The role of serial pre-transplantation positron emission tomography in predicting progressive disease in relapsed lymphoma

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Background and Objectives. ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) appears to be an excellent tool for evaluating early response to chemotherapy in lymphoma patients. As only chemosensitive patients with relapsed lymphoma may benefit from ablative therapy and autologous stem cell transplantation (ASCT), PET may be used to select patients for ASCT. A prospective study was performed to investigate the optimal time point of pre-transplantation PET, using different PET-parameters.

Design and Methods. Three serial whole-body attenuation-corrected FDG-PET scans were performed in 39 consecutive patients with relapsed lymphoma (28 with aggressive non-Hodgkin's lymphoma and 11 with Hodgkin's disease) eligible for second-line chemotherapy followed by ASCT: PET1 before treatment, PET2 after two cycles of induction chemotherapy and PET3 after a third cycle of chemotherapy just before ASCT in cases with an abnormal PET2. Visual analysis and standardized uptake value (SUV) parameters were obtained for each scan. The follow-up lasted a minimun of 6 months after ASCT.

Results. PET2 normalized in 43% (17/39) of the patients, and PET3 normalized in 27% (6/22). Persistent abnormal FDG-uptake was observed in 41% of the patients: 15% showed partial remission and 26% stable or even progressive abnormalities. With a median follow-up of 22 months (range 6-55) 54% of all patients relapsed after ASCT. The results demonstrated that those patients who showed a complete response after the second and third cycles of chemotherapy had a 2-year progression-free survival of 71% and 58%, respectively, while those who showed no response, all relapsed shortly after ASCT. Analysis of the SUV parameters did not reveal additional information compared to that yielded by the visual assessment.

Interpretation and Conclusions. Two serial PET scans predict outcome after ASCT more precisely than one interim PET in patients with relapsed lymphoma.

Key words: relapsed lymphoma, autologous stem cell transplantation, 18F-fluorodeoxy-glucose (FDG), positron emission tomography (PET), standardized uptake value (SUV), prognosis.

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The use of ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) is becoming increasingly important in hematologic practice. In malignant lymphomas, one of the most promising applications is to monitor response to treatment and hence predict outcome early during therapy. Retrospective studies have shown that PET response correlates well with outcome after therapy, in both primary[1-3] and relapsed disease.[4-7] Ultimately, PET may be used to stratify treatment for individual groups of patients. There is no standardized method for evaluating PET response in lymphoma patients. An EORTC workshop on FDG-PET led to recommendations on measuring solid tumor response using maximum and global standardized uptake values (SUV).[8] However, malignant lymphoma usually does not present as localized disease. Furthermore, it is questionable whether response assessment based on SUV parameters is useful in daily practice, in part due to the lack of international standards. Finally the best timing of FDG-PET scans during the treatment of relapsed lymphoma has not been elucidated. Some studies scheduled PET just before ablative therapy,[5,6] others before stem cell mobilization therapy[4] or both.[7] Early response prediction is attractive, but may be less accurate. In the present study we address these issues by evaluating serial PET in a study population with relapsed lymphoma receiving re-induction therapy followed by ablative therapy and autologous stem cell transplantation (ASCT) according to an identical treatment protocol. By performing three PET scans during pre-transplantation treatment, we investigated which scan(s) may be the most useful for selecting those patients who could be cured by ASCT.

