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RESEARCH ARTICLE

Prognostic value of ^{18}F-FDG PET/CT in T-Lymphoblastic lymphoma before and after hematopoietic stem cell transplantation

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Abstract

Purpose We aimed to evaluate the prognostic value of ^{18}F-FDG PET/CT in patients with relapsed or refractory T-Lymphoblastic lymphoma (T-LBL) undergoing hematopoietic stem cell transplantation (HSCT).

Methods PET/CT was performed in 21 consecutive relapsed or refractory T-LBL patients scheduled for HSCT. All PET/CT images were assessed using the Deauville criteria, and patients were divided into negative (Deauville ≤ 3) and positive (Deauville > 3) groups for comparison. The predictive value of sex, age, Ann Arbor stage, presence of B symptoms, lactate dehydrogenase level, presence of extranodal disease, and PET/CT results before and after HSCT were evaluated.

Results Kaplan–Meier analysis showed that only PET/CT after HSCT (post-PET) was correlated with progression-free survival (PFS) ($P = 0.030$). The Cox regression model also showed that the post-PET-positive group had a higher hazard ratio (HR) than the negative group (HR = 3.884 and $P = 0.049$). However, none of the evaluated factors were predictive of overall survival (OS).

Conclusions Pre-PET cannot predict the PFS and OS of patients with T-LBL undergoing HSCT, which means that ^{18}F-FDG PET/CT cannot be used for identifying patients who can benefit from HSCT. Post-PET is not predictive for OS in patients with T-LBL undergoing HSCT. However, post-PET showed strong correlations with PFS, which means that it may be useful for guiding subsequent clinical treatment decisions.

Keywords ^{18}F-FDG · PET/CT · T-lymphoblastic lymphoma · Hematopoietic stem cell transplantation

Introduction

T-Lymphoblastic lymphoma (T-LBL) is a rare type of highly aggressive non-Hodgkin lymphoma (NHL), with an overall incidence of 0.1/100,000 in adolescents and young adults [1]. The diagnosis of T-LBL mainly depends on the histological and immunophenotypic analyses. Due to the similar clinical, morphological, and immunophenotypic features, T-LBL and T-acute lymphoblastic leukemia (T-ALL) were combined together as "T-ALL/T-LBL" in 2008. The main difference between T-LBL and T-ALL is the extent of bone marrow infiltration (< 25% in T-LBL compared to ≥ 25% in T-ALL) [2]. Meanwhile, standard lymphoma-type therapy results in a relatively low complete remission (CR) rate for T-LBL patients [3]. In contrast, T-LBL patients treated with ALL-type regimens have a high CR rate of 90% [3, 4].

The most typical clinical characteristic of T-LBL is a bulky mediastinal mass that does not disappear completely after treatment. Due to the typical persistence of this mass, it is difficult to evaluate the therapeutic effect of treatments in T-LBL patients via anatomical imaging. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) has been routinely used for clinical staging, response evaluation, and prognosis of various types of lymphoma, with high sensitivity and specificity [5–8]. It is widely accepted that ^{18}F-FDG PET/CT has unique advantage in distinguishing active tumors from necrotic or fibrotic masses. Thus, in recent years, the use of ^{18}F-FDG PET/CT has been highly encouraged by experts for response

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evaluation and prognosis in patients with T-LBL. Wang et al. conducted a retrospective study to evaluate the value of ^{18}F-FDG PET/CT in the management of patients with T-ALL/LBL treated with chemotherapy [9]. The results showed that the 2-year progression-free survival (PFS) and 2-year overall survival (OS) rates for the positive interim PET group were 21.1% and 31.6%, respectively, and for the negative group were 56.0% and 63.7%, respectively. These results indicated that interim PET/CT after chemotherapy may predict PFS and OS in T-ALL/LBL patients.

Most patients with T-LBL can achieve CR after chemotherapy. However, there are still poor outcomes for patients who show chemotherapy resistance or relapse, with less than 20% of patients surviving at 5 years from diagnosis [10, 11]. Hematopoietic stem cell transplantation (HSCT) is considered as the optimal option for the patients with relapsed or refractory T-LBL. However, the incidence rate of treatment-related morbidity and mortality is relatively high for HSCT, and a thorough evaluation of candidacy and selection of appropriate patients is crucial.

