(^{18}F) fluorine-D-glucose (^{18}F-FDG). It is taken up in all metabolically active tissues, which are distinguished by increased uptake of glucose. After the transport of ^{18}F-FDG to a cell, phosphorylation to glucose-6-phosphorate occurs and ^{18}F-FDG gathers in the cellular cytoplasm without undergoing further reactions. Malignant cells show increased FDG uptake, especially those proliferating fast.[2] Because of this, PET/CT examination is particularly useful in patients with aggressive lymphomas with a high proliferation rate, such as diffuse large B-cell lymphoma (DLBCL).[3] An undoubted shortcoming of ^{18}F-FDG is that it is not only taken up by malignant cells. Increased glucose metabolism also appears in the course of inflammatory or infectious lesions, which can lead to false-positive results. This of particular clinical importance in the assessment of a patients' response to treatment in both the early assessment and after chemotherapy. In the case of a false-positive PET/CT examination result, a patient can be unnecessarily qualified for treatment intensification.[4,5] In light of this, other radioactive tracers are being sought which can reduce the risk of false-positive results. Test results have indicated that (^{18}F)-fluoro-3'-deoxy-3'-L-fluorothymidine (^{18}F-FLT) may be a more specific tracer. It is transported to the cells and, as a result of a reaction with thymidine kinase type 1 (TK1), it undergoes phosphorylation to monophosphate and is used in DNA synthesis. This makes ^{18}F-FLT a good cell proliferation tracer, in contrast with ^{18}F-FDG, which reflects only increased glucose uptake.[6–8] There is not much clinical data concerning the use of ^{18}F-FLT in PET/CT imaging of lymphomas.

The aim of our study was to compare the staging of DLBCL with PET/CT examination using ^{18}F-FLT and ^{18}F-FDG.

Material and methods

The study included 33 patients with newly diagnosed DLBCL (17 women and 16 men). The median age of the examined group was 57 years (range: 20–74 years). Nine patients (27%) were at stage I according to Ann Arbor staging; 13 patients (40%) were at stage II; 6 (18%) were at stage III; and 5 (15%) at stage IV. In 10 patients a bulky mass tumor (>7 cm) was found. Two PET/CT scans were performed on each patient before treatment: one of them using ^{18}F-FLT and the other with ^{18}F-FDG. The interval between PET/CT scans did not exceed 7 days. Each patient gave written consent to take part in this study. The study protocol was approved by the Wroclaw Medical University Bioethics Commission.

Table 1. The patients' clinical data

Number of patients	33
Sex	17 females 16 males
Age	57 (range: 20–74)
Ann Arbor stage	I: 9 patients II: 13 patients III: 6 patients IV: 5 patients
B symptoms	15 patients
International Prognostic Index	low: 17 low-intermediate: 3 high-intermediate: 8 high: 5
Median of antigen Ki 67(%)	80 (range: 30–99)
Median D-lactate dehydrogenase level [U/L]	391.5 (range: 240–1,199)
Median beta-2 microglobulin level [mg/dL]	3.0 (1.3–4.9)
Bulky mass	10 patients
Bone marrow involvement	2 patients

The patients' clinical data is presented in Table 1.

PET-FDG and PET-FLT examinations

PET/CT examinations using ^{18}F-FDG were performed in patients who had fasted for 6 h; the concentration of glucose in the blood serum was under 150 mg/dL. Imaging from the cranial base to the upper third of the thighs was performed using Biograph 6 and Biograph mCT scanners (Siemens AG, Munich, Germany) 60 ±10 min after injecting FDG intravenously in doses of 5–7 MBq/kg of body mass. The procedure for the PET/CT using ^{18}F-FLT was the same: The patients had not eaten for at least 6 h; imaging was performed with Biograph 6 and Biograph mCT scanners 60 ±10 min after administering 350 MBq/kg of FLT. Whole-body CT scanning was used for attenuation correction and anatomical localization. Standard CT scans were undertaken at 120 kV, 100 mAs, 0.8 s rotation with a 1.25-mm slice width, and with no contrast injection. Image interpretation was performed using the Syngovia application and the MI Oncology workstation (Siemens AG).

