Ann Hematol (2015) 94:431–436
DOI 10.1007/s00277-014-2227-5

ORIGINAL ARTICLE

Post-therapy ^{18}F-fluorodeoxyglucose positron emission tomography for predicting outcome in patients with peripheral T cell lymphoma

Naoto Tomita · Yukako Hattori · Shin Fujisawa · Chizuko Hashimoto · Jun Taguchi · Hirotaka Takasaki · Rika Sakai · Ukihide Tateishi · Yoshiaki Ishigatsubo

Received: 27 February 2014 / Accepted: 30 September 2014 / Published online: 23 October 2014

Abstract The International Harmonization Project on Lymphoma recommends ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) for the routine assessment of treatment efficacy in patients with FDG-avid lymphomas such as Hodgkin's and diffuse large B cell lymphomas. The utility of FDG-PET in predicting outcomes in patients with peripheral T cell lymphomas (PTCL) has not been fully elucidated. We retrospectively determined the predictive value of FDG-PET after first-line treatment (post-PET) for outcome in PTCL. Of the 36 patients enrolled, 16 were histologically diagnosed with PTCL not otherwise specified and 20 were diagnosed with angioimmunoblastic T cell lymphoma. All patients received curative-intent anthracycline-containing chemotherapy regimens. Post-PET images were visually evaluated by local nuclear medicine physicians. The median observation period for the surviving patients was 44 months. Positive and negative post-PET results were obtained in 31 % (11/36) and 69 % (25/36) of patients, respectively. The 3-year progression-free survival rates in the positive and negative post-PET result groups were 18 % and 62 %, respectively (P<0.001). Nine of the 11 patients in the positive post-PET result group experienced progressive disease (PD) (positive predictive value, 82 %), whereas 16 of the 25 patients in the negative post-PET result group did not experience PD (negative predictive value, 64 %). The 3-year overall survival rates in the positive and negative post-PET result groups were 44 % and 84 %, respectively (P=0.03). Our findings indicate that post-PET is predictive of outcome in patients with PTCL.

Keywords Overall survival · Peripheral T cell lymphomas · Positron emission tomography · Prognosis · Progression-free survival

N. Tomita (✉) · Y. Ishigatsubo
Department of Internal Medicine and Clinical Immunology, Yokohama City University Graduate School of Medicine, Yokohama, Japan
e-mail: cavalier@ch-yamate.dlenet.com

Y. Hattori · H. Takasaki · R. Sakai
Department of Medical Oncology, Kanagawa Cancer Center, Yokohama, Japan

S. Fujisawa
Department of Hematology, Yokohama City University Medical Center, Yokohama, Japan

C. Hashimoto
Department of Hematology/Oncology, Yamato Municipal Hospital, Yamato, Japan

J. Taguchi
Department of Hematology, Shizuoka Red Cross Hospital, Shizuoka, Japan

U. Tateishi
Department of Radiology, Yokohama City University Graduate School of Medicine, Yokohama, Japan

Introduction

Peripheral T cell lymphomas (PTCLs) are mature T cell neoplasms derived from post-thymic T cells. Although the PTCL incidence varies geographically [1, 2], it accounts for 20–25 % of non-Hodgkin's lymphomas in Japan [3]. PTCL not otherwise specified (PTCL-NOS) and angioimmunoblastic T cell lymphoma (AITL) are the most common histological categories of PTCL, accounting for more than 40 % of T/natural killer (NK) cell lymphomas [2] with characteristic nodal involvement. PTCL-NOS and AITL exhibit similar clinical behavior including onset at a relatively advanced age and poor

outcomes [4] and, therefore, are often described together in clinical reports [5, 6].

