Annals of Nuclear Medicine Vol. 19, No. 8, 685–690, 2005

Evaluation of tumor FDG transport and metabolism in primary central nervous system lymphoma using [^{18}F]fluorodeoxyglucose (FDG) positron emission tomography (PET) kinetic analysis

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Objective: Although ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) has been used as a promising tool to diagnose primary central nervous system lymphoma (PCNSL) because the tumor shows very high FDG accumulation, no data exist evaluating the extent of tumor FDG transport and metabolism. The aim of this study was to evaluate the feasibility of FDG-PET kinetic analysis in measurement of uptake parameters of FDG in the lymphoma tissues and in the assessment of treatment effects in patients with PCNSL. ***Methods:*** Dynamic FDG-PET examination was performed in 7 histologically proven PCNSL patients before and after methotrexate-based chemotherapy. ***Results:*** Before the chemotherapy, the highest CMRglc in the tumor for all 7 patients was 79.4 ± 27.2 μmol/100 g/min. This value was significantly higher than that observed in the normal cortex in 14 control patients (44.3 ± 6.0 μmol/100 g/min, $p < 0.001$). The phosphorylation (k_3) activity was also significantly higher in the tumor (0.093 ± 0.026 min^{-1}) compared with the normal cortex (0.064 ± 0.014 min^{-1}, $p < 0.05$). On the other hand, the transporter (K_1) activity in the tumor (0.079 ± 0.016 m*l*/min) was similar to that observed in the normal cortex (0.082 ± 0.012 m*l*/min). The chemotherapy significantly reduced the volume of the tumor in 6 of 7 patients and the highest CMRglc in the tumor examined 18.0 ± 5.5 days after the chemotherapy (34.0 ± 21.8 μmol/100 g/min) was significantly lower than that observed before the chemotherapy ($p < 0.01$). This reduction in FDG uptake was concomitant with a significant reduction in both the K_1 and k_3 values ($p < 0.05$). The reduction in the k_3 value after the chemotherapy was marked in 6 of 7 patients in whom the tumor responded to the first chemotherapy. ***Conclusions:*** Dynamic image acquisition can separate regional FDG uptake into FDG transport and phosphorylation activity in the lymphoma tissues. Tumor FDG uptake was significantly higher with accelerated phosphorylation activity compared with that observed in the normal cortex.

Keywords: glucose transport, glucose phosphorylation, fluorodeoxyglucose, PET (positron emission tomography), primary central nervous system lymphoma

INTRODUCTION

PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL) has been increasing in incidence during the past two decades.[1] ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) has been used to diagnose PCNSL because the tumor has very high cellular density with an accelerated glycolytic metabolism, and therefore shows a huge concentration of FDG.[2,3] However, no data exist defining the extent of tumor FDG transport and phosphorylation. With FDG-PET studies, dynamic image acquisition can separate regional FDG uptake into FDG transport and phosphorylation (hexokinase) activities[4] (Fig. 1). In this study, we investigated the value of FDG uptake using kinetic analysis before and after chemotherapy in 7 histologically proven PCNSL patients and identified

Received April 6, 2005, revision accepted August 18, 2005.
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Table 1 Patient characteristics and PET data before and after chemotherapy

Patient	Age/Sex	Location	No. of tumor	Treatment	Before chemotherapy			After chemotherapy			Tumor reduction
					CMRglc	K_1	k_3	CMRglc	K_1	k_3	
1	53/M	PVW	Multiple	M-CHOP	69.6	0.071	0.088	22.7	0.051	0.047	19.8
2	64/F	FL	Single	M-CHOP	109.7	0.073	0.108	13.6	0.033	0.043	26.4
3	74/M	PVW	Single	M	55.1	0.063	0.067	16.0	0.045	0.045	32.4
4	47/M	PVW	Multiple	M-CHOP	90.2	0.091	0.084	31.4	0.073	0.039	26.5
5	66/F	CH	Single	M-CHOP	115.4	0.109	0.088	44.0	0.086	0.037	27.7
6	62/F	PVW	(?)*	M-CHOP	42.0	0.067	0.073	32.9	0.085	0.058	47.3
7	70/M	CC	Single	M	73.7	0.077	0.145	77.4	0.061	0.172	109.1
Mean					79.4	0.079	0.093	34.0	0.062	0.063	
SD					27.2	0.015	0.026	21.8	0.020	0.049	