Previous studies have demonstrated that ^{18}F-FDG PET/CT before and following HSCT were predictive for diffused large B-cell lymphoma (DLBCL), one of the most common types of NHL [12, 13]. However, since the incidence of T-LBL is very low and most patients can be cured by chemotherapy, the prognostic value of ^{18}F-FDG PET/CT in T-LBL patients undergoing HSCT remains unknown. Thus, we conducted this study to evaluate the value of ^{18}F-FDG PET/CT in the management of patients with T-LBL undergoing HSCT.

Materials and methods

Patients

We retrospectively reviewed 21 consecutive patients with T-LBL undergoing ^{18}F-FDG PET/CT before (pre-PET) and/or after (post-PET) HSCT at Shanghai General Hospital between 2012 and 2019. Pre-PET scans were performed no later than 3 months before HSCT. After the pre-PET scan, patients received no more than two cycles of chemotherapy or radiotherapy (< 20 Gy) before HSCT.

PET/CT imaging

All patients fasted overnight and the blood glucose levels were confirmed to be lower than 7.8 mmol/L before PET/CT scan. The patients were intravenously injected with ^{18}F-FDG (4.07–4.44 MBq/kg), and the PET/CT images were acquired 60 min after the injection from the base of the skull to mid-thighs on a Discovery™ STE 16 PET/CT scanner (GE Medical systems, Milwaukee, Wisconsin, USA). Two nuclear medicine experts analyzed all PET/CT images using the Deauville criteria: (1) no uptake above background; (2) uptake ≤ mediastinum; (3) uptake > mediastinum but ≤ liver; (4) uptake > liver; and (5) uptake markedly > liver or area of new disease. Patients were divided into negative (Deauville ≤ 3) and positive (Deauville > 3) groups for comparison.

Statistical analysis

SAS software (version 9.1; SAS Institute, Cary, NC, USA) was used for all statistical analyses. PFS and OS of the patients with T-LBL were estimated by the Kaplan–Meier method and compared using the log-rank test. A Cox regression model was performed to identify the prognostic factors. For all analyses, a p value less than 0.05 was considered statistically significant.

Results

The clinical characteristics of the 21 T-LBL patients are summarized in Table 1. Consistent with previous studies, the majority of patients presented with a mediastinal mass [1, 2]. All patients were treated with hyper-CVAD chemotherapy and then underwent HSCT. The majority (90%, 19/21) of patients received allogeneic stem cell transplantation (allo-HSCT), whereas the remaining two patients received autologous stem cell transplantation (ASCT). Nineteen of the 21 patients underwent both pre-PET and post-PET, whereas the remaining two patients only underwent post-PET. There was no difference in patient characteristics between the pre-PET/post-PET positive and negative groups ($p > 0.05$).

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of ^{18}F-FDG PET/CT

With a median follow-up of 26 months (range, 9–93 months), progression or relapse occurred in seven patients (33%), and the average time was 6 months. Death occurred in four patients, and the average time was 15 months. The median PFS of the patients was 20 months (range, 1–93 months), and the median OS was 25 months (range, 8–93 months).

Pre-PET evaluations

Pre-PET scans were performed 2–10 weeks (median, 4 weeks) before HSCT in 19 of 21 patients, and patients with residual lesions received 1–2 cycles of hyper-CVAD chemotherapy ($n = 6$) or radiotherapy with 6 × 2 Gy ($n = 1$) before HSCT. Based on the Deauville criteria, pre-PET was considered positive in four patients (Deauville score > 3) and negative in 15 patients (Deauville score ≤ 3). One of the four

Table 1 Baseline characteristics of patients

Variables	Patients *n* (%)
Age average (years; range)	25 (14–35)
Gender	
Male	14 (67%)
Female	7 (33%)
Tumor stage at diagnosis (Ann Arbor)	
I	0
II	2 (10.5%)
III	4 (19%)
IV	15 (71%)
B symptoms	16 (76%)
Extranodal disease	7 (33%)
Mediastinal mass	12 (57%)
LDH	
LDH ≤ 245	19 (90%)
LDH > 245	2 (10%)
HSCT	
ASCT	2 (10%)
Allo-HSCT	19 (90%)
Treatment after pre-PET	
Chemotherapy (hyper-CVAD)	6 (32%)
Radiotherapy	1 (5%)
Pre-PET	
Positive	4 (21%)
Negative	15 (79%)
Post-PET	
Positive	4 (19%)
Negative	17 (81%)