Design and Methods

Patients and treatment

During the study period from 2001 to 2003, patients with histologically proven relapse or progression of either aggressive

non-Hodgkin's lymphoma (NHL) or Hodgkin's disease (HD) eligible to receive intensive chemotherapy followed by ASCT were included in this study. Treatment had failed during or after a first-line CHOP-like regimen[9] in patients with NHL or during or after ABVD[10] or MOPP/ABV[11] in patients with HD (Table 1). After restaging, using conventional diagnostic methods, i.e. at least computed tomography of the thorax and abdomen and bone marrow biopsy, patients were treated with second-line chemotherapy consisting of DHAP-VIM[12] (Table 1). Patients who were responsive to DHAP-VIM, based on conventional diagnostic methods, were subsequently eligible for a second cycle of DHAP with peripheral stem cell mobilization followed by BEAM therapy and ASCT[12] (Figure 1). Non-responders were offered rescue treatment (mini-BEAM)[13] or, when resistant, palliative treatment. All patients had a follow-up of at least 6 months after ASCT. Post-transplant follow-up assessment consisted of physical examination, and computed tomography (or PET) scanning within 3 months and was repeated during follow-up in the case of suspected relapse. A reference pathologist from our lymphoma working group confirmed the histology of all biopsies. All included patients gave informed consent. The medical ethics committee of our hospital approved the protocol.

PET imaging

Whole body FDG-PET was performed before the start of treatment (PET1), after DHAP–VIM (PET2) and just before ASCT (PET3) if PET2 was still abnormal (Figure 1). On each occasion, patients received approximately 5 MBq/kg bodyweight FDG intravenously and were scanned from the mid-thigh to the head upwards, starting 90 minutes after the FDG injection. FDG was synthesized according to the procedure described by Hamacher *et al.*[14] using a computer controlled-synthesis module. We used a scanner with an axial field of view of 15.4 cm and a 5 mm resolution (ECAT EXACT HR+, Siemens/CTI, Knoxville, TN, USA). Attenuation corrected FDG-images were obtained using an interleaved protocol (ETTE, 3 minutes emission and 5 minutes transmission per bed position). Data were reconstructed iteratively into coronal, sagittal, and transverse sections and a three-dimensional rotating maximum intensity projection using standard ECAT software.

Table 1. Abbreviations of chemotherapy-schedules used in this article.

CHOP	cyclophosphamide, adriamycin, vincristine and prednisone
ABVD	adriamycin, bleomycin, vinblastine and decarbazine
MOPP/ABV	mechlorethamine, vincristine, procarbazine, prednisone, adriamycin, bleomycin and vinblastine
DHAP	dexamethasone, cytarabine, cisplatin
VIM	etoposide, ifosfamide and methotrexate
(mini) BEAM	carmustine, etoposide, cytarabine and melphalan

PET image analysis

Two independent reviewers prospectively evaluated the scans. A visual assessment score was used to describe abnormal lesions (1=normal/benign, 2=probably benign, 3=intermediate, 4=probably malignant, 5=malignant). Follow-up scans (PET2-3) were also visually assessed and compared to the previous scan. The possible responses were complete PET remission, partial PET remission, no PET response. Complete PET remission was defined as complete disappearance of all lesions with abnormal uptake (only score 1 or 2). These patients were PET-negative. PET-positive patients showed persisting abnormalities suspicious for lymphoma (score 3 to 5). Partial PET remission was defined as only minimal residual PET abnormalities with a clear reduction in number and/or intensity of abnormal lesions compared to the previous scan (scores 3 to 5). No PET response was defined as no distinct change or progression of volume or intensity of any pathologic lesion (score 4 or 5). In the case of a discrepancy between the two observers, an independent panel of PET readers decided on this matter. In addition, the volume and SUV of the three most intense lesions were assessed at each scan using a volume of interest of 70% of the maximum pixel value. For this purpose, a validated software program assessed in several European PET-centers was used (J. Nuyts, KU Leuven, Belgium). In our analysis we used mean and maximal SUV of the lesion with the most intense uptake and a weighted mean SUV of the three mentioned lesions per scan. All SUV were corrected for body weight, body surface area and glucose level (whole blood) at the time of injection according to international correction formulae.[15] The SUV was set at 1.0 (before correction) in the case of no abnormal lesions.