PET/CT examination assessment

To ensure proper interpretation, nuclear medicine and radiology specialists read the scans. Any discrepancies in interpretation were resolved by consensus. The tumors were localized according to the CT scans. Increased focal uptake was detected in the tumor and assessed by measuring the maximum standardized uptake value (SUV_{max}). Ellipsoidal volumes of interest (VOIs) with the diameter of the particular lesion were placed

in the chosen areas of the highest uptake affected by lymphomas. The SUV_{max} from these VOIs was calculated according to the standard formula (Bq/g × body weight [g]/injected activity in Bq).

FLT uptake was compared with FDG uptake for a particular lesion (lesion-to-lesion analysis). Next, the mean SUV values of individual patients were calculated to eliminate any influence connected with the number of lesions in particular patients. The mean SUV_{max} values for FLT and FDG in individual patients were compared (patient-to-patient analysis).

The results were analyzed statistically using STATISTICA v. 8.0 software (StatSoft Inc., Tulsa, USA). The statistical analysis was included the Mann–Whitney U test, Student's t-test, and Pearson and Spearman correlation methods. Differences were considered statistically significant at the $p < 0.05$ level.

Results

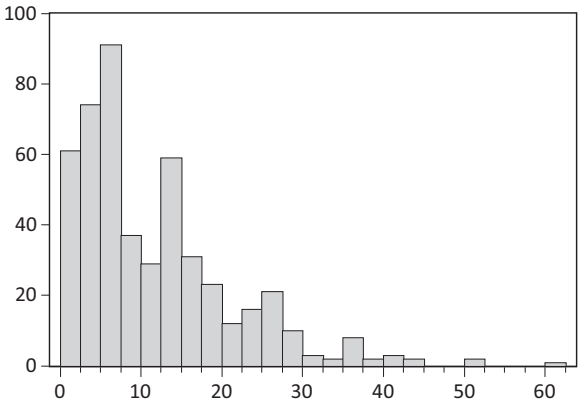
The first PET examination performed on all the patients was the scan using ^{18}F-FLT, followed by the one using ^{18}F-FDG. The time between tests was from 2 to 7 days. In the whole examined group, a total of 450 avid lesions were revealed. The ^{18}F-FLT PET scan found 28 lesions in 3 patients that were not avid during the test using ^{18}F-FDG. In the ^{18}F-FDG PET examination, 17 lesions were found in 7 patients that were invisible in the ^{18}F-FLT PET exam. The differences between the lesions discovered with the use of ^{18}F-FDG and ^{18}F-FLT did not entail any changes in the assessments of the degree of disease progression.

The correlation between FLT and FDG activity

The average SUV_{max} of F-FDG uptake in the whole group of patients was 11.56 (median 8.6), which was significantly higher than the value of the average SUV_{max} of F-FLT uptake, which was 8.62 (median 8.4). There was a statistically significant correlation between the F-FDG and F-FLT uptake values (Pearson product–moment correlation coefficient = 0.37). The results are presented in Fig. 1 and Fig. 2.

Comparison of FDG and FLT uptakes in particular patients

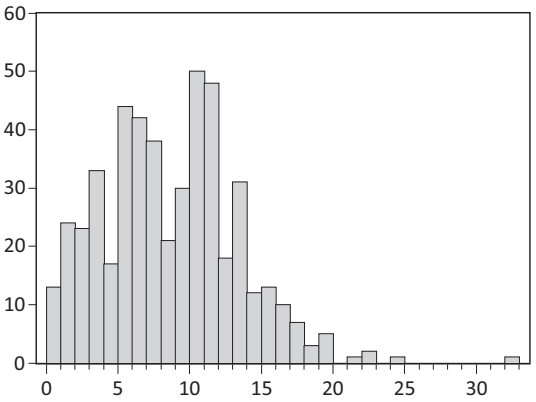
Comparing the average maximum FLT and FDG uptakes between particular patients, it turned out that they were significantly higher in the FDG PET examination than in the FLT PET scan (14.908 vs 7.73) ($p < 0.05$).