PVW: periventricular white matter, FL: frontal lobe, CH: cerebellar hemisphere, CC: corpus callosum
(?)*: the number could not be determined because of non-enhancing tumor
M: methotrexate, CHOP: cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisolone

quantitative uptake parameters of FDG, which may provide physiological and biochemical information on lymphoma tissues and sensitive measures of tumor response after chemotherapy.

MATERIALS AND METHODS

Patients

Seven patients (4 men and 3 women) with newly diagnosed PCNSL were enrolled in this study. The mean age of the patients was 62.7 ± 9.4 years, ranging from 47 to 74 years. All patients were histopathologically verified as having diffuse, large B-cell type malignant lymphoma. The patients underwent chemotherapy using high-dose methotrexate (3.5 g/m^2) alone in 2 patients or high-dose methotrexate in combination with CHOP (cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisolone) in 5 patients.

FDG-PET scanning

FDG-PET was performed before the chemotherapy to determine baseline results and was repeated within 3 weeks after the first chemotherapy. Enteral and parenteral sources of glucose were withheld for at least 6 hours before the PET examination. Transmission scans were obtained before tracer injection with a 5-minute acquisition time by use of germanium-68 rod sources rotating around the head. A 60-minute dynamic PET scan (40 seconds × 1; 20 seconds × 2; 40 seconds × 4; 60 seconds × 4; 180 seconds × 4; 300 seconds × 8) was performed using a Siemens EXACT HR+ PET scanner after an intravenous injection of [^{18}F]fluorodeoxyglucose at a dose of 3.0–4.0 MBq/kg. Emission data corrected for random, dead time, and attenuation were reconstructed with filtered back-projection. Arterial blood samples were withdrawn from the brachial artery at 15-second intervals for the first 3 minutes, followed by increasingly longer intervals to 60 minutes, to measure arterial plasma radioactivity using an auto well gamma counter (ARC-400, Aloka, Tokyo, Japan). The blood sample obtained at 30 minutes after the injection was analyzed for blood glucose concentration.

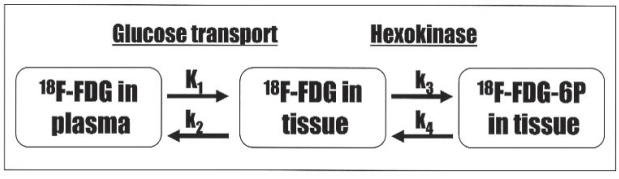

Fig. 1 Schematic expression of a 3-compartment model for ^{18}F-FDG kinetics. 6P = 6-phosphate.

Data analysis

Regions of interest (ROIs) were visually selected as those displaying intense isotope uptake on baseline FDG-PET corresponding to abnormal CT or MRI appearance. We set several ROIs (each 10 mm in diameter) from each patient and selected a ROI which showed maximal uptake of the FDG in the tumor. At follow-up studies, we also selected a ROI which showed maximal uptake of the FDG even if the place of ROI after the treatment was not the same as the place of ROI prior to the treatment. The FDG kinetic parameters were calculated from the dynamic activities obtained from tissue ROIs. Five parameters (K_1, k_2, k_3, k_4, and blood volume) were estimated by use of the nonlinear least-square fitting technique. As an index of the glucose cerebral metabolic rate (CMRglc), the FDG uptake constant (K_i) was calculated as $K_1*[k_3/(k_2 + k_3)]$. With lumped constant (LC) for normal brain and the arterial plasma glucose concentration (Ca_{glc}), absolute values for CMRglc were related to K_i as $(Ca_{glc}*K_i)/LC$.

