¹⁸F-FDG PET in Patients with Primary Systemic Anaplastic Large Cell Lymphoma: Differential Features According to Expression of Anaplastic Lymphoma Kinase

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Abstract

Purpose Primary systemic anaplastic large cell lymphoma (ALCL) is divided into two entities according to the expression of anaplastic lymphoma kinase (ALK). We investigated ¹⁸F-fluorodeoxyglucose positron emission tomography (¹⁸F-FDG PET) findings in primary systemic ALCL according to ALK expression.

Methods Thirty-seven patients who had baseline PET before CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone)-based chemotherapy were enrolled. Among them, patients who underwent interim and/or post-therapy PET were further investigated for the treatment response and survival analysis. Baseline PET was analyzed visually and semi-quantitatively using peakSUV, and interim and post-therapy PETs were visually analyzed.

Results All cases were ¹⁸F-FDG-avid on baseline PET. The peakSUV of ALK-positive ALCL ($n=16$, 18.7 ± 10.5) was higher than that of ALK-negative ALCL ($n=21$, 10.0 ± 4.9) ($P=0.006$). In ALK-negative ALCL, complete response (CR)

rate in negative-interim PET was higher than positive-interim PET (100 % vs 37.5 %, $P=0.02$); however, there was no such difference in ALK-positive ALCL (100 % vs 75 %, $P=0.19$). The 3-year progression-free survival (PFS) was not significantly different between ALK-positive and ALK-negative ALCL (72.7 % vs 47.6 %, $P=0.34$). In ALK-negative ALCL, negative interim and post-therapy PET patients had better 3-year PFS than positive interim (83.3 % vs 25.0 %, $P=0.06$) and post-therapy PET patients (70.0 % vs 20.0 %, $P=0.04$). In contrast, ALK-positive ALCL had no such differences between PFS and PET results.

Conclusions On baseline PET, all cases showed ¹⁸F-FDG-avidity, and ALK expression was related to higher ¹⁸F-FDG uptake. ALK-positive patients tend to have better PFS than ALK-negative patients. Negative-interim PET was a good indicator of CR, and interim or post-therapy PET was helpful for predicting the prognosis only in the ALK-negative group.

Keywords Primary systemic anaplastic large cell lymphoma · Anaplastic lymphoma kinase · ¹⁸F-FDG PET

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Introduction

¹⁸F-Fluorodeoxyglucose positron emission tomography (¹⁸F-FDG PET) performed for the staging, assessing treatment response, and predicting the outcome of lymphomas has been the mainstay of clinical practice [1, 2]. Recently, the clinical usefulness of ¹⁸F-FDG PET for T-cell lymphomas, which comprises 10–15 % of non-Hodgkin's lymphomas (NHL) also has been reported [3–6]. However, although these studies showed the promising results of ¹⁸F-FDG PET in T-cell lymphomas, they usually consisted of heterogeneous histology groups, and were limited by the small numbers of patients.

Anaplastic large cell lymphoma (ALCL) is a type of T-cell lymphoma, representing about 2–3 % of NHL. Depending on the expression of a protein called anaplastic lymphoma kinase (ALK), two different entities are recognized as systemic forms, the ALK-positive and ALK-negative ALCL [7].

There are some distinct clinical features such as age distribution and prognosis between two groups, in addition to their morphologic and immunophenotypic features [8]. Other studies also have demonstrated the differential expression of apoptotic proteins and micro-RNAs according to the ALK expression [9, 10]. Although there have been many advances regarding the clinical, pathological and molecular characterization of primary systemic ALCL with differential characteristics according to the ALK expression, little is known regarding the role of ^{18}F -FDG PET in primary systemic ALCL.

We conducted this study to evaluate the ^{18}F -FDG PET findings according to the ALK expression, and to evaluate the treatment response and prognosis according to ^{18}F -FDG PET and the ALK expression in patients with primary systemic ALCL.