series: FDG
sample 1 487
number of observations 487

mean	11.55920
median	8.600000
maximum	62.40000
minimum	0.000000
standard deviation	9.799912

Fig. 1. FDG activity in the entire patient population



series: FLT
sample 1 487
number of observations 487

mean	8.621684
median	8.400000
maximum	32.10000
minimum	0.000000
standard deviation	4.733251

Fig. 2. FLT activity in the entire patient population

Individual FLT uptake

In 3 patients, the average FLT value was significantly higher ($p = 0.029$) than in other patients. Also, the initial SUV_{max} of FLT in these 3 patients was clearly higher than their FDG SUV_{max} (7.84 ±3.36 vs 5.6 ±4.67). In all 3 patients with an increased FLT uptake, the disease course was more aggressive than in the rest of the participants. These patients died during treatment. Our results may point to a relationship between intensified F-FLT uptake and a poor clinical course of the disease.

Correlations between FDG and FLT SUV values and selected factors

In the entire patient population, an analysis was performed of correlations between FDG and FLT activity and D-lactate dehydrogenase (D-LDH) activity, beta-2 microglobulin concentration, International Prognostic Index (IPI) value, and the value of the proliferation marker Ki-67. We found

Table 2. Pearson correlation index for FDG, FLT and selected factors

Factor	FDG	FLT	IPI	KI67	LDH	B2M
FDG	1.000000	0.581476	–0.172185	0.163427	–0.074044	–0.194903
FLT	0.581476	1.000000	0.267783	0.037243	0.107746	–0.064273
IPI	–0.172185	0.267783	1.000000	–0.108016	0.644455	0.396296
KI67	0.163427	0.037243	–0.108016	1.000000	–0.049231	–0.229803
LDH	–0.074044	0.107746	0.644455	–0.049231	1.000000	–0.172268
B2M	–0.194903	–0.064273	0.396296	–0.229803	–0.172268	1.000000

FDG – fluorine-D-glucose; FLT – fluoro-deoxy-L-fluorothymidine; IPI – International Prognostic Index; Ki67 – antigen Ki67; LDH – lactate dehydrogenase; B2M – beta-2 microglobulin.

a statistically significant positive correlation between FDG and FLT activity. A positive correlation was also found between FLT and D-LDH activity, although that connection was not statistically significant.

The results are presented in Table 2.

FLT activity in relation to gender

The tests found a statistically significant difference between the FLT uptake value in women and in men: FLT uptake was higher in women than in men ($p = 0.0011$).

FDG and FLT activity in the assessment of bone marrow involvement

Each patient in the study population had a bone marrow biopsy performed before the start of chemotherapy. In 2 patients, bone marrow infiltration by lymphoma cells was found in the histopathological examination, although neither the FDG nor the FLT PET exams revealed any bone marrow involvement in either case.

Discussion

PET-CT examination is at present the imaging standard in aggressive non-Hodgkin lymphomas (NHL), both before the start of a therapy and in assessments after the end of treatment.[3] In high-grade NHL like DLBCL, the true negative rate of the PET-CT results is confirmed after the end of chemotherapy.[9] ^{18}F-FDG is a radioactive tracer that is commonly used in PET-CT examinations, but due to the non-specificity of FDG uptake, compounds that could decrease the probability of false-positive results are being sought. ^{18}F-FLT, which was used for the first time by Shields et al., seems to be such a radioactive tracer.[10] That study showed that ^{18}F-FLT PET results correlate with the cell proliferation degree in solid neoplasms and in lymphomas.[5,11,12] In a group of 20 patients with small cell lung cancer, Everitt et al. conducted ^{18}F-FLT PET and ^{18}F-FDG PET scans before the start of treatment and during therapy. It turned out that ^{18}F-FLT PET was more sensitive test than ^{18}F-FDG PET.[13] In a study of 20 patients with breast cancer, ^{18}F-FLT PET was performed before the start of the treatment and before the second chemotherapy cycle.[14] The SUV_{max} ^{18}F-FLT PET value before the treatment significantly correlated with Ki-67 activity, which suggested the role of FLT in defining neoplasm proliferation activity. After the end of chemotherapy a significant decrease in the ^{18}F-FLT PET SUV_{max} value was observed in connection with the reduction of the tumor mass.[14] Cho et al. conducted an study using ^{18}F-FLT PET and ^{18}F-FDG PET scans in patients with cervical and vaginal cancer before therapy and after the end of chemo- and radiotherapy.[15] The FLT SUV_{max} value was significantly lower than the FDG SUV_{max} in the first examination. After treatment, the FLT SUV_{max} value was much lower regardless of the presence of the inflammatory response after radiotherapy. The study results point to the possibility of monitoring gynecological neoplasm treatment results with ^{18}F-FLT PET.