We did not use the values of the normal cortex of the same patient (such as contralateral cortex of the lymphoma) because the FDG uptake in the normal cortex of lymphoma patients is generally suppressed due to mass effect and can not be regarded as truly normal. The values of the normal cortex in 14 control patients presenting an

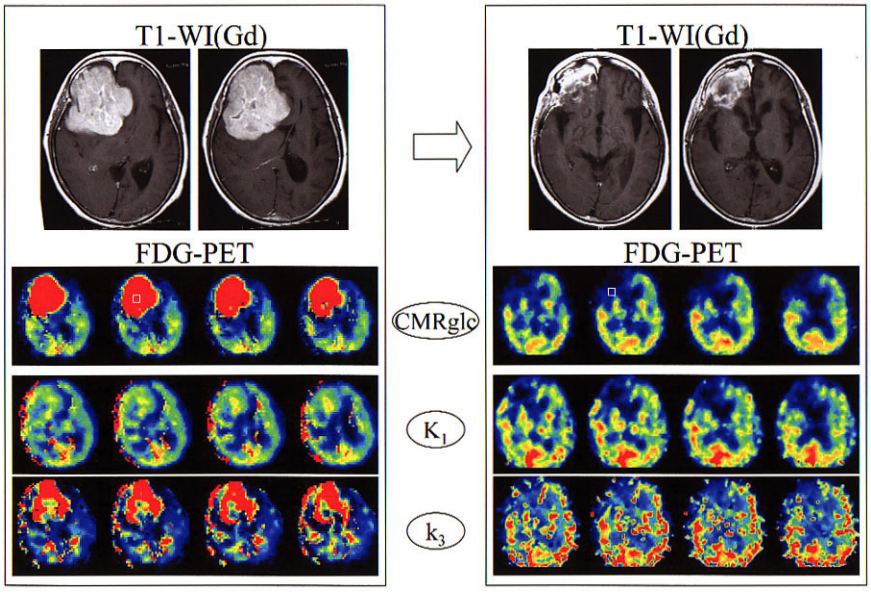

Fig. 2 Axial MR and FDG-PET images before (*left panel*) and 21 days after (*right panel*) the chemotherapy in Case 2. Open squares indicate ROI for FDG-PET quantitative analysis. Before the chemotherapy, axial T1-weighted MRI with gadolinium showed a huge well-defined enhancing tumor in the right frontal lobe with substantial mass effect. The tumor exhibited markedly high FDG uptake relative to surrounding brain on FDG-PET images. Corresponding lesion showed slightly increased K_1 value in the center of the tumor and markedly accelerated k_3 value in the tumor except for the center in the kinetic analysis. Twenty-one days after the chemotherapy, the tumor volume was significantly reduced on gadolinium enhanced T1-weighted MRI. At the same time, the lesion showed substantially low FDG uptake relative to surrounding brain on FDG-PET images with decreased K_1 and k_3 values. The reduction of FDG uptake exceeded the volume reduction on MR imaging at this time.

