Advances in Brief

Positron Emission Tomography-based Boron Neutron Capture Therapy Using Boronophenylalanine for High-Grade Gliomas: Part II

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Abstract

Based on pharmacokinetic findings of fluorine-18-labeled L-fluoroboronophenylalanine by positron emission tomography (PET), methods for estimating tumor 10B concentration were devised. In clinical practice of boron neutron capture therapy (BNCT) for high-grade gliomas, a large amount of L-boronophenylalanine (L-BPA)-fructose solution is used. Under these conditions, a slow i.v. infusion of L-10B-BPA-fructose solution should be performed for BNCT; therefore, the changes over time in 10B concentration in the target tissue were estimated by convoluting the actual time course of changes in plasma 10B concentration with a PET-based weight function including the proper rate constants [k1 (ml/g/min), k2 (min^-1), k3 (min^-1), and k4 (min^-1)]. With this method, the estimated values of 10B concentration in gliomas were very close to the 10B levels in surgical specimens. This demonstrated the similarity in pharmacokinetics between fluorine-18-labeled L-fluoroboronophenylalanine and L-10B-BPA. This method, using the appropriate rate constant, permits the determination of tumor 10B concentration and is widely suitable for clinical BNCT, because the averaged PET data are enough to use in future patients without individual PET study.

Introduction

BNCT requires selective delivery of a boron-containing drug to the tumor, followed by irradiation with neutrons (1–5). For estimation of the radiation dose to the tumor, it is essential to know the concentration of boron in the tumor at the time of BNCT. However, direct measurement at the time of BNCT is impossible; therefore, new approaches to the estimation of the boron content of tumors during BNCT are required. When actually performing BNCT, we must reconfirm the tumor 10B level by measuring the L-10B-BPA in the arterial blood. We administered a large amount of L-10B-BPA-fructose solution i.v. before BNCT, admitted the patient to the irradiation room, and began neutron irradiation, but the collection of arterial blood was possible for at least 1–2 h, until the beginning of neutron irradiation. Thus, the input function of L-10B-BPA can be determined by blood sampling during this 1–2 h, and, finally, the neutron dose must be determined based on the tumor 10B level. Under these conditions, estimation of 10B level based on the incorporation constant (Ic*) and the utilization ratio (Ur*) is often inappropriate. In this study, our main purpose is to solve these actual problems. We evaluated the tumor pharmacokinetics of L-18F-10B-FBPA based on comparison with L-10B-BPA using PET and assessed the similarity of L-18F-10B-FBPA accumulation to that of L-10B-BPA. If the 10B concentration calculated using the rate constant obtained by PET using L-18F-10B-FBPA and the actually measured 10B input function is close to that in the surgical specimens, similarity in pharmacokinetics between L-18F-10B-FBPA and L-10B-BPA will be confirmed. We also designed a basic method for measuring the tumor 10B concentration of L-10B-BPA using L-18F-10B-FBPA for clinical BNCT.

Patients and Methods

Clinical Use of L-18F-10B-FBPA. The performance of L-18F-10B-FBPA PET studies on humans and the quality control of L-18F-10B-FBPA followed the guidelines established by the PET Committee of Nishijin Hospital (Kyoto, Japan) in January 1991. The synthesis method and purification of L-18F-10B-FBPA are detailed in our previous report (9).

Preparation of L-10B-BPA-Fructose Complex. L-10B-BPA is relatively insoluble in water. For i.v. administration, we prepared a L-10B-BPA fructose-complex solution as reported by Yoshino et al. (10). This complex dissociates and reaches an
equilibrium between free molecules and the complex in the diluted condition present in the plasma (Fig. 1B; Ref. 11). The solution of L-\(^{18}\)F-\(^{11}\)B-FBPA-fructose complex consisted of L-\(^{18}\)F-\(^{11}\)B-BPA (1 g):D-(--)-fructose (2.22 g):H\(_2\)O (30 ml):lN NaOH (5.55 ml). Thereafter, the solution was slowly added to 0.8 ml of 1N HCl, and the pH value was adjusted to 7.5. To buffer the solution, 7% NaHCO\(_3\) was added. The molar concentration of HC\(_1\), and the pH value was adjusted to 7.5.