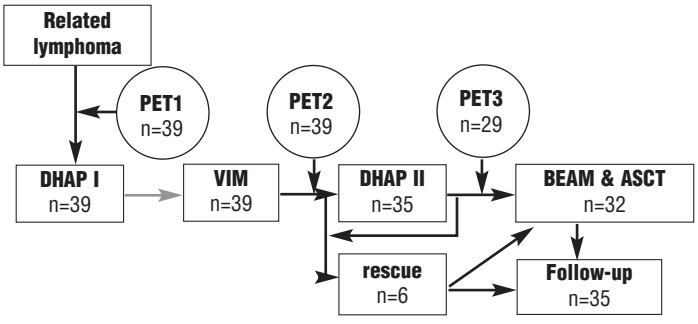

Figure 1. Treatment schedule, PET assessments and patient flow. PET3 was performed in 29/32 patients. DHAP-VIM failed in two patients and four patients progressed after DHAPII. They were offered rescue treatment. Rescue treatment consisted of mini-BEAM (carmustine, etoposide, cytarabine and melphalan). DHAP: dexamethasone, cytarabine, cisplatin; VIM: etoposide, ifosfamide, methotrexate; BEAM: carmustine, etoposide, cytarabine, melphalan; ASCT: autologous stem cell transplantation.

Computed tomography

Computed tomography scans were performed in parallel to FDG-PET scans (at diagnosis of relapse/progression of lymphoma and after two courses of induction chemotherapy), allowing a maximal interval of 2 weeks between the two diagnostic methods. The computed tomography scanning was performed after oral and intravenous contrast. Slice thickness varied from 0.5 cm in the neck region to 1.0 cm in the thorax and abdomen. The number of enlarged lymph nodes was counted and the diameter of the largest lesions was measured in two perpendicular dimensions. After re-staging, remission status was assessed using the standardized response criteria described in the International Working Group Recommendations.[16]

Statistics

The aim of this study was to evaluate the accuracy of FDG-PET in assessing progression-free survival for relapsed lymphoma patients after second-line chemotherapy. Different PET parameters were used. The time to progression was calculated from the date of the second pre-transplant PET scan (PET2) until progressive disease. Progressive disease was defined as biopsy-proven progressive lymphoma or death due to lymphoma. The events used to calculate progression-free survival were progressive disease or death. Progression-free survival was calculated using Kaplan-Meier analysis and compared between groups using a log-rank test. The predictive value of FDG-PET was determined by a χ^2 test. The positive predictive value and negative predictive value were assessed using 2×2 tables. Receiver operating characteristic (ROC) analysis was used to determine optimal cut-off values for the different SUV parameters considered. A p value less than 0.05 was considered statistically significant. Data analysis was performed using the SPSS 12.0 software package (SPSS Inc. Chicago, USA).

Results

Thirty-nine consecutive patients with relapsed lymphoma participated in this study: 28 had NHL and 11 had HD. These patients' characteristics are shown in Table 2. Their median age was 49 years. Twelve patients (31%) had progressed during or within 3 months after first-line chemotherapy. The other 27 patients had relapsed after first-line therapy with a median disease-free interval between first-line chemotherapy and relapse of 8 months (range, 3-144 months). At relapse or progression, 59% of the patients had stage III-IV disease. Most NHL patients had an intermediate risk score according to secondary age-adjusted International Prognostic Index score.[17] Most Hodgkin's patients had a low to intermediate risk score according to Josting's relapsed Hodgkin's risk score.[18]

Treatment and outcome

After two cycles of induction chemotherapy (DHAP-VIM), 35/39 patients had a partial response and were eligible for a second cycle of DHAP followed by peripheral stem cell mobilization and collection. The four non-responding patients received rescue treatment with mini-BEAM (n=2), or radiotherapy for localized disease (n=2). After the second cycle of DHAP, five patients had clinically progressive disease and one patient was not able to undergo BEAM therapy because of heart failure. In total, seven patients with progressive disease received rescue treatment with mini-BEAM, of whom three responded. Finally, 32/39 patients (including three responding to mini-BEAM) went on to ASCT with BEAM as the conditioning regimen (Figure 1). Of the 39 included patients, 54% progressed (5/11 with HD and 16/28 with NHL). The median time to progression after PET3 was 3 months (range, 0-13). The median follow-up for those who did not progress (n=18) was 23 months (range, 7-56) after the second PET scan.