Methods

Study Subjects

From the database of lymphoma registry at Asan Medical Center, 37 patients with primary systemic ALCL who underwent baseline ^{18}F -FDG PET before chemotherapy from January 2004 to April 2012 were retrospectively enrolled. The Institutional Review Board of our hospital approved this study and waived the requirement for informed consent. The diagnosis of ALCL was made using the standard diagnostic criteria described by the World Health Organization with immunohistochemistry staining of a biopsy specimen. Immunohistochemical staining of ALK expression was performed using an autostainer (Benchmark XT; Ventana Medical Systems, Tucson, AZ, USA) with mouse monoclonal anti-ALK (1:50 dilution; Leica Biosystems, Newcastle, UK) and a universal secondary antibody kit (Optiview DAB IHC detection kit; Ventana Medical Systems, Tucson, AZ, USA).

All patients also underwent conventional staging work-up, such as physical examination, complete blood counts (CBC), biochemical profile including lactate dehydrogenase (LDH), bone marrow (BM) examination, and concurrent computed tomography (CT) scans of the neck, chest and/or abdomen. Staging was performed according to the Ann Arbor staging systems and the International Prognosis Index (IPI) was also calculated according to the standard criteria.

Thirty-one patients (83.8 %) were treated with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) alone, four patients received CHOP regimen plus Bortezomib (B-CHOP), and one patient received the CHOP

regimen plus Everolimus (Rad-CHOP). Only one patient did not undergo chemotherapy due to follow-up loss.

Twenty-five patients underwent interim PET after 3–4 cycles of chemotherapy. Twelve patients were excluded from the analysis of interim PET, because five patients had only conventional CT for the interim response evaluation, six patients did not receive enough cycles of scheduled chemotherapy, and one patient was lost to follow-up.

Of these 25 patients, post-therapy PET (after 5–8 cycles of chemotherapy) was available in 22 patients, because three patients had only conventional CT for the response evaluation after the termination of therapy.

^{18}F -FDG PET Imaging

Baseline PET was carried out before chemotherapy within a median interval of 6 days (range 1–76). Median interval between completion of mid-cycle chemotherapy and interim PET was 14 (range 10–45), and median interval between completion of last chemotherapy and post-therapy PET was 14 (range 9–72) days, respectively. Before each PET, patients fasted for at least 6 h prior to ^{18}F -FDG injection. All patients' venous blood glucose levels were under 140 mg/dl, and patients were injected with 370–555 MBq (10–15 mCi) of ^{18}F -FDG. Approximately 60 min after the injection, images were acquired from the skull base to the upper thigh with total of 5–6 bed positions using ECAT HR+ (Siemens Medical Solutions, Malvern, PA, USA), Discovery Ste 8 (GE Healthcare, Pittsburgh, PA, USA), Biograph TruePoint 16 (Siemens Medical Solutions, Malvern, PA, USA) or Biograph TruePoint 40 (Siemens Medical Solutions, Malvern, PA, USA) scanners. The consecutive interim and/or post-therapy PET was acquired using the same scanner and protocol as for the baseline PET.

PET Analysis

Baseline PET images were analyzed by two methods. First, two nuclear medicine physicians visually analyzed with consensus. A positive lesion was defined if there was an abnormally increased ^{18}F -FDG uptake in the histologically proven tissue or radiographically suspected lesion compared with background tissue. Then, for the semi-quantitative analysis [11], the peak standardized uptake values (SUVs) based on lean body mass of the most intense ^{18}F -FDG uptake lesion per patient was measured using a software program (TrueD 2010A; Siemens, Knoxville, TN, USA), in which 1-cm³ spherical volume of interest was centered around the hottest point in the tumor focus [12].

Interim and post-therapy PET images were analyzed by a dichotomized method based on visual analysis with consensus of two nuclear medicine physicians blinded to all clinical data about the treatment response. Any residual hypermetabolic lesion was recorded as positive, whereas no residual

hypermetabolic activity compared with background was considered as negative.

Assessment of Treatment Response and Patient Follow-up

After the end of treatment, the response was assessed and categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to the Revised International Workshop Criteria (IWC), which includes ^{18}F -FDG PET (IWC-PET) [13, 14].

All patients had a routine 3– to 6-month follow-up after the completion of the treatment with subject symptoms, physical examination, CBC, biochemical profile, CT and/or PET. A median follow-up period was 27 months (range 7–75).