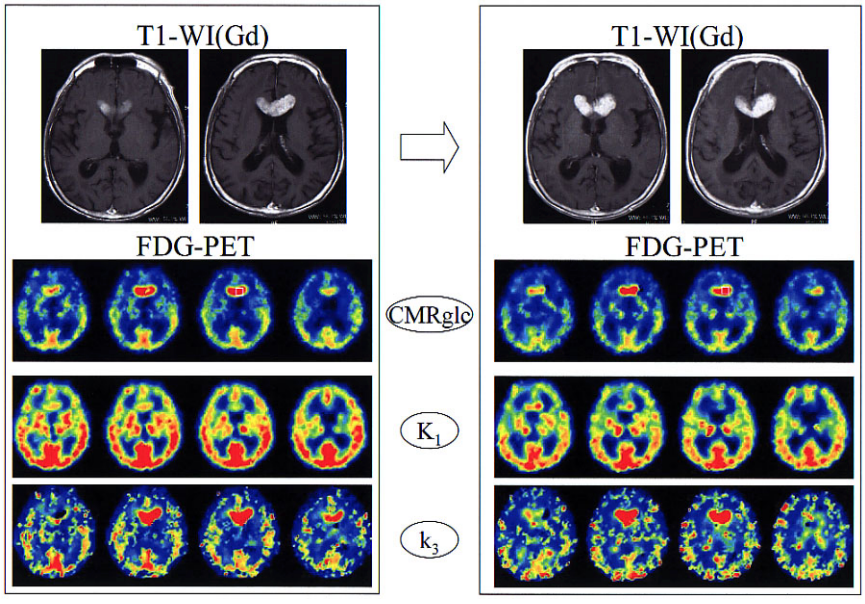

Fig. 3 Axial MR and FDG-PET images before (*left panel*) and 15 days after (*right panel*) the chemotherapy in Case 7. Open squares indicate ROI for FDG-PET quantitative analysis. Before the chemotherapy, axial T1-weighted MRI with gadolinium showed a well-defined enhancing tumor in the corpus callosum. The tumor exhibited substantially high FDG uptake relative to surrounding brain on FDG-PET images. Corresponding lesion showed a markedly accelerated k_3 value in the tumor in the kinetic analysis. Fifteen days after the chemotherapy, the tumor volume was increased on gadolinium enhanced T1-weighted MRI and the neurological status of the patient deteriorated progressively. At the same time, the lesion showed still high FDG uptake on FDG-PET images with increased k_3 values similar to those obtained before the chemotherapy.

