ORIGINAL ARTICLE

Interim FDG-PET/CT as a predictor of prognosis for HIV-related malignant lymphoma: Preliminary study

Ryogo Minamimoto[1], Junko Tanuma[2], Miyako Morooka[1], Kimiteru Ito[3], Momoko Okasaki[1], Yoko Miyata[1], Takuro Shimbo[4], Shinichi Oka[2], Kazuo Kubota[1]

1. Division of Nuclear Medicine, Department of Radiology, National Center for Global Health and Medicine, Tokyo, Japan. 2. AIDS Clinical Center, National Center for Global Health and Medicine, Tokyo, Japan. 3. Department of Radiology, National Center of Neurology and Psychiatry, Tokyo, Japan. 4. Department of Clinical Research and Informatics, National Center for Global Health and Medicine, Tokyo, Japan

Correspondence: Ryogo Minamimoto. Address: Division of Nuclear Medicine, Department of Radiology, National Center for Global Health and Medicine, 1-21-1, Toyama, Shinjyuku-ku, Tokyo 162-8655, Japan.
E-mail: ryogominamimoto@yahoo.co.jp

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Abstract

Object: The aim of this retrospective study was to clarify the potential of fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) for predicting prognosis in HIV-related malignant lymphoma (ML).

Methods: Participants comprised 24 patients (23 men, 1 woman; mean age, 42.2 years; range, 25-66 years) with histologically proven ML, classified as either diffuse large B-cell lymphoma (DLBCL) or Burkitt lymphoma according to the classification of the World Health Organization. We compared relationships between overall survival (OS) and several indices, including FDG uptake into the lesion site on pretreatment PET and findings on interim PET. Diagnostic criteria for response evaluation followed International Harmonization Project criteria.

Results: Negative findings on interim PET were associated with significantly longer OS (932±549 days) compared to positive cases (454±442 days, p=0.043). Cox regression analysis showed strong prognostic influences of interim PET findings (Hazard ratio 4.57, 95%CI 0.88-23.73) and Eastern Cooperative Oncology Group performance status (Hazard ratio 10.52, 95%CI 1.26-87.82) on OS. No other indices showed significant relationships with OS. No significant correlation was confirmed between OS and both age and lesion uptake of FDG on pretreatment PET.

Conclusion: HIV-related ML patients with negative findings on interim FDG-PET showed longer OS than patients with positive findings. Interim FDG-PET offers a predictor of prognosis for HIV-related ML.

Key words

Fluorodeoxyglucose, Positron emission tomography, HIV, Lymphoma, Overall survival, Interim positron emission tomography

1 Introduction

Highly active antiretroviral therapy (HAART) has made a substantial impact on the disease spectrum and decreasing mortality rate among HIV-infected patients [1]. Improved prognosis among HIV-infected patients has resulted from

decreases in the incidence of opportunistic infections, but a malignant complication due to HIV infection is still increasing [2]. Non-Hodgkin's lymphoma (NHL) is extremely common, along with Kaposi sarcoma and Hodgkin's disease, as HIV-related malignancies, and the incidence of developing lymphoma is about 60-fold higher in patients with AIDS than in the general population [3, 4]. HIV-related malignant lymphoma (ML) is still a leading cause of mortality in HIV-infected patients, despite the improvements achieved with HAART.

HIV-related ML usually shows an aggressive histological subtype, such as diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma, and is frequently diagnosed at a relatively advanced stage. This malignancy tends to involve extranodal sites, and the incidences of central nervous system (CNS) and bone marrow invasion are higher than with non-HIV-related ML [5]. Another distinctive characteristic of HIV-related ML is that CD4 counts and levels of HIV plasma RNA are associated with prognosis [6].

Positron emission tomography (PET) is a noninvasive, quantitative imaging modality that allows visualization of physiological and biological processes. ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) is useful for management of ML in terms of staging, treatment response and predicting prognosis [7]. Several reports have evaluated findings from FDG-PET/CT in HIV-positive patients [8, 9], and the potential of FDG PET/CT for HIV-related malignancy has been reviewed [5, 10]. However, the role of FDG-PET/CT in HIV-associated lymphomas is still very poorly studied [11]. This study aimed to clarify the potential of FDG-PET/CT for predicting the prognosis of HIV-related ML.

