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).

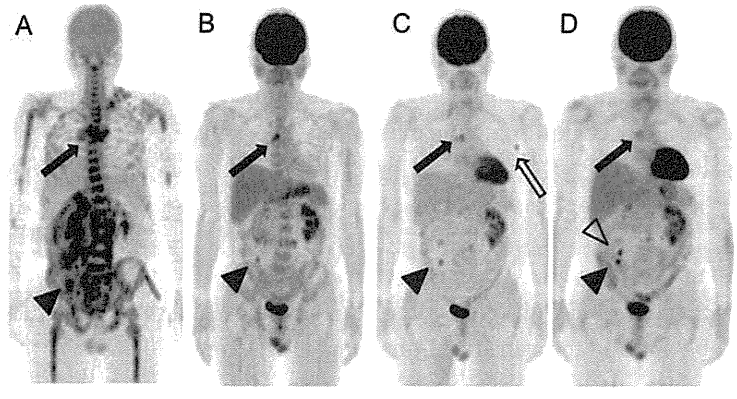

Figure 4. A. The pretreatment PET/CT shows FDG avid lesions at the mediastinum (arrow), cecum (arrow head). Interim (B) and follow up (C, D) PET/CT shows residual FDG uptake at both lesion. New FDG uptake appears at left axilla (C, white arrow) but disappeared (D), considered as HIV-related lymphadenopathy. 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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発行所　研究班事務局
(独)国立国際医療研究センター
エイズ治療・研究開発センター
〒162-8655　東京都新宿区戸山1-21-1