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Lymphoma

Prognostic Value of Interim Positron Emission Tomography in Patients With Peripheral T-Cell Lymphoma

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Peripheral T-cell lymphoma • Positron emission tomography • Complete response • Progression-free survival • Computed tomography scan

Abstract

The definition of the role of positron emission tomography (PET) in peripheral T-cell lymphomas (PTCLs) is still under investigation. The purpose of the present observational retrospective study was to assess the early prognostic value of PET after the first three cycles of therapy (PET+3), evaluating visual data in de novo PTCL patients treated in first line with standard chemotherapy and followed by both PET and computed tomography scan. Of 27 PET+3-negative patients, 19 also had a negative PET at the end of treatment (PET+6), whereas 8 of 27 had a positive final one; 6 of 7 PET+3-positive patients had a positive PET+6, whereas only 1 patient had a negative PET+6. Estimated overall survival plotted according to PET+3 results showed 78.6% for negative patients and 21.4% for positive patients at 88.7 months with a significant difference. Patients with negative PET+3 had superior progression-free survival of 72.6% compared with 16.7% of PET+3-positive patients. At the time of this analysis, 17 of 19 (89.5%) patients with negative PET+3 are in continuous complete response (CCR) and only 1 of 7 (14.2%) patients with positive PET+3 is still in CCR. In conclusion, our results indicate that positive PET+3 is predictive of a worse outcome in PTCL, and this significant statistical difference between the two curves could be clinically informative. Larger and prospective studies and harmonization of PET reading criteria are needed. ***The Oncologist*** 2014;19:746–750

Implications for Practice: Interim computed tomography is the most frequent tool for interim assessment in T-cell lymphomas, but positron emission tomography (PET) could be a valid imaging support. Our study indicates that interim PET results are independent predictors of progression-free and overall survival. In addition, our data seem to show the important implication of interim PET in earlier identification of the potential candidates for an intensive therapeutic strategy with the aim of improving their clinical outcome.

Introduction

The different lymphoma histologies present different ^{18}F-fluorodeoxyglucose (FDG) avidity: for example, several subtypes—Hodgkin's lymphoma, diffuse large B-cell lymphoma, and mantle cell lymphoma—are routinely FDG-avid [1–3].

Several studies have confirmed interim positron emission tomography (PET) as an early prognostic factor [4–7]. Observations for non-Hodgkin's lymphomas are mainly based on B-cell lymphomas, whereas only a few studies with a relatively small number of patients have investigated the role of PET in T-cell and natural killer (NK)-cell lymphomas.

PET data in peripheral T-cell lymphoma (PTCL) are limited and suggest that FDG avidity is less predictable in PTCL than in other lymphomas [8–12]. The role of PET in T-cell lymphomas is still under investigation. Recently, in fact, Feeney et al. reported variations in PET positivity and maximum standardized uptake value across the different T-cell lymphoma subtypes [13]. PET positivity ranged from 50% in cutaneous anaplastic large-cell lymphoma (ALCL) to 78% in angioimmunoblastic T-cell lymphoma (AITL) to 100% in adult T-cell leukemia/lymphoma.

Twenty-nine percent of patients had sites of disease that were not picked up on diagnostic total body computed tomography (CT) scan. The sites that were not detected by CT scan included cutaneous, subcutaneous, and muscular masses of the scalp and upper and lower extremities, and lymphadenopathies in the epitrochlear and popliteal regions, indicating a probable role of PET imaging from vertex to feet for patients with T-cell lymphoma [14, 15]. The use of PET scan is therefore very useful in pointing out disease involvement in anatomical sites not detected by CT scan. Recently, Casulo et al. reported retrospective data showing PET as an early indicator of

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Table 1. Patient characteristics

Characteristic	Statistic
n	34
Median (range) age at diagnosis (yr)	46 (21–81)
Sex, *n* (%)	
Female	15 (44.1)
Male	19 (55.9)
Ann Arbor stage, *n* (%)	
III	9 (26.5)
IV	25 (73.5)
Histology, *n* (%)	
Peripheral T-cell lymphoma not otherwise specified	11 (32.4)
Angioimmunoblastic T-cell lymphoma	6 (17.6)
ALCL ALK+	9 (26.5)
ALCL ALK−	6 (17.6)
Natural killer/T-cell lymphoma	2 (5.9)
IPI, *n*	
I/II	26
III/IV	8
PIT, *n*	
0/I	21
II/III	13
Bulky disease, *n* (%)	
Yes	4 (11.8)
No	30 (88.2)
Bone marrow involvement, *n* (%)	
Yes	8 (23.5)
No	26 (76.5)
Extranodal involvement, *n* (%)	
Yes	15 (44.1)
No	19 (55.9)