To buffer the solution, 7% NaHCO\(_3\) was added. The spatial resolution in PET imaging was 8.2 mm at full-width half-maximum with plane resolution, whereas the average axial resolution was 12.8 mm. X-ray computed tomography and magnetic resonance imaging were also performed for all patients. Dynamic images of L-\(^{18}\)F-\(^{11}\)B-FBPA were obtained using PET in all cases. PET scans were conducted with a tomograph using a HEADTOME III (Shimadzu Co., Kyoto, Japan). The planes of the PET scans were the same as those in the parallel computed tomography studies. Local cerebral blood volume was measured after bolus inhalation of \(^{13}\)O-labeled carbon monoxide gas (12). A dose of 1–1.5 mCi/10 kg body weight of L-\(^{18}\)F-\(^{11}\)B-FBPA was injected i.v. over 40 s. Dynamic PET study was begun when whole brain activity reached a value greater than that of the background activity. PET data were collected continuously for nine 2-mm periods and six 4-mm periods, making a total of 15 periods over a period of 42 min (Fig. 2, A and B). The four initial arterial blood samples were obtained at 5-s intervals; subsequent samples were obtained at gradually longer intervals (0.5–10 min), making a total of 21 samples over a period of 42 min (Fig. 3A). The time course changes in plasma L-\(^{18}\)F-\(^{11}\)B-FBPA levels were fitted using Equation A (see "Appendix").

Dynamic PET Method. The spatial resolution in PET imaging was 8.2 mm at full-width half-maximum with plane resolution, whereas the average axial resolution was 12.8 mm. X-ray computed tomography and magnetic resonance imaging were also performed for all patients. Dynamic images of L-\(^{18}\)F-\(^{11}\)B-FBPA were obtained using PET in all cases. PET scans were conducted with a tomograph using a HEADTOME III (Shimadzu Co., Kyoto, Japan). The planes of the PET scans were the same as those in the parallel computed tomography studies. Local cerebral blood volume was measured after bolus inhalation of \(^{13}\)O-labeled carbon monoxide gas (12). A dose of 1–1.5 mCi/10 kg body weight of L-\(^{18}\)F-\(^{11}\)B-FBPA was injected i.v. over 40 s. Dynamic PET study was begun when whole brain activity reached a value greater than that of the background activity. PET data were collected continuously for nine 2-min periods and six 4-min periods, making a total of 15 periods over a period of 42 min (Fig. 2, A and B). The four initial arterial blood samples were obtained at 5-s intervals; subsequent samples were obtained at gradually longer intervals (0.5–10 min), making a total of 21 samples over a period of 42 min (Fig. 3A). The time course changes in plasma L-\(^{18}\)F-\(^{11}\)B-FBPA levels were fitted using Equation A (see "Appendix").

Choice of ROIs. All regions of macroscopically necrotic tumor were excluded when ROIs were designated. The variation in radioactivity associated with each pixel was less than 18% of the mean value. Using this as a criterion, we limited macro-

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**Table 1** Rate constants of L-\(^{18}\)F-\(^{11}\)B-FBPA in patients with gliomas