2 Methods

2.1 Study design

All study protocols in this retrospective observation study were approved by the institutional review board. We retrospectively examined 24 HIV-infected patients with histologically confirmed ML classified as either DLBCL or Burkitt lymphoma in accordance with the classification of the World Health Organization (WHO), who had undergone FDG-PET/CT between July 2005 and September 2009.

Before initiation of therapy, all patients were staged by clinical examination, laboratory screening, contrast-enhanced CT of the thorax and abdomen, and pathological diagnosis based on lesion and bone marrow biopsies. Among the 24 patients included in this study, 15 patients underwent baseline FDG-PET/CT for staging and confirmation of FDG uptake. The other 9 patients did not undergo baseline FDG-PET/CT, because these case had an aggressive lymphoma which had no time to undergo FDG-PET/CT scan before immediate treatment. Twenty patients had received first-line chemotherapy at the time of interim PET imaging, while 4 patients had received second-line chemotherapy. The chemotherapy regiments used were R-CHOP (n=9), RHyperCVAD (n=7), HyperCVAD (n=3), EPOCH (n=1), modEHSAP (n=1), EHSAP and DICE (n=1), or R-ESHAP (n=2). All patients underwent FDG-PET/CT during treatment, which was scheduled for before the start of the next course of chemotherapy.

2.2 PET/CT imaging

The ^{18}F-FDG used in this study was synthesized with an in-house cyclotron and an automated synthesis system (F100; Sumitomo Heavy Industries) following authorized procedures. All subjects fasted for 5 h before receiving an intravenous injection of 370 MBq of ^{18}F-FDG, and serum glucose levels measured at the time of ^{18}F-FDG injection were <150 mg/dL in all examinations. PET/CT images were obtained using a PET/CT system (Biograph 16; Siemens) consisting of a PET scanner and multidetector-row CT (16 detectors), and measuring from the vertex to the mid-thigh or knee joints 60 min after intravenous injection of ^{18}F-FDG. Low-dose CT was performed first and used for attenuation correction and image fusion. Emission images were acquired in 3-dimensional mode for 2 min per bed position. Data from PET were reconstructed using a Gaussian filter with an ordered-subset expectation maximization algorithm (3 iterations, 8 subsets).

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2.3 Evaluation of pretreatment and interim PET images

Pretreatment FDG-PET/CT was performed for 15 cases, and the maximum standardized uptake value (SUV) of the most FDG-avid lesion was measured. Interim FDG-PET scan was performed after 1 cycle of chemotherapy in 4 cases, after 2 cycles of chemotherapy in 10 cases, after 3 cycles of chemotherapy in 7 cases and after 4 cycles of chemotherapy in 3 cases. Image evaluation was performed by physicians with >5 years of experience in nuclear medicine. Diagnostic criteria for response evaluation followed International Harmonization Project criteria [12].

2.4 Statistical analysis

Data were expressed as mean ± SD. Mann-Whitney's U-test was used for evaluating differences in diagnostic performance between DLBCL and Burkitt lymphoma. Overall survival (OS) was defined as the interval from interim PET to death from any cause. Univariate analysis by proportional hazards (Cox) regression was used to assess the value of prognostic factors for predicting OS. Survival curves were calculated according to the methods of Kaplan and Meier [13], with differences between groups analyzed using the log-rank test. Values of $p<0.05$ were considered statistically significant.

Table 1. Patient characteristics

Characteristic	Total	DLBCL	Burkitt	UN
Patients	24	13	11	—
Male	23	13	10	—
Median age, y (range)	42.2 (25-66)	45.6 (27-66)	38.3 (25-61)	—
ECOG performance status 3-4	10	5	5	1
Stage III/IV	17/24	6/13	11/11	—
Extranodal sites	22	12	10	—
Bonemarrow involvement	9	0	9	3
CNS involvement	4	0	4	—
Median Soluble IL-2 level	1,649	1,239	2,184	1
Median LDH level	1,779	273	3,149	—
LDH level (<400 IU/L)	20	9	11	3
Median CD4 count (cells/mm^3)	204	149	259	2
17 - 100 cells/L	8	6	2	—
101 - 493 cells/L	14	5	9	—
Median HIV viral load (range)	789,060	231,060	1,347,060	2
cART naive	15	6	9	—
EBER positive in biopsy tissue sample	12	6	6	6
CD20 positive	22	12	10	—