Abbreviations: ALCL ALK, anaplastic large-cell lymphoma anaplastic lymphoma kinase; IPI, international prognostic index; PIT, prognostic index for T-cell lymphoma.

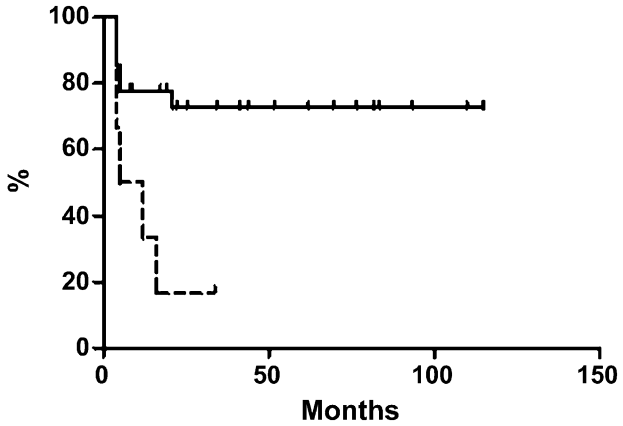

Figure 1. Progression-free survival of peripheral T-cell lymphoma patients with positive positron emission tomography after three cycles of treatment (dashed line) versus those with negative positron emission tomography (solid line) ($p = .02$).

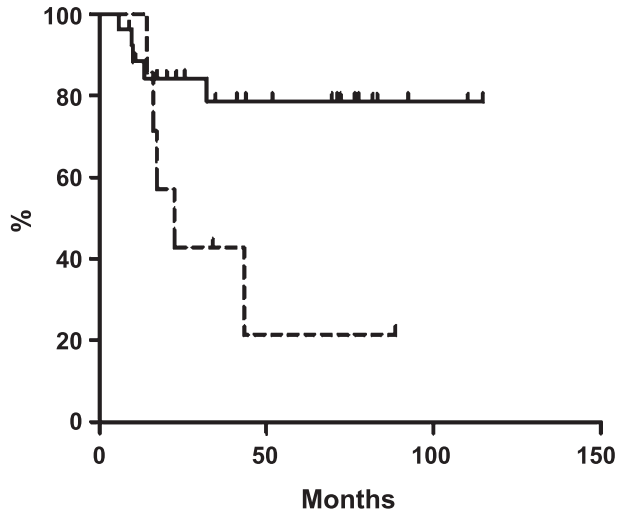

Figure 2. Overall survival of peripheral T-cell lymphoma patients with positive positron emission tomography after three cycles of treatment (dashed line) versus those with negative positron emission tomography (solid line) ($p = .02$).

chemosensitivity in both previously untreated and relapsed PTCL patients [16].

The purpose of the present study was to evaluate the prognostic utility of an interim PET scan following three cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy in patients with previously untreated PTCL.

Patients and Methods

Eligibility

An observational retrospective study was conducted. After obtaining approval from our institutional review board, a computer-based search into our electronic registry was performed to identify patients receiving initial therapy for PTCL. Cases were consecutively considered to avoid selection bias. Written informed consent was obtained from the identified alive patients to collect retrospectively their data. Furthermore, the Italian law, through the Ethical Committee, allows collecting data of dead people or of patients who are lost at follow-up to prevent bias in researches. The main inclusion criteria were diagnosis of PTCL according to the World Health Organization (WHO) classification, standard chemotherapy in first line, and availability of PET and CT scans at baseline, ad interim, and at final restaging (end of treatment).

From September 2003 to July 2010, 34 advanced-stage patients were diagnosed and then treated at our institute. All diagnostic biopsies were reviewed by an expert pathologist (SP) to ensure that diagnoses of PTCL were in accordance with the WHO classification.