The use of ^{18}F-FLT PET in imaging lymphoid tumors is not a diagnostic standard and there are very few data concerning the use of this method in this group of patients. Lee et al. assessed the role of early ^{18}F-FLT PET scans as a prognostic index in a group of 61 patients with NHL.[16] The population examined included patients with DLBCL, mantle cell lymphoma (MCL), follicular lymphoma (FL), Burkitt lymphoma, natural killer cell lymphoma, and T-cell lymphoma. ^{18}F-FLT PET scans were performed before the treatment, after the first chemotherapy cycle and after the treatment. The patients with a positive result in the early ^{18}F-FLT PET examination had shorter progression-free survival (PFS) and shorter overall survival (OS) in comparison to the patients with negative PET results (PFS 52% vs 80.7% and OS 56.2% vs 81.4%).[16] In a group of 17 patients with FL and FL transformation, Wondergem et al. compared the SUV_{max} values for ^{18}F-FLT PET and ^{18}F-FDG PET. In patients with FL transformation, the SUV_{max} values for both ^{18}F-FLT and ^{18}F-FDG were significantly higher than in the group of patients with FL without transformation. In the population with FL transformation, ^{18}F-FDG PET revealed higher SUV_{max} values than ^{18}F-FLT PET, and the authors of the study therefore suggested that imaging with ^{18}F-FDG PET is a better diagnostic option in cases of FL transformation.[17]

In the group of 33 untreated DLBCL patients in our study, we compared ^{18}F-FLT PET and ^{18}F-FDG PET examinations. In the whole population and also in individual patients, SUV_{max} values for ^{18}F-FDG were higher than for ^{18}F-FLT. In 3 patients with an especially aggressive disease course, 28 avid lesions were found in the ^{18}F-FLT PET examinations that were not visible in the ^{18}F-FDG PET examination. The SUV_{max} values for ^{18}F-FLT PET in those patients were significantly higher than their ^{18}F-FDG PET SUV values. These results suggest that ^{18}F-FLT PET-CT can be used as an indicator of an aggressive clinical course in patients with DLBCL. In the population we assessed, the ^{18}F-FLT PET examinations were conducted before the start of therapy. Herrmann et al. conducted ^{18}F-FLT PET scans in patients with DLBCL before the treatment and a week after the first chemotherapy cycle (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone).[18] The reduction of SUV_{max} values for ^{18}F-FLT after the first chemotherapy cycle was significantly higher in patients who achieved complete remission after chemotherapy. It seems that early ^{18}F-FLT PET examinations can be useful in assessing the efficacy of treatment.[18] In aggressive NHLs such as DLBCL, a negative PET test result has a confirmed predictive value after the end of treatment. However, early ^{18}F-FDG PET scans can carry a risk of false-positive results in connection with the immunochemotherapy used, which can lead to reactive changes caused by treatment itself.

We also noticed that in our study group ^{18}F-FLT values were significantly higher in the females than in the males. This observation requires further analysis in a larger patient population.

Conclusions

The results of our study suggest that ^{18}F-FLT PET-CT can be a useful diagnostic method in the assessment of patients with DLBCL. Data from the available literature also indicates this. Our analysis concerned a small group of patients and the results are preliminary, requiring confirmation in a larger population of patients.

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