The application of ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) for disease staging and assessing treatment response in lymphoma patients has rapidly gained prominence. In 2007, the International Harmonization Project on Lymphoma recommended the routine use of FDG-PET for staging and assessing treatment response in patients with lymphoma [7, 8]. The use of PET for mid-treatment assessment was recommended only for clinical trials [9–13]. FDG-PET use was only recommended for FDG-avid lymphomas such as Hodgkin's lymphoma and diffuse large B cell lymphoma (DLBCL) and not for T/NK cell lymphomas, as data concerning PET utility in the latter were more limited at that time. Subsequently, the utility of FDG-PET for staging T/NK cell lymphomas has been described by many investigators [14–21], and the FDG avidity of T/NK cell lymphomas has become recognized. Furthermore, additional, albeit limited, data on the application of FDG-PET for response assessment in T/NK cell lymphomas have also been published. The purpose of this study was to elucidate the predictive value of FDG-PET performed after the completion of first-line treatment (post-PET) for clinical outcomes in patients with PTCL-NOS and AITL.

Materials and methods

The study was approved by the Yokohama City University Hospital Clinical Research Ethics Board and was performed in accordance with the Declaration of Helsinki. This was a multi-institutional retrospective study involving five hospitals of the Yokohama City University Hematology Group in Japan. Fifty-seven patients who were diagnosed as having PTCL between 2005 and 2011 at one of the participating institutions were identified, and of these, 36 patients who underwent post-PET were enrolled. The histological diagnosis was PTCL-NOS in 16 patients and AITL in 20 patients. All 36 patients received a doxorubicin (adriamycin [ADR])- or pirarubicin (THP)-ADR-containing regimen as first-line treatment with curative intent. Clinical staging was performed according to the Ann Arbor system, which is based on physical examination; computed tomography (CT) of the neck, chest, abdomen, and pelvis; bone marrow aspiration; and biopsy. International Prognostic Index (IPI) factors and score [22], bone marrow involvement, B symptoms, presence of a bulky mass, and the Prognostic Index for Peripheral T cell lymphoma, unspecified (PIT) were assessed. A bulky mass was defined as any mass exceeding 10 cm in diameter in a horizontal plane or a mediastinal mass with a maximum diameter exceeding one third of the maximum chest diameter. Upper and/or lower gastrointestinal endoscopy, lumbar puncture, and brain magnetic resonance imaging were performed as needed to obtain additional information. PET was performed as a staging procedure when possible.

After completion of first-line treatment, PET; physical examination; and CT of the neck, chest, abdomen, and pelvis were performed to evaluate the therapeutic efficacy. In patients with initial bone marrow involvement, re-biopsy was performed. None of the patients underwent interim PET during first-line therapy. Post-PET was performed at least 3 weeks after the last exposure of patients to anticancer drugs. Therapeutic efficacy was classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to the criteria described by Cheson et al. [8]. Staging PET and post-PET were performed at individual institutions or regional PET centers. Local nuclear medicine physicians visually evaluated the post-PET images and submitted detailed reports. The association between the post-PET results and outcomes was evaluated.

Statistical analysis

The chi-square test was used to determine statistically significant differences between the characteristics of the groups. Survival curves were constructed using the Kaplan-Meier method and compared using the log-rank test. P values <0.05 were considered statistically significant. Overall survival (OS) was calculated from the date of initiation of first-line treatment to the date of death or last contact, whichever occurred first. Progression-free survival (PFS) was calculated from the date of initiation of first-line treatment to the date of PD, death, or last contact, whichever occurred first. PFS and OS were alternatively calculated from the date of response assessment. Data were analyzed using the Statistical Package for the Social Sciences (IBM PASW Statistics 18.0, IBM Corporation, Armonk, NY, USA).

Results

Patient characteristics according to histological diagnosis (PTCL-NOS vs. AITL) are shown in Table 1. Gender distribution, IPI factors and score [22], bone marrow involvement, B symptoms, presence of a bulky mass, and the PIT were not significantly different between PTCL-NOS and AITL patients [23]. Therefore, we pooled the data from these patients.

Treatment and outcome details are listed in Table 2. All 36 patients underwent anthracycline-based chemotherapy with curative intent. Most patients (81 %) received THP-ADR, an analogue of ADR. The dose of ADR in the THP-ADR regimen was the same as that used in standard cyclophosphamide, ADR, vincristine, prednisolone (CHOP) therapy (50 mg/m^2). The doses of other chemotherapeutic drugs (cyclophosphamide and vincristine) were also based on the CHOP regimen.