Table 2. Characteristics of patients with relapsed lymphoma.

Number of cases	39
Sex (m/f)	23/16
Age (median-range)	49 (19-68) years
Resistant disease	12
Recurrent disease	27
With DFI (median-range)	8 (4-144) months
Hodgkin's lymphoma	11
Non Hodgkin's lymphoma	28
Diffuse large B-cell lymphoma	20
Mantle cell lymphoma	1
Follicular cell lymphoma, grade III	2
Peripheral T-cell lymphoma	2
Anaplastic large cell lymphoma	3
Stage at relapse	
I and II	16
III and IV	23
sAA-IPI (NHL)	
0-1	12
2-3	16
sHRS (HD)	
0-1	9
2-3	2

DFI: disease-free interval between last treatment and relapse; sAA-IPI : secondary age adjusted International Prognostic Score; sHRS: (secondary). Hodgkin's Risk Score according to Josting et al.[17]

Computed tomography

Computed tomography was used in parallel to PET1 and PET2 to assess tumor response and to select patients for further treatment. Only chemosensitive patients, based on at least partial remission according to standardized criteria, were offered the second cycle of DHAP. Twelve percent of the patients achieved complete remission and 74% of the patients had a partial remission. One patient with less than 50% tumor reduction evidenced by computed tomography was considered chemosensitive based on clinically evaluated complete disappearance of palpable lymph nodes. Thus, 89% of the patients were selected for the second DHAP course. Computed tomography assessment of response after DHAP-VIM was not accurate for predicting outcome following transplantation: the positive predictive value was 56% and the negative predictive value 60% (p=0.060).

Table 3. Statistical analysis of visual and SUV data.

	PPV	NPV	p
A.			
PET2			
PETpos	0.73	0.71	0.006
PETresp	0.89	0.57	0.011
SUV>1	0.78	0.58	0.060
PET3			
PETpos	0.82	0.60	0.073
PETresp	1.00	0.55	0.005
SUV>1	0.83	0.40	0.219
	2-year PFS (%)		*p*
B.			
PET2			
PETpos	27 (18-36) vs 71 (59-81)		0.001
PETresp	26 (16-36) vs 64 (52-74)		0.011
SUV>1	22 (9-35) vs 56 (46-66)		0.015
PET3			
PETpos	18 (8-26) vs 60 (38-82)		0.05
PETresp	0 vs 56 (40-70)		0.0001
SUV>1	17 (6-26) vs 47 (25-55)		0.036

PET and outcome: statistical analysis using the χ^2 test. (A) and log-rank test (B). PET pos: any versus no abnormal PET lesion; PETresp: visual response evaluation showing non-response versus complete or partial response. SUV>1: weighted standardized uptake value of maximal three most intense lesions (corrected for body surface area and glucose) >1. PPV = positive predictive value; NPV: negative predictive value; 2-year PFS: % (95% CI) of patients free of progression at 2 years.