DLBCL: diffuse large B cell lymphoma, UN: unknown, ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase, CNS: central nervous system, IL-2: interleukin-2 receptor, cART, combination antiretroviral therapy, EBER: Epstein-Barr virus-encoded small RNA.

3 Results

3.1 Patient characteristics

We retrospectively examined 24 HIV-infected patients (23 men, 1 woman; mean age, 42.2 years; range, 25-66 years). Patient characteristics are summarized in Table 1. After a median follow-up of 24 months (range, 2-57 months), 17 of 24 patients remained alive and 7 had died due to progression of ML. Patient characteristics are shown in Table 1. According to the malignancy criteria of the WHO, ML in the 24 HIV-infected patients was classified in DLBCL (n=13) or Burkitt lymphoma (n=11). Burkitt lymphoma in HIV-infected patients typically shows a more advanced stage at first diagnosis,

and a high incidence of bone marrow and CNS involvements. Mean CD4 counts, HIV viral load and Lactate Dehydrogenase (LDH) level were higher in Burkitt lymphoma than in DLBCL, however statistical significance was confirmed in LDH alone.

3.2 FDG-PET/CT images

Figures 1and 2 show the paradigm for FDG-PET/CT during the course of treatment for ML in HIV-infected patients (Figures 1 and 2). Pretreatment FDG-PET/CT was performed for 15 patients, comprising 12 patients for initial staging and 3 patients for restaging suspected ML recurrence. Interim FDG-PET/CT for the evaluation of therapeutic responses was performed in all 24 cases, and 10 cases were evaluated as "positive interim PET" and 14 cases were evaluated as "negative interim PET". Mean interval between pretreatment PET and interim PET was 56.4±21.9 days (range, 27-99 days).

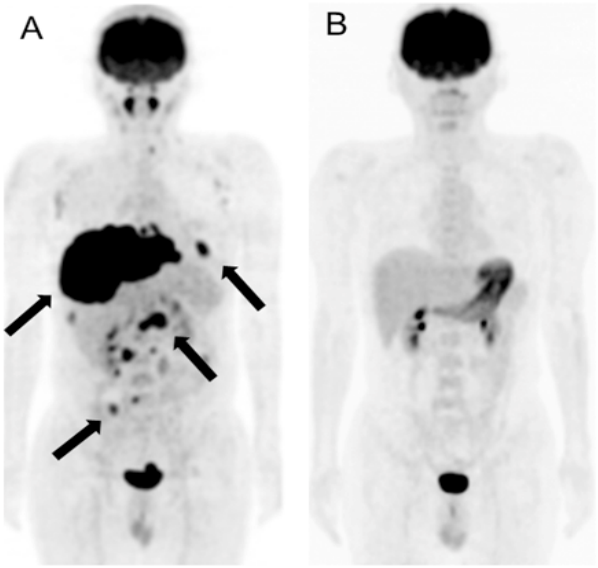

Figure 1. A. The pretreatment PET/CT shows multiple FDG avid lesions (arrows) for HIV related ML (DLBCL) and small focal FDG uptakes. B. Interim PET/CT shows disappearance of all FDG avid lesions. Long OS with 1,328 days was confirmed in this case.