Complete tumor staging was performed at baseline by PET scan (eyes to midthigh). CT scan of the neck, thorax, abdomen, and pelvis, both with and without administration of contrast agent (i.v.), and bone marrow biopsy were also performed. Disease stage was established according to the Ann Arbor staging system [17]. Bulky disease was defined as the presence of a mediastinal mass more than one third of transthoracic diameter or an extranodal mass with the major diameter equal to or greater than 7 cm, as documented on the CT scan. At

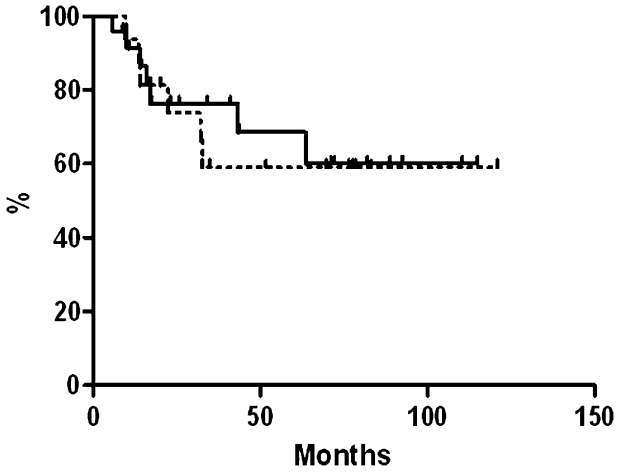

Figure 3. Overall survival of peripheral T-cell lymphoma patients who underwent autologous stem cell transplantation (dashed line) and those who did not (solid line) ($p = .17$).

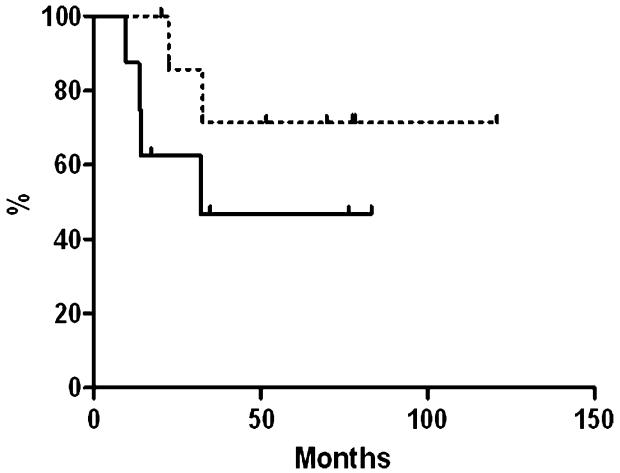

Figure 4. Overall survival of peripheral T-cell lymphoma patients who performed autologous stem cell transplantation as second-line treatment (solid line) and patients who performed it for response consolidation (dashed line) ($p = .08$).

each visit, patients' performance status and vital parameters were recorded, and physical examination, along with complete blood sampling, was performed.

Treatment

As per institutional guidelines, induction chemotherapy for PTCL consisted of 6 cycles of CHOP chemotherapy regimen every 21 days. Interim PET (PET+3) evaluation was performed after completion of the third cycle of therapy, immediately before the fourth cycle. At the end of treatment, all patients were completely restaged: both PET (PET+6) and CT scans were performed at least 1 month (±1 week) after the end of therapy.

Efficacy and Safety Assessments

Relapse was determined after a complete response (CR) when new disease was identified; in patients with partial response (PR) or stable disease (SD), relapse or progression was defined as an increase of at least 50% in the products of the diameter of any previously identified individual abnormality or with the appearance of any new lesion. Disease recurrences were always confirmed by biopsy. PET data were reviewed by the same expert reader assessing visual data according to the criteria of the International Harmonization Project [18]. Long-term outcome and further prospective therapies (including stem cell transplantation) were also considered. Safety and tolerability were assessed by recording the incidence, severity, and type of any adverse events, which were graded according to the WHO criteria for toxicity (National Cancer Institute Common Terminology Criteria of Adverse Events v4.0). Responses were classified according to the International Workshop for Response Criteria for non-Hodgkin's lymphomas [19].