<table>
<thead>
<tr>
<th>Grade</th>
<th>n</th>
<th>(K_1) (ml/g/min)</th>
<th>(k_2) (min(^{-1}))</th>
<th>(k_3) (min(^{-1}))</th>
<th>(k_4) (min(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBM</td>
<td>11</td>
<td>0.040 ± 0.007</td>
<td>0.034 ± 0.009</td>
<td>0.018 ± 0.007</td>
<td>0.011 ± 0.005</td>
</tr>
<tr>
<td>AIII</td>
<td>6</td>
<td>0.039 ± 0.025</td>
<td>0.030 ± 0.013</td>
<td>0.025 ± 0.014</td>
<td>0.011 ± 0.007</td>
</tr>
<tr>
<td>All</td>
<td>4</td>
<td>0.021 ± 0.006</td>
<td>0.030 ± 0.005</td>
<td>0.025 ± 0.005</td>
<td>0.009 ± 0.009</td>
</tr>
<tr>
<td>Control</td>
<td>21</td>
<td>0.011 ± 0.003</td>
<td>0.025 ± 0.009</td>
<td>0.033 ± 0.015</td>
<td>0.009 ± 0.010</td>
</tr>
</tbody>
</table>
Table 2 Segmental convolution method for estimation of the tumor $^{10}$B level

The values shown under “Estimated $^{10}$B” were obtained by the segmental convolution method using rate constants obtained by PET (Equations C–H, see “Appendix”). These $^{10}$B levels were estimated according to the resection time on operation (see Fig. 6). L-$^{10}$B-BPA solution (3.38–113.6 mg/kg body weight) was infused for 20–45 min. “Tumor $^{10}$B” shows the $^{10}$B levels in tumor tissue resected after an infusion of L-$^{10}$B-BPA, as measured using the prompt $\gamma$ method.

<table>
<thead>
<tr>
<th>Case</th>
<th>Grade, total injection dose of L-$^{10}$B-BPA (mg/kg body weight)</th>
<th>Rate constants</th>
<th>Estimated $^{10}$B (µg/ml)</th>
<th>Tumor $^{10}$B (µg/ml)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>All., 51.0</td>
<td>$k_1$ (mL/g/min)</td>
<td>0.031</td>
<td>0.034</td>
</tr>
<tr>
<td>2</td>
<td>GBM, 33.8</td>
<td>$k_2$ (min$^{-1}$)</td>
<td>0.022</td>
<td>0.004</td>
</tr>
<tr>
<td>3</td>
<td>All., 113.6</td>
<td>$k_3$ (min$^{-1}$)</td>
<td>0.027</td>
<td>0.025</td>
</tr>
<tr>
<td>4</td>
<td>GBM, 71.4</td>
<td>$k_4$ (min$^{-1}$)</td>
<td>0.039</td>
<td>0.018</td>
</tr>
<tr>
<td>5</td>
<td>GBM, 83.3</td>
<td>$k_1$ (min$^{-1}$)</td>
<td>0.027</td>
<td>0.011</td>
</tr>
<tr>
<td>6</td>
<td>GBM, 76.9</td>
<td>$k_3$ (min$^{-1}$)</td>
<td>0.035</td>
<td>0.018</td>
</tr>
<tr>
<td>7</td>
<td>GBM, 76.9</td>
<td>$k_4$ (min$^{-1}$)</td>
<td>0.041</td>
<td>0.019</td>
</tr>
</tbody>
</table>

![Fig. 2](image-url) Time-activity data of L-$^{18}$F-$^{10}$B-FBPA and the fitting results. A, time-activity data in the tumor region. B, time-activity data in the normal brain region. Fine dotted lines represent the fitting results obtained by the nonlinear least squares best regression method. The pharmacokinetics of L-$^{18}$F-$^{10}$B-FBPA were analyzed using a three-compartment model, as shown in Fig. 1A. The equation (Equation B in “Appendix”) proposed by Huang et al. (20) is a generalized model of the theorem on which the three-compartment model is based. The nonlinear least squares best regression method was used to obtain the rate constants ($k_1$, $k_2$, $k_3$, and $k_4$). For the nonlinear least squares best regression method, an appropriate initial value is required. The method for obtaining this initial value is described in our previous report (9).