Statistical Analysis

Student's *t*-test was used to compare the peakSUVs between two groups. A receiver operating characteristic (ROC) curve analysis was used to set up the cut-off value for distinguishing two groups.

Progression-free survival (PFS) was defined as the time from the initiation of initial treatment to progression, relapse or death from any-cause, with censoring at the time of the last follow-up. Overall survival (OS) was calculated from the diagnosis to death as a result of any cause, which was censored at the last follow-up. The Kaplan-Meier method and log-rank tests were used to assess and compare the survival data. It was thought to be of statistical significance when the *P* value was less than 0.05.

Results

Patient Demographic and Clinical Characteristics

Basic characteristics are presented in Table 1. Sixteen patients were ALK-positive and 21 patients were ALK-negative. ALK-positive patients were significantly younger than ALK-negative patients (31.5 ± 11.6 vs 53 ± 13.8 years, $P < 0.001$). No other clinical parameters had a significant correlation according to the ALK expression.

Analysis of Baseline ^{18}F -FDG PET

On visual analysis, all patients showed increased ^{18}F -FDG uptake with heterogeneous involvement of nodal and/or extra-nodal sites. Twenty-eight patients (75.7 %, 12 ALK-positive, 16 ALK-negative) presented with both nodal and extra-nodal involvements, and 3 patients had only extra-nodal lymphoma in the stomach, chest wall and bone, respectively. Compared with CT imaging, PET detected more lesions of lymphoma involvement in various sites such as lymph node, BM, breast, stomach, mesentery, pleura or muscle in 16 cases (43.2 %, 6 ALK-positive, 10 ALK-negative), and among them, 4 cases (2

Table 1 Characteristics of 37 patients with primary systemic ALCL

Clinical parameters		ALK (+) (<i>n</i> =16)	ALK (–) (<i>n</i> =21)	<i>P</i> value
Age		31.5±11.6	53.0±13.8	<0.001
Sex	M/F	13/3	15/6	0.50
Stage	I-II/III-IV	2/14	6/15	0.25
B symptom	Yes/No	11/5	10/11	0.21
ECOG	0–1/2>	14/2	17/4	0.60
IPI score	0–1/2>	4/12	5/16	0.93
LDH level	Normal/ elevated	5/11	5/16	0.62

ALK-positive, 2 ALK-negative) were upstaged by the detection of BM involvement. Ultimately, 8 patients (21.6 %, 1 ALK-positive, 7 ALK-negative) were revealed BM infiltration by iliac aspiration examination, and PET detected BM involvement in half of them.

On semi-quantitative analysis, the mean peakSUV of the hottest lesion in 37 patients was 13.8 ± 8.8 (range 3.1–39.2). The peakSUV of the hottest lesion according to the ALK expression is shown in Fig. 1. The mean peakSUV of ALK-positive was significantly higher than that of ALK-negative (18.7 ± 10.5 vs 10.0 ± 4.9 , $P = 0.006$). We used the ROC curve analysis to set up the cut-off value of peakSUV for distinguishing ALK-positive from ALK-negative. The area under the curve was 0.765. With a cut-off value of 12.7, the sensitivity and the specificity was 68.8 % and 85.7 %, respectively. The representative ^{18}F -FDG PET images of each subgroup are shown in Figs. 2 and 3.

Treatment Response and Outcome

Among 25 patients (11 ALK-positive, 14 ALK-negative), the overall response rate after the completion of first-line

Fig. 1 The distribution of peakSUV of the hottest lesion among patients with primary systemic ALK-positive and ALK-negative ALCL in baseline ^{18}F -FDG PET. The mean value of each group is marked with a horizontal line and the cut-off value (peakSUV 12.7) is presented with a dashed line

Fig. 2 A representative ^{18}F -FDG PET images of the patient with primary systemic ALK-positive ALCL. Maximum intensity projection (a), transaxial PET (b), non-enhanced CT (c), and PET/CT fusion (d) images show increased ^{18}F -FDG uptake in the enlarged retroperitoneal lymph nodes. The peakSUV of the hottest lesion (arrow) is 18.3

Fig. 3 Representative ^{18}F -FDG PET images of the patient with primary systemic ALK-negative ALCL. Maximum intensity projection (a), transaxial PET (b), non-enhanced CT (c), and PET/CT fusion (d) images show increased ^{18}F -FDG uptake in liver right lobe. The peakSUV of the hottest lesion (arrow) is 9.7

chemotherapy was 84.0 % with CR in 76.0 % ($n=19$, ten ALK-positive, nine ALK-negative) and PR in 8.0 % ($n=2$, two ALK-negative). The remaining four patients (one ALK-positive, three ALK-negative) were PD. The CR rates of ALK-positive and ALK-negative patients was 90.9 % and 64.3 %, respectively ($P=0.13$).