Statistical Analysis

Demographics and patients' characteristics were summarized by descriptive statistics. Progression-free survival (PFS) was measured from the date of start of treatment to the date of either lymphoma progression or death as a result of any cause. Overall survival (OS) was measured from the date of diagnosis to the date of death from any cause. Survival functions were estimated by using the Kaplan-Meier method and were compared using log-rank tests. Statistical analyses were performed with Stata 11 (StataCorp, College Station, TX, http://www.stata.com) and p values were set at .05.

Results

Patient Characteristics

The demographic details of the patients are summarized in Table 1. Of the 34 patients, 9 (26.5%) presented with stage III and the remaining 25 (73.5%) had stage IV. Fifteen were males and 19 were females; the median age at diagnosis was 46 years (range, 21–81 years). B-symptoms were present in 14 (41%) patients, and bulky disease was documented in 4 (12%) patients; 8 (23.5%) patients showed bone marrow involvement at baseline and 15 (44%) patients had one extranodal site. According to the histology, there were 11 PTCL-not otherwise specified, 15 ALCL (9 anaplastic lymphoma kinase [ALK] positive and 6 ALK negative), 6 AITL, and 2 NK/T-cell lymphoma.

Sixteen patients underwent autologous stem cell transplantation (ASCT): in particular, 8 patients as consolidation of response (partial or complete response after the induction phase with CHOP regimen) and 8 as second-line treatment.

Response

Twenty-seven patients (79.5%) had a negative and 7 (20.5%) had a positive PET+3. Twenty patients (59%) had a negative and 14 (41%) had a positive PET+6. Only 1 of 7 PET+3-positive patient converted to negative at PET+6, whereas only 8 of 27 (29.6%) PET+3-negative cases had a positive PET+6. No common characteristics in patients who never achieved a PET CR were observed. After three cycles, the 7 PET-positive patients obtained the following responses: 6 partial responses and 1 progression of disease. At the end of therapy, 20 patients (59%) achieved CR, 3 (9%) PR, and 11 (32%) were non-responders because of progression of disease (PD) or disease recurrence. The concordance between clinical CR and PET+6 negativity was 100%. PET did not downgrade CT responses.

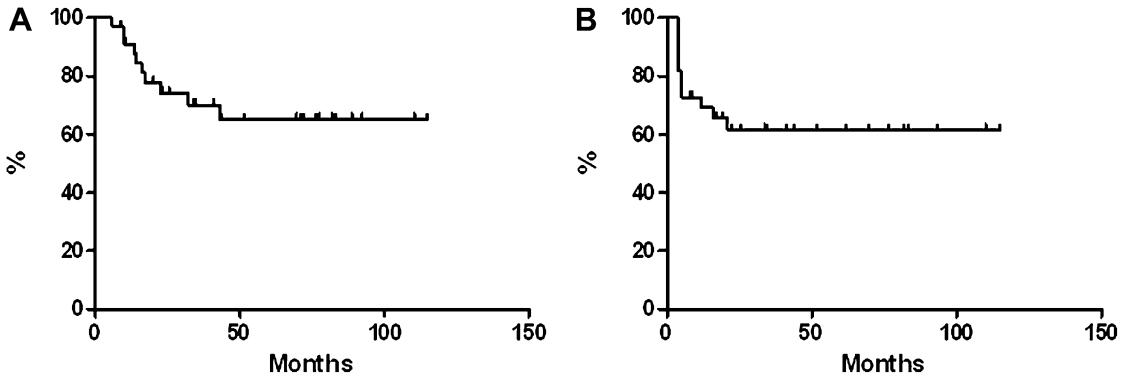

Figure 5. Overall **(A)** and progression-free **(B)** survival of whole study population.

Table 2. Recent reports on interim PET role in peripheral T-cell lymphoma

Report	Patients (*n*)	Overall survival: interim PET− vs. interim PET+	Progression-free survival: interim PET− vs. interim PET+
Cahu et al. [22]	54	76% vs. 47% ($p = .16$ at 4 years)	69% vs. 49% ($p = .10$ at 4 years)
Casulo et al. [16]	50	65% vs. 48% ($p = .17$ at 3 years)	63% vs. 25% ($p = .03$ at 3 years)
Li et al. [21]	88	80% vs. 47% ($p = .02$ at 2 years)	72% vs. 21% ($p < .001$ at 2 years)
This study	34	79% vs. 21% ($p = .02$ at 3 years)	73% vs. 17% ($p = .02$ at 3 years)

Abbreviation: PET, positron emission tomography.