Fig. 2 Time-activity curve of L-$^{18}$F-$^{10}$B-FBPA and the fitting results. A, time-activity data in the tumor region. B, time-activity data in the normal brain region. Fine dotted lines represent the fitting results obtained by the nonlinear least squares best regression method. The pharmacokinetics of L-$^{18}$F-$^{10}$B-FBPA were analyzed using a three-compartment model, as shown in Fig. 1A. The equation (Equation B in “Appendix”) proposed by Huang et al. (20) is a generalized model of the theorem on which the three-compartment model is based. The nonlinear least squares best regression method was used to obtain the rate constants ($K_1$, $K_2$, $K_3$, and $K_4$). For the nonlinear least squares best regression method, an appropriate initial value is required. The method for obtaining this initial value is described in our previous report (9).

**Correction of Blood Concentration Data.** Generally, plasma:whole blood ratios of $^{18}$F radioactivity and $^{10}$B level are 1.3 for both L-$^{18}$F-$^{10}$B-FBPA and L-$^{10}$B-BPA. We determined the time course changes in both ratios. The plasma:whole blood ratios of $^{18}$F radioactivity and $^{10}$B levels changed little over time. Based on these results, we judged it reasonable to treat the ratio as a constant. When $^{10}$B levels of whole blood are measured by the prompt $\gamma$ method, they should be corrected by multiplication using a factor of 1.3, because the input function is based only on plasma concentrations. Ishiwata et al. (13) reported that the amounts of labeled metabolites of L-$^{18}$F-$^{10}$B-FBPA in arterial plasma were small during the 1-h animal experiments. In our human PET studies, the metabolic fractions were negligible during the 42-min period after injection, because we observed that more than 95% of the total radioactivity in plasma was due to the free $^{18}$F-$^{10}$B-FBPA fraction during the 42-min arterial sampling. These findings suggest that plasma metabolite correction is not necessary, and that the metabolism of L-$^{10}$B-BPA can be treated like that of L-$^{18}$F-$^{10}$B-FBPA.

**Three-Compartment Model of L-$^{18}$F-$^{10}$B-FBPA and L-$^{10}$B-BPA.** Our previous data obtained by dynamic PET studies using $^{18}$F-$^{10}$B-FBPA suggested that the time-activity curves reveal a characteristic accumulation of $^{18}$F activity. After a rapid increase to a quasi-steady state, accumulation remained stable (Fig. 2, A and B). When the dynamic PET data were...
Fig. 3  Input functions of L-[18F]-[10B]-FBPA on two differential i.v. administrations. A, all pharmacokinetic analyses were performed by using the input function administered by a bolus injection for 40 s and arterial blood sampling for 42 min after the injection. X axis, time course; Y axis, [18F] radioactivity of plasma or whole blood. Radioactivity in the blood increased rapidly until 1 min after the bolus injection and subsequently decreased rapidly, permitting three-exponential fittings, as shown in Equation A (see “Appendix”). Plasma:whole blood ratios of [18F] radioactivity and the [10B] level are 1.3. We determined the time course changes in ratios. The plasma:whole blood ratios of [18F] radioactivity changed little over time. Based on these results, we judged it reasonable to treat the ratio as a constant (6). B, with slow infusion of L-[18F]-[10B]-FBPA over 20 min, radioactivity in the blood increased gradually and then decreased rapidly after discontinuation of the infusion. In this case, the input function permits two-exponential function, but we adopted the segmental convolution method to obtain the accurate C(t).