LDH lactate dehydrogenase, *HSCT* hematopoietic stem cell transplantation, *ASCT* autologous stem cell transplantation, *Allo-HSCT* allogeneic stem cell transplantation, *pre-PET* PET/CT prior to HSCT, *post-PET* PET/CT after HSCT. There was no difference in patient characteristics between the pre-PET/post-PET positive and negative groups ($P > 0.05$)

pre-PET-positive patients progressed and died after HSCT. In contrast, nine of the 15 pre-PET-negative patients were progression-free at follow-up. As a result, the sensitivity, specificity, PPV, NPV, and accuracy of pre-PET in predicting the survival of T-LBL patients undergoing HSCT were 14.3%, 75.0%, 25.0%, 60.0%, and 52.6%, respectively.

Post-PET evaluations

All 21 patients underwent PET/CT scans 1–6 months (median, 3 months) after HSCT. Based on the Deauville criteria, there were five patients presenting positive post-PET and 16 patients presenting negative post-PET. Four of five post-PET-positive patients progressed or relapsed after HSCT. In contrast, 13 of 16 post-PET-negative patients were progression-free at follow-up. As a result, the sensitivity, specificity, PPV, NPV, and accuracy of post-PET in predicting the survival of T-LBL patients undergoing HSCT were 57.1%, 92.9%, 80.0%, 81.3%, and 81.0%, respectively.

Table 2 Kaplan–Meier analysis of PFS and OS

Variables	PFS (*p* value)	OS (*p* value)
Age	0.668	0.279
Gender	0.149	0.753
Tumor stage at diagnosis (Ann Arbor)	0.563	0.055
B symptoms	0.103	0.183
Extranodal disease	0.940	0.976
Mediastinal mass	0.911	0.397
LDH	0.880	0.411
Pre-PET	0.266	0.572
Post-PET	0.030	0.080

LDH lactate dehydrogenase, *ASCT* autologous stem cell transplantation, *Allo-HSCT* allogeneic stem cell transplantation, *pre-PET* PET/CT before HSCT, *post-PET* PET/CT after HSCT

Kaplan–Meier analysis

Kaplan–Meier analysis was performed to evaluate the prognostic value of clinical characteristics (sex, age at HSCT [< 18 vs. ≥ 18 years], Ann Arbor stage at diagnosis, presence of B symptoms, serum lactate dehydrogenase (LDH) level, presence of extranodal disease, presence of mediastinal mass) and PET/CT (Table 2). Results showed that the clinical characteristics and pre-PET had no statistically significant influence on PFS and OS ($P > 0.05$) (Fig. 1), whereas post-PET showed a strong relationship with PFS ($P < 0.05$) (Fig. 2). However, there was no correlation between post-PET and OS (Fig. 2).

Cox regression

Cox regression analysis was also performed to evaluate the prognostic value of clinical characteristics (sex, age at HSCT [< 18 vs. ≥ 18 years], Ann Arbor stage at diagnosis, presence of B symptoms, serum lactate dehydrogenase (LDH) level, presence of extranodal disease, presence of mediastinal mass) and PET/CT. For PFS, the univariate Cox regression analysis showed that only post-PET positive group had a higher hazard ratio (HR) than the negative group (HR = 3.884 and $P = 0.049$). Consistent with the results of the Kaplan–Meier analysis, post-PET was not prognostic for OS.