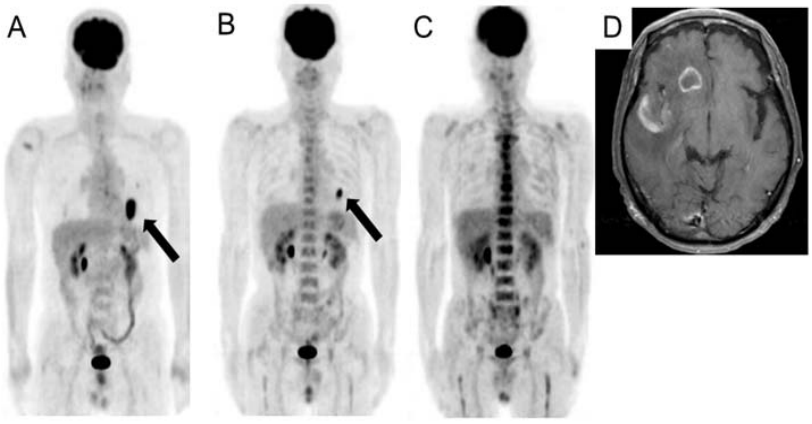

Figure 2. A. The pretreatment PET/CT shows FDG avid lesions at the left lung. B. Interim PET/CT shows residual FDG uptake at the lung. C. Follow-up PET/CT shows disappearance of the lesions but CNS ML was confirmed. This case showed short OS (134 days).

Mean SUVmax of FDG uptake by lymphoma lesions was 15.6±7.3 in ML patients on pretreatment FDG-PET/CT. No significant difference in FDG accumulation was seen between DLBCL (n=10, 15.7±8.0) and Burkitt lymphoma (n=5, 15.3±5.3).

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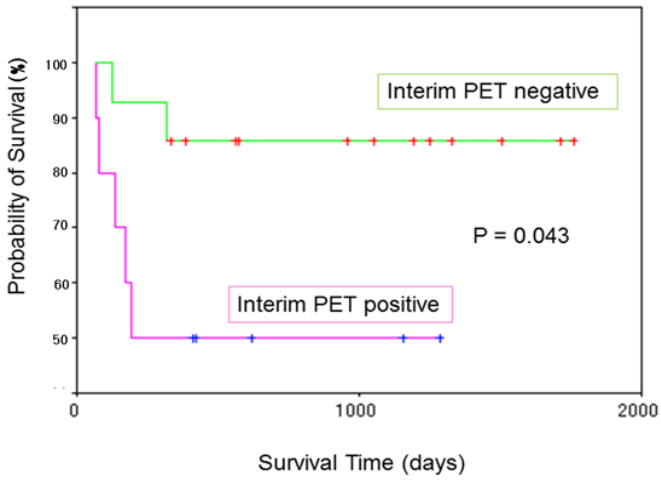

Figure 3. Kaplan-Meier Survival Estimates: Negative findings on interim PET showed longer OS compared with positive cases (p=0.043). Over all two year survival rate of negative findings on interim PET was 80%, which was higher than 29% in positive cases

3.3 Prediction of survival by FDG-PET/CT and other indices

Negative findings on interim PET were significantly associated with longer OS (932±549 days) compared with positive cases (454±442 days; p=0.043, log-rank test) (Figure 3). Over all two year survival rate of negative findings on interim PET was 0.80 (95%CI 0.69-0.91), which was higher than 0.29 (95%CI 0.16-0.41) in positive cases. A similar trend was found according to the type of ML (DLBCL, 934±593 vs. 557±556 days; Burkitt lymphoma, 931±550 vs. 229±136 days), but the difference was not significant (p=0.15-0.16). Over all two year survival rate in DLBCL was 0.80 (95%CI 0.69-0.91) in negative findings on interim PET, which was higher than 0.40 (95%CI 0.27-0.53). Over all two year survival rate in Burkitt lymphoma was 0.80 (95%CI 0.69-0.91) in negative findings on interim PET and no alive patient in positive cases. The result of Cox regression analysis is summarized in Table 2. Cox regression analysis showed strong prognostic influences of Eastern Cooperative Oncology Group performance status (ECOG-PS) (p=0.03) and interim PET findings (p=0.07) in OS.