Table 1 Patient characteristics

	Total	PTCL-nos	AITL	*P* value
Number of patients	37	16	20	
Male gender (%)	19 (53)	7 (44)	12 (60)	NS
Age over 60 years, *n* (%)	23 (64)	8 (50)	15 (75)	NS
Performance status 2–4, *n* (%)	4 (11)	1 (6)	3 (15)	NS
Elevated LDH, *n* (%)	20 (56)	6 (38)	14 (70)	NS
Advanced clinical stage, *n* (%)	29 (81)	11 (69)	18 (90)	NS
Extranodal involvement sites over 1, *n* (%)	10 (28)	6 (38)	4 (20)	NS
Positive bone marrow involvement, *n* (%)	5 (14)	2 (13)	3 (15)	NS
Presence of B symptoms, *n* (%)	14 (39)	4 (25)	10 (50)	NS
Presence of bulky mass, *n* (%)	0 (0)	0 (0)	0 (0)	NS
IPI				
0–1	7	5	2	
2–3	22	9	13	NS
4–5	7	2	5	
PIT				
Group 1: 0–1 factor	5	4	1	NS
Group 2: 2–4 factors	31	12	19	

PTCL-nos peripheral T cell lymphoma not otherwise specified, *AITL* angioimmunoblastic T cell lymphoma, *LDH* lactate dehydrogenase, *IPI* international prognostic index, *PIT* prognostic index for T cell lymphoma

CHOP and THP-COP regimens were administered at 3-week intervals for 6–8 cycles. In seven cases, biweekly THP-COP therapy for 6 cycles was administered as part of a clinical study [24]. One patient who was initially diagnosed as having DLBCL received R-CHOP (rituximab-CHOP). A biopsy specimen obtained on relapse revealed PTCL-NOS, and the initial diagnostic specimen was also re-diagnosed as PTCL-NOS. Therefore, we included this case in the study. Additional radiation therapy was not performed as part of the first-line treatment except in two cases of localized PTCL. In these cases, patients received 3 cycles of THP-COP, followed by involved field radiation (IFRT). IFRT is frequently used for the treatment of localized aggressive lymphomas [25]. Stem cell transplantation was also not included in the first-line treatment.

Table 2 First-line treatment and outcome

First-line treatment	
CHOP	5
THP-COP	21
THP-COP + IFRT	2
Biweekly THP-COP[a]	7
R-CHOP[b]	1
Results of post-PET	
Positive	11
Negative	25
Evaluation of first-line treatment[c]	
CR	25
PR	9
SD	0
PD	2
CT-based evaluation of first-line treatment[d]	
CR	27
CRu	4
PR	4
NR	0
PD	1

IFRT involved field radiation therapy, *PET* positron emission tomography

[a] Phase 2 clinical study

[b] One case initially diagnosed as diffuse large B cell lymphoma and re-biopsy at relapse revealed that specimen at presentation (and at relapse) was re-diagnosed as PTCL-nos

[c] According to the standardized criteria of the international Harmonization Project

[d] According to Cheson Criteria

Post-PET results were considered positive when a mass lesion with FDG accumulation, presumably due to residual lymphoma, was identified. Of the 36 patients, 11 patients had positive post-PET results, and 25 patients had negative post-PET results. According to the standard criteria of International Harmonization Project, CR, PR, and PD were noted in 25, 9, and 2 patients, respectively [7]. For comparison, we also evaluated response according to the CT-based Cheson criteria [26]. Among the 36 patients, four patients were judged as having PR according to the Cheson criteria, and all of these patients were judged as having PR according to the International Harmonization Project criteria (CT and PET). According to the Cheson criteria, 31 patients were judged as having CR or CR uncertain, and of these, six patients were not judged as having CR according to the International Harmonization Project criteria (five had a PR and one had PD).