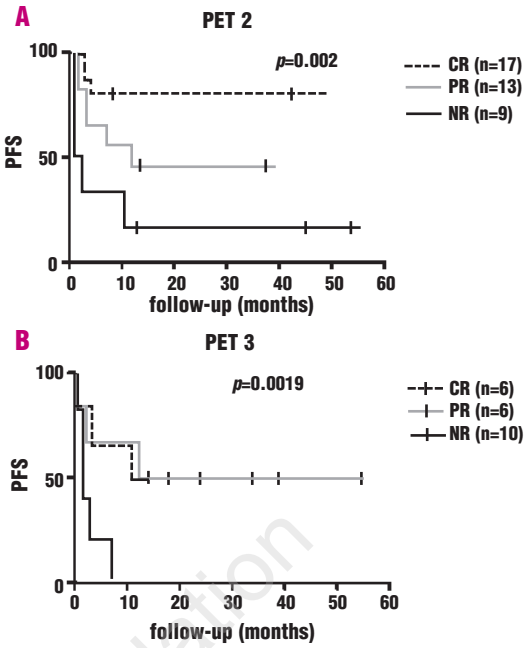

Figure 2. Analysis of PET2 and PET3 results and progression-free survival in 39 relapsed lymphoma patients. Kaplan-Meier curves showing PET response, analyzed visually, and progression-free survival (PFS) for PET2 (A) and PET3 (B). CR: complete response; PR: partial response; NR: no response.

PET scanning

PET1 was performed in 37 patients, PET2 in 39 patients and PET3 in 22 patients (Figure 1). PET3 was not performed in 17 patients in whom the PET2 scan normalized. Visual assessment of the second PET scan showed normalization in 44% of the patients (including two patients who lacked PET1 but had a normal PET2), a partial response in 33% of the patients and non-response in 23% of the patients.

The PET3 demonstrated a complete response in 27% of the patients, a partial response in 27% of the patients and non-response in 45% of the patients. Seven of these patients who had no response judged by PET did not have clinical progression according to conventional diagnostic methods, so they received BEAM and stem cell reinfusion. In total, 59% of the patients had normalization of PET scans after the second or third cycle of chemotherapy. Persistent abnormal FDG-uptake was seen in 41% of the patients.

PET and outcome: visual analysis

PET-positive patients had a significantly worse median progression-free survival than did PET-negative patients, with 2-year progression-free survivals of 27% versus 71% (p=0.001) for patients with a positive or negative PET2, respectively, and 18% versus 60% (p=0.05) for positive or negative PET3 (Table 3). The positive and negative predictive values of PET2 and PET3 for progression-free survival were 73% vs. 82% and 71% vs. 60%, respectively. Normalization of PET during induction therapy was associated with a median progression-free survival of more than 50 months, while the median progression-free survival for patients with persistent PET abnormalities was 3 months (range, 2-4). Using visual PET response criteria, we were able to identify three risk groups based on PET2 and PET3 findings (Figure 2): complete responders with a 2-year progression-free survival of 71% (PET2) and 60% (PET3), partial responders with a 2-year progression-free survival of 38% (PET2) and 50% (PET3) and non-responders with a 2-year progression-free survival of 11% (PET2) and 0% (PET3). PET non-responsive versus PET responsive patients had a significantly worse prognosis at both PET2 (p=0.011) and PET3 (p=0.0001). The positive predictive value was much better than the negative predictive value of both PET2 (89% versus 57%) and PET3 (100% versus 55%).

PET and outcome: SUV analysis

Standardized uptake values could be assessed in 86/98 (88%) scans. The weighted mean SUV at diagnosis (PET1) showed a large variation both in patients with and without progression: 2.1-13.9 versus 1.3-19.7, respectively (p=not significant). Corrected for body surface area and glucose the range was 3.6-1 7.8 for relapsing patients versus 2.8-19.7 for non-relapsing patients (p=not significant). In our analysis there was no difference between predictive value of mean or maximal SUV of one hottest lesion and weighted mean SUV of the