Table 2. Univariate analysis of OS to pretreatment prognostic factors and interim PET/CT interpretation

Index	HR	95% CI for HR	P value
Age ≦40 vs. < 40	1.37	0.28 - 0.68	0.704
ECOG performance status 2-4 vs. 1	10.52	1.26 - 87.82	0.030
Stage III/IV vs. I/II	3.91	0.06 - 27.84	0.274
Bone marrow involvement	1.17	0.24 - 5.83	0.844
CNS involvement	2.21	0.43 - 11.52	0.346
Bulky mass	1.13	0.21 - 6.17	0.888
Soluble interleukin-2 receptor ≦1000 vs. < 1000	2.27	0.42 - 12.46	0.344
CD4 count, cells/L (cells/mm^3) ≦100 vs. < 100	0.47	0.10 - 2.36	0.362
HIV viral load	2.33	0.27 - 19.98	0.440
LDH level (< 400 IU/L)	0.47	0.09 - 2.58	0.385
cART naive	0.69	0.13 - 3.56	0.656
Pathology (DLBCL or Burkitt)	1.36	0.30 - 6.11	0.686
EBER positive in biopsy tissue sample	0.94	0.13 - 6.67	0.950
SUVmax of lesion in pretreatment PET ≦15 vs. < 15	1.64	0.10 - 26.35	0.726
Interim PET/CT positive vs. negative	4.57	0.88 - 23.73	0.070

OS: overall survival, HR: hazard ratio, ECOG: Eastern Cooperative Oncology Group, CNS:central nervous system, LDH: lactate dehydrogenase, cART:combination antiretroviral therapy, EBER: Epstein-Barr virus-encoded small RNA, DLBCL: diffuse large B cell lymphoma, SUV: standardized uptake value

4 Discussion

The present findings indicate that negative findings on interim FDG-PET/CT were strongly associated with improved OS in HIV-related ML. No other indices related to HIV or HIV-related ML (excluding ECOG-PS) showed a close relation to OS.

FDG-PET and PET/CT are well established for initial staging and restaging of ML, and have been adopted for determining therapeutic response in DLBCL [12, 14]. Although FDG-PET and PET/CT have demonstrated promising results for managing ML other than DLBCL, the role of FDG-PET/CT in other histologies (including HIV-related lymphoma) is not guaranteed [15].

DLBCL and Burkitt lymphoma account for the majority (90%) of ML cases [16], and these lymphomas are intensely FDG-avid [17, 18]. AIDS-related NHLs are characterized by high grade, aggressive nature and wide dissemination at the time of diagnosis, with the frequent involvement of extranodal sites [3]. Burkitt lymphoma is an aggressive disease requiring short-duration high-intensity chemotherapy regimens, and poor prognosis is strongly associated with a failure to achieve complete remission [18]. FDG-PET/CT can contribute to screening for viable disease that is considered reversible upon successful implementation of treatment [19].

In our study, 9 patients did not undergo PET in the pretreatment stage, but these cases must have had a high potential for FDG-avidity in the pretreatment lesion confirmed by CT, considering the characteristics of HIV-related ML. Moreover, DLBCL and Burkitt's lymphoma tended to progress rapidly, therefore it sometimes could not have time to perform baseline FDG-PET/CT scan before initiation of therapy. It appeared to be a limitation of our study and inducing FDG-PET/CT for assessment of treatment response in HIV-related ML.

A small case study of patients with AIDS-related lymphoma showed that FDG-PET/CT provided more accurate initial staging compared with conventional examinations, and was useful to monitor treatment response. PET/CT is regarded as a reliable method for managing lymphoma in HIV-infected patients [20, 21].

Although there is little evidence for the utility of FDG-PET/CT in HIV-related lymphoma, this modality is expected to offer a potent imaging technique for managing HIV-related lymphoma, as for ML in non-HIV patients [2].

Our result suggested that interim FDG-PET/CT reflected prognosis in terms of the OS rate for patients with HIV-related ML. On the other hand, baseline FDG uptake for DLBCL and Burkitt lymphoma showed no significant correlations with OS. From the perspective of pathological type analysis, interim PET predicted OS but showed no significant difference between types of ML. This might be attributable to the small number of study cases, so further study with a larger number of cases is needed. Prediction of OS using interim PET would allow reconsideration of the therapeutic strategy for each individual case in the early stages. According to our study results, HIV-related ML (which mainly comprises high-grade ML) might be expected to achieve complete response by existing therapeutic strategies. Early prognostic prediction using interim PET may contribute to improved outcomes of therapy. However, the incidence of therapeutic stumbling blocks such as infection is higher among HIV-infected patients than among other patients, regardless of the decreasing incidence of opportunistic infections thanks to HAART. Mortality in our study was caused by progression of lymphoma, so further studies with HIV-related ML cases in various situations are needed.