Discussion

HSCT has been used as a final consolidation therapy for T-LBL, especially for patients who show chemotherapy resistance or relapse. HSCT has a favorable outcome in

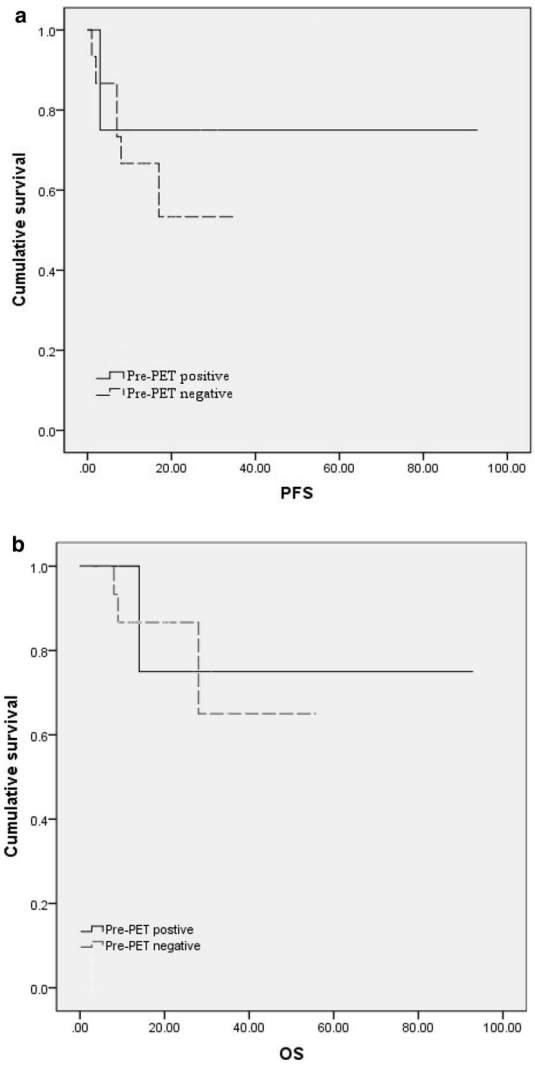

Fig. 1 Kaplan–Meier estimates for PFS (**a**) and OS (**b**) in T-LBL patients by ^{18}F-FDG PET/CT before HSCT (pre-PET). There was no statistical difference between pre-PET negative and positive patients for both PFS ($P=0.266$) and OS ($P=0.572$)

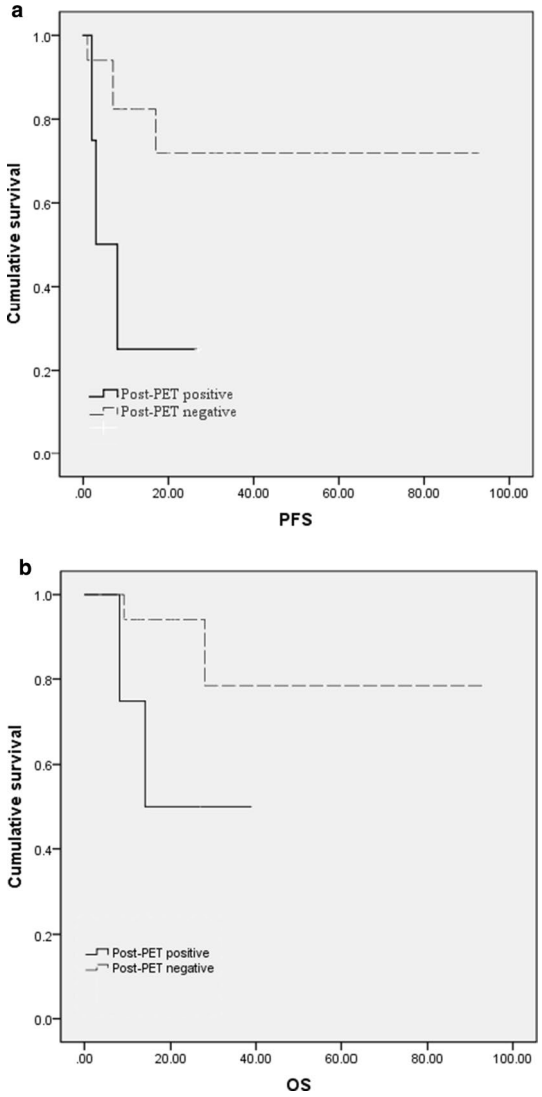

Fig. 2 Kaplan–Meier estimates for PFS (**a**) and OS (**b**) in T-LBL patients by ^{18}F-FDG PET/CT after HSCT (post-PET). KM analysis showed a better PFS for post-PET negative patients than positive patients ($P=0.030$). However, for OS, there was no statistical difference between post-PET negative and positive patients ($P=0.080$)