Four CR patients and all PR patients had recurrence and disease progression. Overall, ten patients had disease progression or relapse (40.0 %, three ALK-positive, seven ALK-negative). After the progression or relapse, nine patients received second-line chemotherapy and/or followed by the autologous stem cell transplantation. The remaining one patient did not undertake any second-line chemotherapy due to poor performance status (ECOG PS 4). Afterwards, seven consecutive patients (two ALK-positive, five ALK-negative) died due to tumor-related disease until the last follow-up. The overall 3-year PFS rate was 59.4 % and 3-year OS rate was 69.1 %.

In sub-group analysis, a median follow-up period was 37 months in ALK-positive patients, whereas 20.5 months in ALK-negative patients. PFS (3-year PFS rate 72.7 % vs 47.6 %, $P=0.34$) and OS (3-year OS rate 81.8 % vs 57.5 %, $P=0.30$) between ALK-positive and ALK-negative patients were not significantly different (Fig. 4). In addition, any other clinical parameters were not statistically significant in terms of PFS and OS as well.

Analysis of Interim ^{18}F -FDG PET

The patients with negative interim PET ($n=13$, seven ALK-positive, six ALK-negative) showed higher CR rate than those with positive interim PET ($n=12$, four ALK-positive, eight ALK-negative) (100 % vs 50 %, $P=0.004$). In ALK-negative, negative interim PET also showed significantly more CR than positive interim PET (100 % vs 37.5 %, $P=0.02$). However,

in ALK-positive, CR rate was not significantly different between negative interim and positive interim PET (100 % vs 75 %, $P=0.19$).

Among 25 patients, 3-year PFS rate for patients with negative interim PET was 76.9 % compared with 41.7 % for patients with positive interim PET ($P=0.10$). The 3-year OS rate was 83.1 % for those with negative interim PET and 53.5 % for those with positive interim PET ($P=0.12$).

In ALK-positive group, one of four patients with positive interim PET had progression and five of seven patients with negative interim PET had no events (positive predictive value 25 % and negative predictive value 71.4 %). There was no statistical difference in PFS between patients with positive interim PET and those with negative interim PET (3-year PFS rate 75.0 % vs 71.4 %, $P=0.99$) (Fig. 5). Also, OS between two groups was not statistically different (3-year OS rate 75.0 % vs 85.7 %, $P=0.61$).

In ALK-negative group, six of eight patients with positive interim PET had progression and five of six patients with negative interim PET had no events (positive predictive value 75.0 % and negative predictive value 83.3 %). The PFS for the patients with negative interim PET was better than the patients with positive interim PET, but it was not statistically significant (3-year PFS rate 83.3 % vs 25.0 %, $P=0.06$) (Fig. 5). The OS between the patients with negative-interim PET and those with positive interim PET was not also statistically different (3-year OS rate 75.0 % vs 43.7 %, $P=0.22$).

Analysis of Post-Therapy ^{18}F -FDG PET

Among 22 patients, 8 patients (3 ALK-positive, 5 ALK-negative) showed positive PET and 14 patients showed negative PET. There was no statistical significance between two sub-groups in PFS (3-year PFS rate 37.5 % vs 69.8 %, $P=0.12$) and OS (3-year OS rate 57.1 % vs 76.0 %, $P=0.23$).

Fig. 4 Survival curves according to ALK status in primary systemic ALCL. **a** Kaplan-Meier estimates of progression-free survival and **b** Kaplan-Meier estimates of overall survival

Fig. 5 Progression-free survival curves of interim ^{18}F -FDG PET status according to ALK expression. **a** Kaplan-Meier estimates of ALK-positive group and **b** Kaplan-Meier estimates of ALK-negative group

In the ALK-positive group, there was no significant difference in PFS (3-year PFS rate 66.7 % vs 66.7 %, $P=0.87$, Fig. 6) and OS (3-year OS rate 66.7 % vs 83.3 %, $P=0.52$) between the patients with positive and negative PET.