In two cases, second malignancies were detected by chance on post-PET. In one patient with PTCL-NOS, a residual mass with FDG accumulation was detected in the uterus. FDG

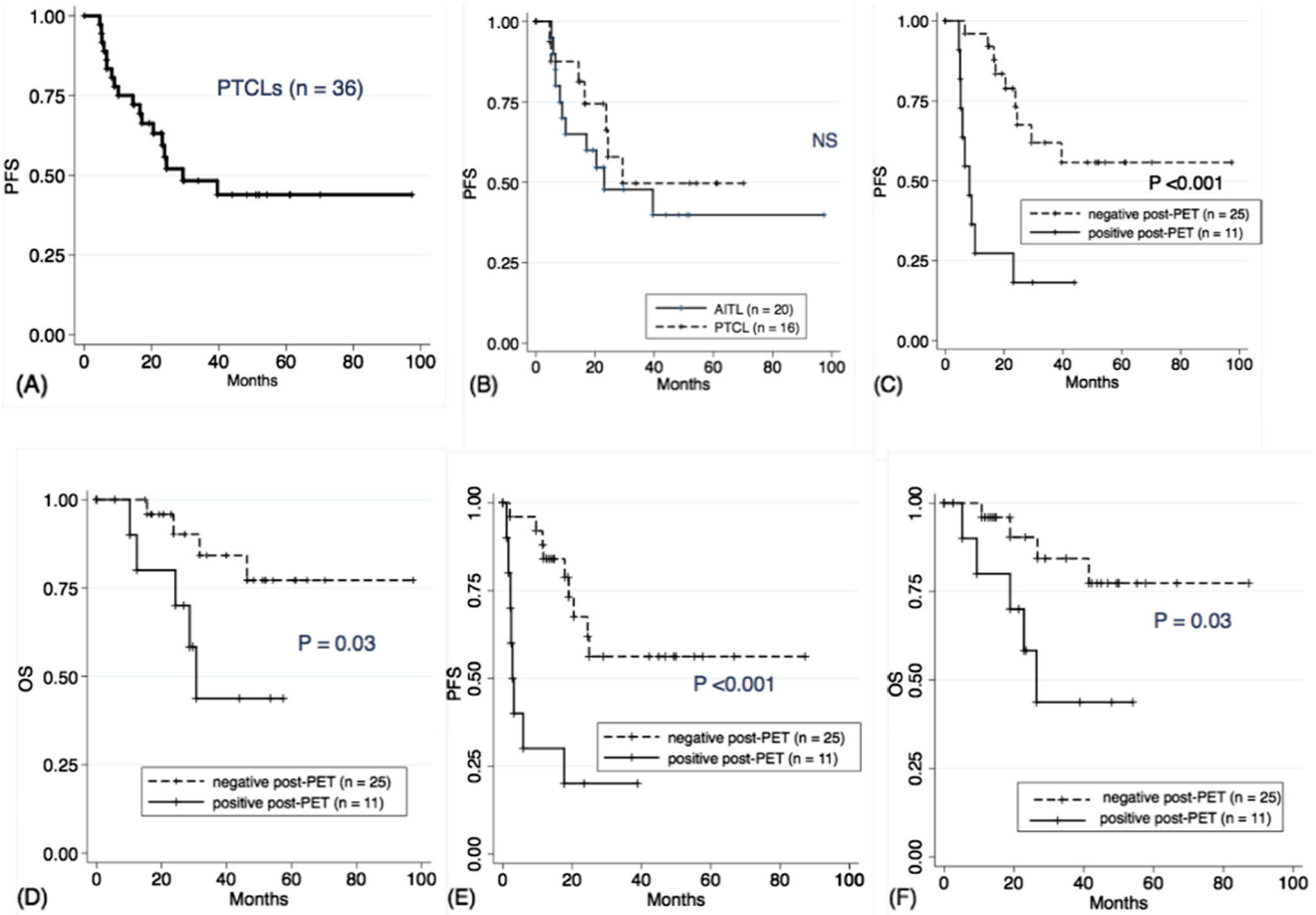

Fig. 1 **a** Progression-free survival (PFS) in 36 patients with peripheral T cell lymphoma. **b** PFS according to histological diagnosis. PFS was not significantly different between PTCL, not otherwise specified (n=16) and angioimmunoblastic T cell lymphoma (n=20) patients. **c** PFS from the initiation of therapy according to the post-therapy ^{18}F-fluorodeoxyglucose-positron emission tomography (post-PET) result. The negative post-PET result group showed significantly superior PFS compared with the positive post-PET result group (P<0.001). **d** Overall survival (OS) from the initiation of therapy according to the post-PET result. The negative post-PET result group showed superior OS compared with the positive post-PET result group (P=0.03). **e** PFS from response assessment according to the post-PET result. The negative post-PET result group showed superior PFS compared with the positive post-PET result group (P<0.001). **f** OS from response assessment according to the post-PET result. The negative post-PET result group showed superior OS compared with the positive post-PET result group (P=0.03)

accumulation in all other cases had disappeared on the post-PET. Diagnostic imaging showed the residual mass to be suspicious for uterine cancer. The patient was subsequently diagnosed as having carcinoma of the corpus uteri at surgery. In another PTCL-NOS case, a mediastinal mass was detected on post-PET and revealed Epstein-Barr virus-positive DLBCL, which was distinct from the initial diagnostic specimen. These patients were included in the negative post-PET result group. In the 25 patients who reached CR after completion of first-line treatment, additional consolidation or maintenance therapy was not initiated until relapse. Of the 11 patients who did not reach CR (nine with PR and two with PD), four patients received immediate salvage therapy, and six patients did not receive salvage therapy until disease progression. The clinical course of the remaining patient is unknown because of transfer. The decision of immediate salvage therapy

Table 3 Predictive value for survival

	PD	PV for PES (%)	Death	PV for OS (%)
Positive post-PET (n=11)	9	82	5	45
Negative post-PET (n=25)	9	64	4	84