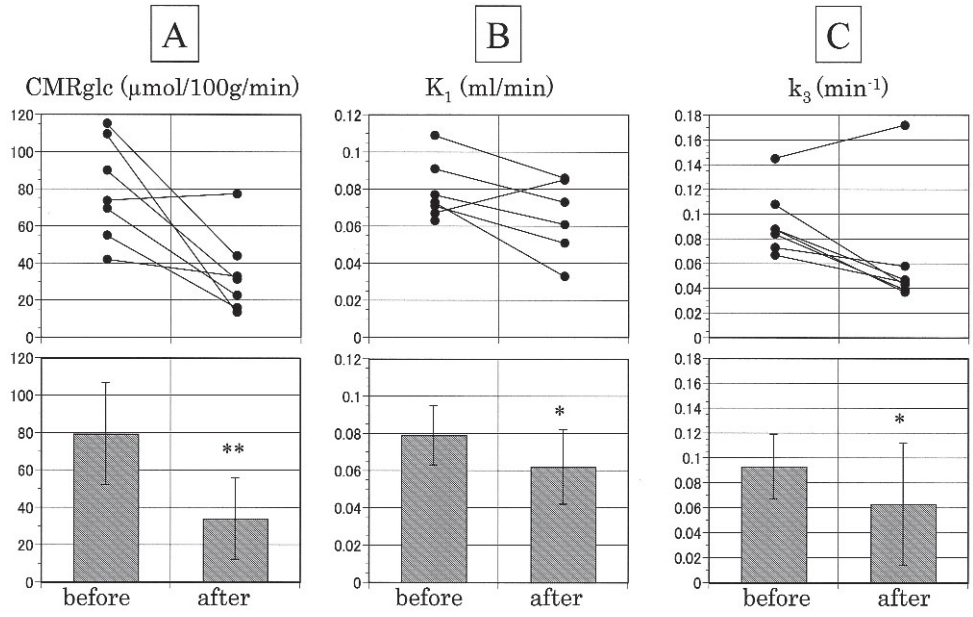

Fig. 4 (*upper*) Comparison of the CMRglc (A), the K_1 value (B) and the k_3 value (C) before and after the chemotherapy in each patient. Tumor FDG uptake in each patient decreased considerably and was lower than that at baseline determination. The K_1 value in the tumor in each patient was lower than that at baseline determination, except 1 case (Case 6) in whom the tumor was non-enhancing and the k_3 value in the tumor after the chemotherapy in each patient was lower than that at baseline determination, except 1 case (Case 7) in whom the tumor did not respond to the first chemotherapy and showed an increased k_3 value after the chemotherapy. (*lower*) Comparison of the highest CMRglc (A), the K_1 value (B) and the k_3 value (C) for all patients before and after the chemotherapy. Values are means ± SD. The highest CMRglc for all patients was significantly decreased from 79.4 ± 27.2 μmol/100 g/min at baseline to 34.0 ± 21.8 μmol/100 g/min after the chemotherapy (**: $p < 0.01$). The K_1 value was significantly decreased from 0.078 ± 0.016 ml/min at baseline to 0.062 ± 0.020 ml/min after the first chemotherapy (*: $p < 0.05$) and the k_3 value was also significantly decreased from 0.093 ± 0.027 min^{-1} at baseline to 0.063 ± 0.048 min^{-1} after the first chemotherapy (*: $p < 0.05$).

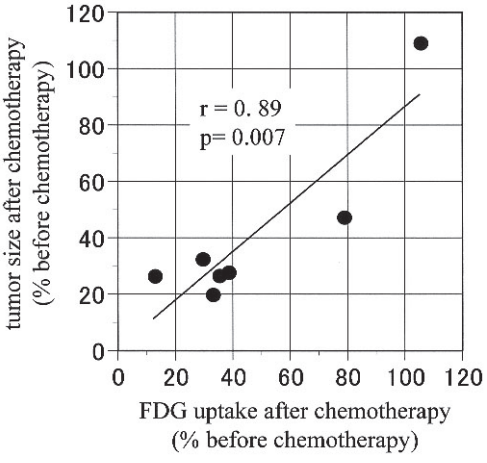

Fig. 5 The correlation between percent reduction of the tumor size after the chemotherapy and percent reduction of FDG uptake into the tumor after the chemotherapy (r = 0.89, p = 0.007).

extra-axial brain tumor without significant mass effect (meningioma in 5 cases, pituitary adenoma in 4 cases, acoustic neurinoma in 2 cases, and miscellaneous in 3 cases) were chosen as controls.

Statistical analysis

All parametric data were expressed as mean ± SD. Differences in the CMRglc and the FDG kinetic parameters between the tumor and the normal cortex in control patients were analyzed by unpaired Student's t test. Changes in regional FDG uptake and kinetic parameters before and after the chemotherapy were compared by use of paired t test. Correlation between the reduction of highest CMRglc in the tumor after the chemotherapy and the decrease of tumor size on the follow-up MRI were evaluated by a simple regression analysis. Two-tailed probability values of <0.05 were considered statistically significant.

RESULTS

Patient and tumor characteristics are shown in Table 1. The tumors were single in 5 cases and multiple in 2 cases and located in the periventricular white matter in 4 cases, frontal lobe in 1 case, corpus callosum in 1 case, and cerebellar hemisphere in 1 case. Histopathological confirmation of the tumor was performed by stereotactic biopsy in 5 cases and open surgery in 2 cases. Plasma glucose concentrations were within the normal range (below 110