In the ALK-negative group, the patients with negative PET showed significantly better PFS than patients with positive PET (3-year PFS rate 70.0 % vs 20.0 %, $P=0.04$, Fig. 6). However, OS was not significantly different between two groups (3-year OS rate 66.7 % vs 50.0 %, $P=0.36$).

Discussion

We observed different ^{18}F -FDG PET features in patients with primary systemic ALCL according to ALK expression. First, the degree of ^{18}F -FDG uptake was higher in ALK-positive ALCL than in ALK-negative ALCL, as seen on baseline PET, and thus suggesting that semi-quantitative measurement using ^{18}F -FDG PET could distinguish between the two groups.

Second, negative-interim PET was a good indicator of CR and negative-interim or post-therapy PET reflected better PFS, although only in ALK-negative ALCL, and not in ALK-positive ALCL. Together these findings support the view that primary systemic ALK-positive and ALK-negative ALCL are different disease entities [7–10].

ALK-positive patients were significantly younger than ALK-negative patients, being consistent with the established correlation between ALK expression and young age [7–10].

Baseline PET was positive in all patients and this is concordant with previous reports that ^{18}F -FDG-avidity ranged from 90 to 100 % in primary systemic ALCL [3–5]. PET showed 50 % sensitivity for detecting BM infiltration in our study, and this is akin to the meta-analysis of PET sensitivity of 43 % (95 % CI, 28–60) for detecting marrow infiltration in NHL [15].

Schoder et al. [11] utilized maxSUV as intensity of ^{18}F -FDG uptake to distinguish the subgroups and predict the histologic behavior in lymphoma. However, maxSUV may

Fig. 6 Progression-free survival curves of post-therapy ^{18}F -FDG PET status according to ALK expression. **a** Kaplan-Meier estimates of ALK-positive group and **b** Kaplan-Meier estimates of ALK-negative group

show considerable variation, depending on the scanner performance, scanner diameter, slice thickness, matrix size, image noise, and reconstruction methods. Instead of maxSUV, we used peakSUV for the quantitative measurement and only used the highest SUV per patient, because the highest ^{18}F -FDG uptake lesion likely represents the site of the most aggressive disease, and it is important not to underestimate the metabolic activity and aggressiveness of the disease [11].

Feeney et al. [3] also used maxSUV for the quantitative measurement, and primary systemic ALCL appeared to be one of the most ^{18}F -FDG-avid lymphomas among varied histology of T-cell types. However, there were no differences of ^{18}F -FDG-avidity according to ALK expression with a small number of patients. Cahu et al. [4] evaluated the ^{18}F -FDG PET/CT of mature T/NK lymphomas according to the ALK status. However, they neglect differential ^{18}F -FDG-avidity according to ALK expression in baseline PET/CT.

We could speculate regarding the cause of differential ^{18}F -FDG-avidity between the two groups, using the basic principle of ^{18}F -FDG PET seen in clinical practice and the molecular biology of ALK protein in oncogenesis. The increased glucose uptake imaged with ^{18}F -FDG PET is largely dependent on the rate of glycolysis, rather than that of mitochondrial oxidative phosphorylation, and this altered glucose metabolism, “aerobic glycolysis” or “Warburg effect” enables the visualization and allows quantitation of malignant tumors [16]. It is assumed that glucose transporters and hexokinases are the key molecules regulating glycolytic flux, and the key regulator of the glycolytic response is the transcription factor, hypoxia-inducible factor-1 α (HIF-1 α) [17]. It is commonly believed that the mammalian target of rapamycin (mTOR) complexes are responsible for increasing the translation of HIF-1 α [18]. Therefore, higher glucose uptake in ALK-positive ALCL indicates activated mTOR/HIF-1 α pathway with subsequently increased glycolytic flux compared with ALK-negative ALCL.