PD progression of disease, *PV* predictive value,; *PFS* progression-free survival, *OS* overall survival, *PET* positron emission tomography

was made by the attending physician and not according to response criteria. Of these 11 patients, only 1 patient underwent re-biopsy and was diagnosed as having relapsed AITL.

During the observation period, nine patients died of lymphoma. The median observation period for surviving patients was 44 months. The 3-year PFS rate was 48 % (Fig. 1a), and the 3-year OS rate was 72 % (data not shown). PFS was not significantly differently different between PTCL-NOS and AITL patients (Fig. 1b). The 3-year PFS rate was significantly lower in the positive post-PET result group (n=11) than in the negative post-PET result group (n=25) (18 vs. 62 %; P<0.001; Fig. 1c). Similarly, OS was also inferior in the positive post-PET result group compared with the negative post-PET result group (P=0.03; Fig. 1d). PFS and OS times calculated from the time of response assessment were also significantly inferior in the positive post-PET result group compared with the negative post-PET result group (P<0.001 and P=0.03, respectively; Fig. 1e and Fig. 1f). Nine of the 11 patients in the positive post-PET result group experienced PD (positive predictive value, 82 %), whereas 16 of the 25 patients in the negative post-PET result group did not experience PD (negative predictive value, 64 %; Table 3). In addition, the positive and negative predictive values of post-PET for OS were 42 and 84 %, respectively.

Discussion

CHOP is still the standard treatment for PTCL despite poor patient outcomes [6]. In our study, THP-ADR was administered as the first-line treatment in 30 patients (83 %), and 7 patients received biweekly THP-COP therapy as part of a clinical study [24]. THP-ADR, a 4′-*O*-substitution product of ADR [27] is one of the most common anthracycline agents used for lymphoma treatment [28]. The antitumor efficacy of single-agent THP-ADR is thought to be equal to, if not, better than that of ADR. In a cohort of elderly T cell lymphoma patients, THP-COP therapy administered at 3-week intervals showed a superior CR rate compared with standard CHOP therapy (51.4 vs. 19.4 %). However, THP-COP therapy was not superior to CHOP therapy in terms of survival [29]. Although most patients received THP-ADR, we consider our findings to be applicable to patients treated with CHOP.