approximately 67% of T-LBL patients, and the challenge for clinicians is to identify patients who could benefit from HSCT. The prognostic value of clinical characteristics, such as age, sex, stage at diagnosis, serum LDH level, and presence of mediastinal mass, has been evaluated by previous study [11]. The results showed that only the stage at diagnosis, which was divided into limited stage (stage I and II) versus advanced stage (stage III and IV), can be used for risk stratification. However, most T-LBL (> 90%) patients are diagnosed with stage III and IV disease [14]. Thus, the stage at diagnosis is insufficient for identifying T-LBL patients at low risk of mortality. Our study is the first attempt to evaluate the prognostic value of ^{18}F-FDG PET/CT in patients with T-LBL treated with HSCT.

Various studies have confirmed the prognostic value of ^{18}F-FDG PET/CT for patients with Hodgkin lymphoma (HL) and NHL [15, 16]. However, recent studies have reported that for patients with mediastinal HL or NHL, the specificity of ^{18}F-FDG PET/CT is very low [17–19]. Unfortunately, the most typical clinical presentation of T-LBL is a mediastinal mass. A retrospective study found that ^{18}F-FDG PET/CT was not useful for predicting the relapse in T-LBL patients [20]. Lepretre et al. proved that ^{18}F-FDG PET/CT cannot offer enough information regarding event-free survival, disease-free survival, OS, or mediastinal relapse in patients with T-LBL [21]. Our study also demonstrated

that pre-PET was not predictive for the prognosis of T-LBL patients undergoing HSCT.

In recent years, some new cytostatic drugs (such as nelarabine) and T cell targeting immunotherapy have been examined or approved for refractory or relapsed T-LBL patients [3]. A large-scale prospective study found that ^{18}F-FDG PET/CT after the treatment yielded positive results in partial responders (10/22, 45%) of patients with T-LBL and the researchers concluded that PET/CT may be used for guiding salvage therapy decisions [22]. Our study found that post-PET was not prognostic for OS in T-LBL patients undergoing HSCT; however, it showed strong correlations with PFS, meaning that post-PET may also be useful for response evaluation of HSCT and guiding subsequent clinical treatment.

In addition, only two patients had received ASCT in our study. One patient died, and the other patient relapsed. A retrospective study reported that compared to ASCT, allo-HSCT resulted in fewer relapses [11]. Our results may support the findings of this previous study; however, the number of cases in our study was small, and the results need to be further confirmed.

There are several limitations in our study. First, as it was retrospective in nature, our study design could have potential bias that cannot be ignored. Secondly, the number of cases was limited due to the rare nature of the condition itself and the rare instance that chemotherapy was ineffective as a treatment. However, we designed the study to be strictly limited in regard to the treatment and the time point of the PET/CT scan in order for it to be easily compared to similar studies and to ultimately help elucidate the value of ^{18}F-FDG PET/CT in T-LBL patients undergoing HSCT in the future.

Conclusion

T-LBL is a rare and highly aggressive lymphoma with unique characteristics. Our study proved that pre-PET cannot predict the PFS and OS of patients with T-LBL undergoing HSCT, which means that PET/CT cannot be used for identifying patients who can benefit from HSCT. Post-PET is not prognostic for OS of patients with T-LBL undergoing HSCT; however, it showed strong correlations with PFS, which means it may be useful for guiding subsequent clinical treatment decisions.

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Author contributions NS and WQ contributed the research ideas, analyzed most of the data, and wrote the initial draft of the paper. The remaining authors contributed to refining the ideas, carrying out additional analyses and finalizing this paper.

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Availability of data and materials The dataset used during the present study is available from the corresponding author upon a reasonable request.

Compliance with ethical standards

Conflict of interest Authors declare that they have no conflict of interest.

Consent to participate For this type of retrospective study, formal consent is not required.

Consent for publication For this type of retrospective study, formal consent is not required.

Ethics approval This is a retrospective study. The Shanghai General Hospital Research Ethics Committee has confirmed that no ethical approval is required.

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