mg/dl) in all patients at 30 minutes after the initiation of dynamic PET scan. Visually, the tumors showed increased FDG uptake compared with the surrounding or contralateral brain corresponding to the abnormal enhanced area in CT or MR imaging, except 1 case in whom the tumor was non-enhancing and the FDG uptake did not increase compared with the surrounding brain tissue. CMRglc in the tumor and kinetic parameters for FDG before and after the first chemotherapy are summarized in Table 1. Figures 2 and 3 show MRI and FDG-PET images from 2 representative patients (Cases 2 and 7), in whom the tumors showed a marked response and non-response to the chemotherapy, respectively. The highest CMRglc in the tumor for all 7 patients was 79.4 ± 27.2 μmol/100 g/min. This value was significantly higher than that observed in the normal cortex (44.3 ± 6.0 μmol/100 g/min, $p < 0.001$) in 14 control patients. When kinetic parameters for the tumor were compared with parameters for the normal cortex in 14 control patients with an extra-axial brain tumor, the k_3 value in the tumor (0.093 ± 0.027 min^{-1}) was significantly higher than that obtained in the normal cortex (0.064 ± 0.014 min^{-1}, $p < 0.05$). On the other hand, the K_1 value in the tumor (0.079 ± 0.016 ml/min) was not significantly different from that of the normal cortex (0.082 ± 0.012 ml/min).

Figure 4 shows the changes in the highest CMRglc in the tumor and the kinetic parameters (K_1 and k_3) for FDG in each case before and 18.0 ± 5.5 days after the chemotherapy. Follow-up MRI was obtained on 17.6 ± 4.4 days after the chemotherapy and MR images exhibited a partial response (more than 50% reduction in tumor size) in 6 patients (Table 1), while 1 patient (Case 7) showed non-response after the chemotherapy (Fig. 3). Tumor highest FDG uptake in each patient decreased considerably in 6 of 7 patients and was lower than that at baseline examination, and the highest CMRglc for all patients was significantly decreased from 79.4 ± 27.2 μmol/100 g/min at baseline to 34.0 ± 21.8 μmol/100 g/min after the chemotherapy (Fig. 4A; $p < 0.01$). The reduction of the highest CMRglc in the tumor after the chemotherapy showed a significantly positive correlation with the decrease of tumor size on the follow-up MRI ($p < 0.05$) (Fig. 5). The k_3 value in the tumor after the chemotherapy in each patient was lower than that at baseline determination (Fig. 4B), except 1 case (Case 7) in whom the tumor did not respond to the first chemotherapy and showed an increased k_3 value (Fig. 3), and the k_3 value for all patients was significantly decreased from 0.093 ± 0.026 min^{-1} at baseline to 0.063 ± 0.048 min^{-1} after the first chemotherapy ($p < 0.05$). The K_1 value in the tumor in each patient was also lower than that at baseline determination (Fig. 4C), except 1 case (Case 6) in whom the tumor was non-enhancing, and the K_1 value for all patients was also significantly decreased from 0.079 ± 0.016 ml/min at baseline to 0.062 ± 0.020 ml/min after the first chemotherapy ($p < 0.05$). Six patients in whom the tumor responded to the chemotherapy continued to receive the second and third chemotherapy followed by whole brain radiotherapy and achieved complete remission based on radiographic data at the end of the treatment. One patient (Case 7) in whom the tumor did not respond to the first chemotherapy received whole brain radiotherapy and achieved a partial response.

DISCUSSION

FDG-PET kinetic analysis

Physiological or biochemical alterations of brain tumors, which distinguish neoplastic tissue from normal brain tissue, allow visualizing the tumors with PET using a radiolabeled tumor tracer. Fluorodeoxyglucose (FDG) is a glucose analogue, which is taken up rapidly and metabolized intensely by most neoplastic cells. FDG-PET has been used to diagnose PCNSL because the tumor has very high cellular density with an accelerated glycolytic metabolism, and therefore shows a huge concentration of FDG, higher not only than that of normal brain tissue but also high-grade gliomas.[2,3] For the exact interpretation of tumor tracer uptake, it is essential to determine whether the changes are related to tracer transport and/or metabolism. This analysis is based upon dynamic PET data acquisition and requires serial arterial blood samplings. With human FDG-PET studies, dynamic image acquisition (measuring the rate of accumulation of FDG in the brain over time) allows modeling of regional FDG transport and phosphorylation rates.[4,5] The model separates FDG uptake into 2 compartments with flux rates characterized by kinetic parameters (K_1, k_2, k_3, k_4),[6] as shown in Figure 1. In this model, the movement of FDG from the plasma to the tissue compartment represents primarily the BBB-related transport of FDG and thus reflects the activity of the glucose transporter (K_1). However, it may be argued that the application of this model to brain tumor is not valid because this model of FDG kinetics and interpretation is originally based upon normal brain tissue. With this consideration in mind, the FDG kinetic method should be used only with caution, and the measured values for CMRglc require careful interpretation in primary brain tumors.[6] For example, the K_1 may also include extravasation of the tracer into the extracellular space through a disrupted BBB in the tumor.