Recent studies have evaluated the utility of post-PET evaluation in T/NK cell lymphomas. In a study by the Groupe Ouest Est d'Etude des Leucemies et Autres Maladies du Sang (GOELAMS), Cahu et al. [30] reported that negative post-PET results were not associated with improved PFS in a series of 54 T/NK cell lymphoma patients, including 15 PTCL-NOS and 11 AITL cases. In this study, first-line treatments included irradiation, chemotherapy, and autologous or allogeneic stem cell transplantation. Li et al. [31] evaluated interim PET and post-PET results in 88 T/NK cell lymphoma patients (including 23 PTCL-NOS and 3 AITL cases) treated with various chemotherapy regimens such as CHOP and anthracycline-free regimens. They found that both interim PET and post-PET results were independent predictors of PFS and OS in T/NK cell lymphoma patients. However, only 13 patients with PTCL (all PTCL-NOS cases) underwent post-PET evaluation in this study [31]. Differences in treatment regimens and histological type may have contributed to the conflicting findings of these studies. In our study, patients were relatively uniformly treated with anthracycline-containing chemotherapeutic regimens. Furthermore, post-PET evaluation was limited to patients with a histological diagnosis of PTCL-NOS and AITL, the most common and aggressive types of T cell non-Hodgkin's lymphomas. We found that PFS and OS from post-PET assessment were superior in patients with negative post-PET results compared with patients with positive post-PET results. Based on this observation, post-PET might be useful to assess the need for immediate salvage therapy in PTCL patients. We believe that our study reflects a more common clinical picture than the studies of Cahu et al. [30] and Li et al. [31]. However, our study and the studies of Cahu et al. [30] and Li et al. [31] are all retrospective analyses. Further prospective randomized studies are needed to confirm the predictive role of post-PET for the outcome of PTCL.

In conclusion, PTCLs, both PTCL-NOS and AITL, are FDG-avid malignancies for which post-PET results are predictive of outcome. We recommend that all patients with PTCL undergo FDG-PET evaluation after completion of first-line treatment.

Conflict of interest The authors declare no competing financial interests.

References

1. Rüdiger T, Weisenburger DD, Anderson JR et al (2002) Peripheral T-cell lymphoma (excluding anaplastic large-cell lymphoma): results from the Non-Hodgkin's Lymphoma Classification Project. Ann Oncol 13:140–9
2. Vose J, Armitage J, Weisenburger D et al (2008) International T-cell lymphoma project. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol 26:4124–30
3. [No authors listed] [2000] The World Health Organization classification of malignant lymphomas in Japan: incidence of recently recognized entities. Lymphoma Study Group of Japanese Pathologists. Pathol Int 50:696–702
4. Weisenburger DD, Savage KJ, Harris NL et al (2011) Peripheral T-cell lymphoma, not otherwise specified: a report of 340 cases from the International Peripheral T-cell Lymphoma Project. Blood 117:3402–8
5. Tomita N, Motomura S, Hyo R et al (2007) Comparison of peripheral T-cell lymphomas and diffuse large B-cell lymphoma. Cancer 109:1146–51