three most intense lesions, with or without correction for body surface area and glucose. Subsequently we used weighted mean SUV corrected for body surface area and glucose. Patients who did not relapse had a clear reduction of mean SUV during treatment, corresponding with responsive disease. In the group of patients who relapsed after transplantation, SUV at PET2 and PET3 was significantly higher: mean SUV 1.24 (0.87-1.61) versus 0.32 (0.20-0.43) (p=0.028) for PET2 and 4.04 (2.48-5.60) versus 0.59 (0.27-0.90) (p=0.20) for PET3. However, the predictive values did not appear to be superior to those obtained by visual analysis (Table 3). Using ROC-analysis, a cut-off level for corrected SUV of 1.0 was found to be the most informative. This led to a positive predictive value of PET2 of 78% and a negative predictive value of 58%. The positive predictive value of PET3 was 83%, and the negative predictive value was 40%. PET2 non-responders (as defined by SUV>1.0) showed a worse progression-free survival at 2 years (22% versus 56%, p=0.015), as did PET3 non-responders (17% versus 40%, p=0.036).

Discussion

The present study demonstrates that pre-transplantation PET can be used to select relapsed lymphoma patients for ASCT. Those patients who meet conventional criteria of responsive disease, but fail to show an adequate PET response will relapse after ASCT: 89% of the patients without response at PET2 and 100% of those without a response at PET3 relapsed after ASCT. This failure of induction chemotherapy was not predicted by either clinical parameters or computed tomography. Those patients who have complete metabolic response after two or three courses of induction chemotherapy will have a good chance of remaining in remission. In our analysis, 71% of patients with PET2 normalization and 58% with PET3 normalization showed continued complete remission at 2 years after a median follow-up of 22 months. These figures suggest that patients who have a slow PET response have a worse prognosis than those with a faster PET response.

Moreover, in this analysis we showed that careful visual assessment of serial PET provides equivalent results to those obtained from measurement of SUV of the most intense pathologic lesions. The visual response assessment may even be improved in the future with the combined use of computed tomography and PET data.

In our previous study, FDG-PET was scheduled before and after two courses of induction chemotherapy,[4] while others performed PET just before ASCT.[5-6] Cremerius *et al.*[7] performed pre-transplant serial PET scanning in 24 patients with untreated NHL. The best timing of FDG-PET before transplantation is presently unknown. In daily clinical practice, there are two moments during intensive chemotherapy at which a re-evaluation is scheduled i.e. after re-induction chemotherapy and just before ablative therapy to ensure minimal residual lymphoma. The second PET evaluation in our study was planned after two cycles of re-induction chemotherapy while the third PET scan was planned just before ASCT. Our results indicate that the combined information from PET2 and PET3 is highly predictive for treatment outcome. PET3 had a slightly better predictive accuracy than PET2, especially for identifying those patients who will have a poor prognosis. Although PET2 and PET3 both correlated with outcome after transplantation, no single PET scan could predict outcome precisely enough to be used for treatment decisions in these patients. In our study, only response failure demonstrated by two serial PET scans indicated that ASCT would be futile. Therefore, based on our results, at least two serial pre-transplantation PET scans are needed during re-induction treatment.

Our analysis indicates that in the setting of pre-transplantation evaluation, FDG-PET has a higher positive predictive value for relapse than negative predictive value. These findings are in contrast with most PET studies showing a better negative predictive value.[19] The difference might be due to differences in pre-test probability (high risk of relapse) or to differences in cell biology between various types of tumor.

In summary, the results presented indicate that in order to predict treatment outcome in relapsed lymphoma patients, two FDG-PET scans should be performed: one early during therapy and the other shortly before ASCT. A careful visual assessment of response provides the same results as the more laborious SUV calculations.

BS, JP, GWvI, EV: performed the clinical study; The PET studies were performed by the group from Vaalburg under the direction of JP. Statistical analysis was performed by WS. BS, WJS and EV wrote the manuscript with contributions from other authors. Financed by a grant from the University Medical Center Gröningen, the Netherlands. We thank Carolien J.M. Verhoogt and Miryam F. de Brouwer for data collection and Professor Dr. Philip M. Kluin (Department of Pathology, University Medical Center Groningen, The Netherlands) for pathological review.The authors declare that they have no potential conflict of interest.

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