We then wondered how come the mTOR/HIF-1 α pathway could be activated by ALK expression. Many primary systemic ALK-positive ALCLs express the NPM-ALK fusion protein, and this protein can elicit multiple signaling pathways, which are responsible for both cell transformation and maintenance of the neoplastic phenotype [19]. Of these signaling pathways, the Ras–extracellular signal-regulated kinase (ERK) pathway primarily takes charge of translating the downstream effectors, mTOR and its target proteins for ALCL proliferation [20–22]. The phosphatidylinositol 3-kinase (PI3K)–Akt pathway also accounts for the small role for the ALCL proliferation [22]. Briefly, expression of the ALK protein could be a contributing factor to enhanced glycolysis as it activates the oncogenic signalings such as Ras-ERK, PI3K-Akt pathways and the consecutive mTOR/HIF-1 α pathway.

^{18}F -FDG-avidity or increases in SUV reflect in parallel the likelihood for an aggressive disease or a poor prognosis for

malignant tumors including lymphoma [11, 23–26]. Interestingly, however, ALK-positive ALCL which is known to have a better prognosis and clinical outcome than ALK-negative ALCL, showed more ^{18}F -FDG-avidity on baseline PET. Therefore, increased ^{18}F -FDG uptake of ALK-positive ALCL should not be considered as indicating aggressiveness or a poor prognosis compared with ALK-negative ALCL, and this paradoxical phenomenon is undoubtedly caused by the unique oncogenic behavior of ALK protein affecting glycolysis.

As all baseline PETs showed high ^{18}F -FDG-avidity, it could facilitate the interpretation of interim and post-therapy PET [1]. Thus, the baseline ^{18}F -FDG PET should be strongly encouraged in primary systemic ALCL, not only for the staging but also for the baseline information of interim and post-therapy PET.

In ALK-positive patients, the negative-interim PET did not appear to be a good indicator of CR and the negative-interim or post-therapy PET did not reflect better PFS contrast to the ALK-negative patients. This goes against the classical concept of clinical usefulness of ^{18}F -FDG PET in response evaluation and predicting the prognosis of lymphoma [1, 2]. Although we cannot draw a firm conclusion due to the small number of patients, this could be possibly explained by the good treatment outcome of ALK-positive ALCL after CHOP-based chemotherapy regardless of ^{18}F -FDG PET response [27].

The study of Cahu et al. [4] showed results which differed from ours. A negative interim or post-therapy PET does not translate into prolonged PFS in ALK-negative T/NK lymphoma, whereas the negative predictive value was high in both interim (100 %) and post-therapy (83 %) PET of ALK-positive T/NK lymphoma. The reasons for the discordant results are not clear; however, the difference in tumor histology, its clinical outcome, and the different ethnic groups in their study and ours might be potential causes.

Summarizing the results of our study, it appears that ^{18}F -FDG is not a suitable tracer either for judging the natural course and aggressiveness or for predicting the response evaluation and prognosis after chemotherapy in patients with ALK-positive ALCL. Rather, the proliferation marker, 3'-[^{18}F] fluoro-3'-deoxythymidine (^{18}F -FLT) would be an alternative option, given the unique oncogenic feature of ALK protein and the study results of Zhoulei et al. [28], which demonstrated the superiority of ^{18}F -FLT for predicting the early response of targeted therapy in NPM-ALK-positive lymphoma compared with that of ^{18}F -FDG using microPET.

The major limitation of our study is due to its retrospective design, including patient selection and the treatment strategy. In this retrospective clinical study, we also indirectly analyzed the association of ALK expression and glycolysis using ^{18}F -FDG uptake. Further prospective studies in a large patient cohort are warranted in order to arrive at a firm conclusion regarding the relationship of ALK expression, ^{18}F -FDG PET findings before and after therapy, and the patient outcome.

Conclusions

All patients showed ^{18}F -FDG-avid lesions on baseline PET, and ALK expression might be related with higher ^{18}F -FDG uptake in patients with primary systemic ALCL. ALK-positive ALCL tends to have better PFS and OS compared with ALK-negative ALCL. The negative interim PET was a good indicator of CR, and interim or post-therapy PET was helpful for predicting the prognosis only in patients with ALK-negative ALCL.

Conflicts of Interest The authors declare that they have no conflict of interest.

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