6. Schmitz N, Trümper L, Ziepert M et al (2010) Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood 116:3418–25
7. Juweid ME, Stroobants S, Hoekstra OS et al (2007) Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. J Clin Oncol 25:571–8
8. Cheson BD, Pfistner B, Juweid ME et al (2007) Revised response criteria for malignant lymphoma. J Clin Oncol 25:579–86
9. Haioun C, Itti E, Rahmouni A et al (2005) 18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in aggressive lymphoma: an early prognostic tool for predicting patient outcome. Blood 106:1376–81
10. Hutchings M, Loft A, Hansen M et al (2006) FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. Blood 107:52–9
11. Gallamini A, Hutchings M, Rigacci L et al (2007) Early interim 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study. J Clin Oncol 25:3746–52
12. Lin C, Itti E, Haioun C et al (2007) Early 18F-FDG PET for prediction of prognosis in patients with diffuse large B-cell lymphoma: SUV-based assessment versus visual analysis. J Nucl Med 48: 1626–32
13. Itti E, Lin C, Dupuis J et al (2009) Prognostic value of interim 18F-FDG PET in patients with diffuse large B-Cell lymphoma: SUV-based assessment at 4 cycles of chemotherapy. J Nucl Med 50:527–33
14. Hadithi M, Mallant M, Oudejans J et al (2006) 18F-FDG PET versus CT for the detection of enteropathy-associated T-cell lymphoma in refractory celiac disease. J Nucl Med 47:1622–7
15. Bishu S, Quigley JM, Schmitz J et al (2007) F-18-fluoro-deoxy-glucose positron emission tomography in the assessment of peripheral T-cell lymphomas. Leuk Lymphoma 48: 1531–8
16. Kako S, Izutsu K, Ota Y et al (2007) FDG-PET in T-cell and NK-cell neoplasms. Ann Oncol 18:1685–90
17. Karantanis D, Subramaniam RM, Peller PJ et al (2008) The value of [(18)F]fluorodeoxyglucose positron emission tomography/computed tomography in extranodal natural killer/T-cell lymphoma. Clin Lymphoma Myeloma 8:94–9
18. Khong PL, Pang CB, Liang R et al (2008) Fluorine-18 fluorodeoxyglucose positron emission tomography in mature T-cell and natural killer cell malignancies. Ann Hematol 87:613–21
19. Suh C, Kang YK, Roh JL et al (2008) Prognostic value of tumor 18 F-FDG uptake in patients with untreated extranodal natural killer/T-cell lymphomas of the head and neck. J Nucl Med 49:1783–9
20. Wu HB, Wang QS, Wang MF et al (2010) Utility of 18F-FDG PET/CT for staging NK/T-cell lymphomas. Nucl Med Commun 31:195–200
21. Zinzani PL (2011) PET in T-cell lymphoma. Curr Hematol Malig Rep 6:241–4
22. [No authors listed] [1993] A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med 329:987–94
23. Gallamini A, Stelitano C, Calvi R et al (2004) Peripheral T-cell lymphoma unspecified (PTCL-U): a new prognostic model from a retrospective multicentric clinical study. Blood 103:2474–9
24. Tomita N, Kodama F, Tsuyama N et al (2014) Biweekly THP-COP therapy for newly diagnosed peripheral T-cell lymphoma. Hematol Oncol (in press)
25. Miller TP, Dahlberg S, Cassady JR et al (1998) Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Engl J Med 339:21–6
26. Cheson BD, Horning SJ, Coiffier B et al (1999) Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas NCI sponsored international working group. J Clin Oncol 17:1244–53
27. Tsuruo T, Iida H, Tsukagoshi S, Sakurai Y (1982) 4′ -O-tetrahydropyranyladriamycin as a potential new antitumor agent. Cancer Res 42:1462–7
28. Savage KJ (2011) Therapies for peripheral T-cell lymphomas. Hematology Am Soc Hematol Educ Program 2011:515–24
29. Mori M, Kitamura K, Masuda M et al (2005) Long-term results of a multicenter randomized, comparative trial of modified CHOP versus THP-COP versus THP-COPE regimens in elderly patients with non-Hodgkin's lymphoma. Int J Hematol 81:246–54
30. Cahu X, Bodet-Milin C, Brissot E et al (2011) 18F-fluorodeoxyglucose-positron emission tomography before, during and after treatment in mature T/NK lymphomas: a study from the GOELAMS group. Ann Oncol 22:705–11
31. Li YJ, Li ZM, Xia XY et al (2013) Prognostic value of interim and posttherapy 18F-FDG PET/CT in patients with mature T-cell and natural killer cell lymphomas. J Nucl Med 54:507–15