FGD-PET in PCNSL

Our results indicate that the K_1 value of the tumor (0.079 ± 0.016 ml/min) in patients with PCNSL did not deviate from that observed in the normal cortex (0.082 ± 0.012 ml/min) in 14 control patients with an extra-axial brain tumor. The K_1 value observed in patients with PCNSL may include the factor of FDG extravasations through a disrupted BBB, because 6 of 7 patients in our series showed typical well-enhancing tumors. On the other hand, the k_3 value of the tumor (0.094 ± 0.027 min^{-1}) in

patients with PCNSL was significantly higher than that observed in the normal cortex (0.064 ± 0.014 min^{-1}) in 14 control patients with an extra-axial brain tumor. The K_1 and k_3 values of the normal cortex in 14 control patients were compatible with the previously reported value observed in the normal human gray matter (K_1: 0.084 ± 0.016 ml/min, k_3: 0.061 ± 0.004 min^{-1}).[4] These results suggest that accelerated FDG phosphorylation rather than increased FDG transport and/or extravasation is the main mechanism responsible for the high degree of FDG uptake in PCNSL. In an animal brain tumor model, it has been demonstrated that in the presence of normal glucose influx into the tumor cells, the glucose metabolism is doubled compared with the normal grey matter and that there is an uncoupling between glucose transport and phosphorylation.[7]

Although FDG-PET has been described as a useful method for evaluating the response to chemotherapy for malignant lymphoma,[8–10] only a few reports propose the use of PET in monitoring the effects of tumor treatment in PCNSL.[3,11] In our study, the FDG-PET after the first chemotherapy showed decreased FDG uptake in the tumor compared with that obtained before the chemotherapy. These changes were closely associated with clinical recovery and improvement of the MRI abnormality. With regard to the follow-up of patients during and after chemotherapy, we consider that both changes in clinical condition, as well as morphological changes demonstrated with contrast-enhanced CT or MRI are sufficient indicators of treatment response. However, these assessments do not necessarily reflect the quantity of remaining viable tumor cells. Based upon morphological change alone, residual tumor mass cannot be differentiated from scar tissue.[12] In this study, the superiority of FDG-PET kinetic analysis over semi-quantitative analysis using SUVs for the early evaluation of treatment response was undetermined because we did not compare the FDG-PET uptake parameters and SUVs, despite being less invasive and more commonly used in clinicians.[13] The reduction in FDG uptake was concomitant with both decreased transporter (K_1) and phosphorylation (k_3) activities. The reductions in the K_1 (78%) and k_3 (68%) values for all patients after the chemotherapy did not significantly differ between the two kinetic parameters because of 1 exceptional case (Case 7). The reduction in the k_3 values after the chemotherapy in 6 other cases was marked (53%), suggesting that reduced metabolism of the damaged cells might be largely associated with decrease of tumor FDG uptake.

CONCLUSION

Dynamic image acquisition can separate regional FDG uptake into FDG transport and phosphorylation activity in lymphoma tissues. Tumor FDG uptake was significantly higher with accelerated phosphorylation activity compared with that observed in the normal cortex. Further studies comparing detailed FDG-PET kinetic data and semi-quantitative FDG uptake (SUVs) and morphological data are required to define the usefulness of early therapy monitoring in patients with PCNSL.

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