At a median follow-up of 36 months, patients with negative PET+3 had superior PFS of 73% as compared with 17% of PET+ 3-positive patients ($p = .02$) (Fig. 1). Figure 2 shows OS plotted according to PET+3 results: 79% for negative patients and 21% for positive patients at 89 months ($p = .02$).

In Figure 3, the OS curves are plotted for two different groups: 60% for those patients who did not undergo ASCT and 59% for patients who underwent ASCT, at 115 months (*p* value is not statistically significant). Figure 4 summarizes the OS curves for the 16 patients who underwent ASCT: 47% for patients who performed ASCT in second-line treatment and 71% in patients for whose ASCT was consolidation treatment. The difference between the two curves is not statistically significant. There was a PFS difference for patients who had a positive versus negative PET after therapy going into transplant (100% for negative patients vs. 14.3% for positive patients, $p = .0047$).

With a median follow-up of 4 years, OS for the whole study population was 65% (13 deaths; Fig. 5A) and PFS was 61% at 115 months (Fig. 5B). At the time of present analysis, 17 of 19 (89.5%) patients with negative PET+3 are in continuous CR (CCR) and only 1 of 7 (14%) patients with positive PET+3 is still in CCR. The outcomes for patients who were PET negative but became positive were as follows: 6 patients underwent ASCT (at the latest follow-up 3 were dead, 1 alive in PD, and 2 in CR after further therapies); the other 2 patients died because of PD after subsequent therapies.

Discussion

PET has become an important component of the management of patients with B-cell non-Hodgkin's and Hodgkin's lymphoma. However, the role of PET in PTCL is still under investigation. There is no recommendation for the routine use of PET in PTCL as studies focusing on the prognostic value of interim or post-therapy PET are indeed rare and the results are contradictory [14, 20, 21]. Because most PTCLs are not curable, PET should be used for restaging only if CR is a major study endpoint.

Recently, Cahu et al. analyzed the role of interim PET in 54 patients with NK/T-cell lymphomas and concluded that there is no significant difference in terms of OS and PFS between patients with negative versus positive interim PET [22]. On the contrary, Casulo et al. reported on 94 PTCL patients (the interim restaging cohort included only 50 patients); patients with negative interim PET had superior PFS compared with patients with positive interim PET [16]; regarding OS, there were no differences.

In the present study, the prognostic value of interim PET was assessed in a series of 34 patients with PTCL. Our data indicate that persistent FDG uptake after three cycles of therapy can be predictive of PFS and OS: only 14% of patients with a positive interim PET scan achieved CCR, whereas almost all patients (89.5%) with a negative scan are in CCR. The strong prognostic impact of a negative interim PET scan is also confirmed by a 3-year PFS rate of 73% and a 3-year OS rate of 79%. As no common characteristics in patients who never achieved a PET CR were found, it could indicate that interim PET has an independent prognostic value. Table 2 summarizes four recent reports indicating the discordant situation regarding the role of interim PET in PTCL, but three of the studies are similar for the significant association between interim PET findings and PFS data.

Like previous retrospective studies, our study has some limitations, including the relatively small size of our cohort and the inclusion of ASCT in the initial therapy program of some patients as probable confounding bias [16, 21, 22]. Noteworthy, in comparison with the others in whom there was an important variation in front-line chemotherapy regimen, we

reported on a more homogenous cohort as induction therapy was the same for all the study population. In addition, all our patients underwent interim PET after 3 cycles; in the other reports, there were evident variations in the interval between end of treatment (range, 1–10 cycles) and interim PET. Furthermore, previous studies reported a limited number of patients with baseline PET [16, 21, 22].

Conclusion

Despite these limitations, our study indicates that interim PET results are independent predictors of PFS and OS in PTCL patients. In addition, our data seem to show the important implication of interim PET in the earlier identification of potential candidates for an intensive therapeutic strategy with the aim of improving their clinical outcome. Larger and perspective studies with uniform front-line chemotherapy regimen and interim PET timing are needed to better evaluate the prognostic role of interim PET in PTCL patients.

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Author Contributions

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Disclosures

Stefano Pileri: Takeda/Millennium (C/A). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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