As for pretreatment indicators, poor ECOG-PS (PS 2-4) was associated with shorter OS. ECOG-PS has been an important parameter in prognostic models for aggressive lymphomas [22, 23], and is included in the International Prognostic Index for aggressive NHL as a significant risk factor. According to our results, extranodal site involvement and stage beyond III or IV showed relatively higher hazard rate than other factors but having no statistical significance. LDH levels were not considered a risk factor, and age seemed to be an inadaptable factor because HIV-related ML was caused by HIV infection, which is more common among young adults. In addition, extranodal involvement is frequently observed in HIV

related ML despite of the OS. As a result, ECOG-PS offers a prognostic index in the pretreatment state, but may be problematic given the subjective nature of evaluation.

This study did not examine relationships between PET findings and progression-free survival (PFS). Lymphadenopathy is a common symptom among HIV-infected individuals, as HIV is disseminated throughout lymphoid tissues after gaining entry to the human body. Trapping of HIV-positive effector cells in lymphoid tissues induces inflammation and lymphocytes are activated and switch to glycolysis, resulting in increased ^{18}F-FDG uptake into lymph nodes among HIV-infected individuals [24-26]. Differentiation of HIV-related lymphadenopathy from ML thus poses a diagnostic problem. Lymphadenopathy related to ML is generally larger and shows more intense FDG uptake than HIV-related lymphadenopathy [27] and the differentiation of common sites of lymphadenopathy between HIV-related lymphadenopathy and HIV-related ML may contribute to correct diagnosis [2]. However, no reliable cut-off values have yet been determined. Moreover, the difficulty in differential diagnosis compounds the problem of interim PET, which is intended to evaluate therapeutic response based on variations in FDG uptake into lesions and/or eruption of new lesions. As a result, making clear decisions for PFS appears very difficult in HIV-infected subjects (Figure 4).

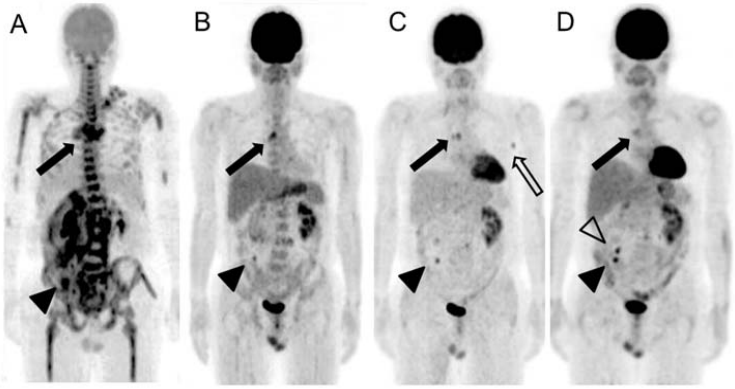

Figure 4. A. The pretreatment PET/CT shows FDG avid lesions at the mediastinum (arrow), cecum (arrow head). Interim (B) and follow up (C, D) PET/CT shows residual FDG uptake at both lesion. New FDG uptake appears at left axilla (C, white arrow) but disappeared (D), considered as HIV-related lymphadenopathy. New FDG uptake at cecum was caused by infection of tuberculosis (D white arrow head).

Key limitations in this study were the small sample size, variation of treatment regimens and 4 cases with evaluation of interim PET after only a single cycle of chemotherapy. Larger prospective studies with longer follow-up are needed to clarify our findings.

5 Conclusion

OS was longer for patients with HIV-related ML showing negative findings on interim FDG-PET than for patients with positive findings. Over all two year survival rate of negative findings on interim PET was higher than in positive cases. The strong prognostic influences for OS was ECOG-PS and interim PET findings. Interim FDG-PET can predict the prognosis of HIV-related ML. However, because of the limitations of the study, further prospective studies are needed in order to evaluate the value of FDG-PET/CT for HIV-related ML.

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