Fig. 4  Segmental convolution method for estimation of the tumor [10B] level. The input function [C/i(t)] was obtained by arterial blood sampling. j, segment number; t, time (minutes); C/i(t), the estimated [10B] level at time t; Gj, slope of the first order function, C/p(t); Kj, Y axis intercept of C/p(t).

represented as Gjedde-Patlak plots (14, 15), a positive slope was obtained, suggesting the involvement of the putative metabolic pool of this tracer in tumor cells (9). We used a compartment model that is adapted to a four-parameter model by adding an additional serial tissue compartment with anabolic and reverse process rate constants k3 and k4, respectively; the incorporation into proteins is then described by rate constant k5, but it should be ignored because of less incorporation into proteins (13). This method has already been established as an analytical model of amino acids by Wienhard et al. (16); a similarity in the model analysis between the characteristics of L-(2-[18F])fluorotyrosine in their report and the characteristics of L-[18F]-[10B]-FBPA was found (9, 17–19). Therefore, the pharmacokinetics of L-[18F]-[10B]-FBPA were analyzed using a modified three-compartment model by K1 (ml/g/min), k2 (min⁻¹), k3 (min⁻¹), and k4 (min⁻¹) as shown in Fig. 1A. The equation (Equation B in “Appendix”) proposed by Huang et al. (20) is a generalized model of the theorem on which the three-compartment model is based. The nonlinear least squares best regression method was used to obtain the rate constants (K1, k2, k3, and k4). Using this method of analysis, the rate constants were determined in each glioma patient. Details of the relationship between each rate constant and malignancy were presented in our previous study (9).

Segmental Convolution Method for Estimation of the Tumor [10B] Level. In clinical practice of BNCT, 600–800 ml of L-[10B]-BPA-fructose solution are used, and infusion requires about 60–80 min. Under these conditions, convolution of the time course changes in plasma [10B] concentration in the form of L-[10B]-BPA determined by Equation D (in “Appendix”), as shown in Fig. 4, can be used in Equation C (in “Appendix”). In the segmental convolution method, the estimated values of tissue [10B] concentration of L-[10B]-BPA can be calculated from the values of K1, k2, k3, and k4 obtained by PET using L-[18F]-[10B]-FBPA for each patient or the mean values shown in Table 1. If the [10B] concentration calculated using the rate constant obtained by L-[18F]-[10B]-FBPA PET and the actually measured [10B] input function is close to that in surgical specimens, similarity in pharmacokinetics between L-[18F]-[10B]-FBPA and L-[10B]-BPA will be confirmed. Using this method, we also preoperatively compared the estimated values with the [10B] levels in seven patients with high-grade gliomas (anaplastic astrocytoma.
and GBM). The estimated $^{18}$B levels were obtained using Equations B–H (in "Appendix").

**Results**

**Input Function of L-$^{18}$F-$^{18}$B-FBPA Obtained by Arterial Sampling.** To facilitate the evaluation of pharmacokinetics, a bolus injection of L-$^{18}$F-$^{18}$B-FBPA over 40 s was used for dynamic PET studies. Radioactivity in the blood increased rapidly until 1 min after the bolus injection and subsequently decreased rapidly, permitting three-exponential fittings, as shown in Equation A (Fig. 3A). With the slow infusion of L-$^{18}$F-$^{18}$B-FBPA, radioactivity in the blood increased gradually and then decreased rapidly after discontinuation of the infusion (Fig. 3B). These findings suggest that L-$^{18}$F-$^{18}$B-FBPA is cleared immediately from the blood. Fig. 3B shows the changes in blood radioactivity after a slow infusion of L-$^{18}$F-$^{18}$B-FBPA.

*Fig. 5* Assessment of the suitability of the segmental convolution method. Representative images (A and B) are of patients with glioblastoma. As shown in both A and B, the estimated values by the segmental convolution correspond well with the actual measurements by PET in each case. The estimated curves were plotted by the convolution of the input function $\left[C_1(t)\right]$ of $^{18}$F radioactivity obtained by continual arterial blood specimen collection at the same time, with the mean values of $k_1$–$k_2$ shown in Table 1 substituted into the weight function. $\square$, $C_1(t)$ of tumor lesion based on actual PET study (tumor $^{18}$F level on PET); $\square$, the estimated $C_1(t)$ (the estimated tumor $^{18}$F level). $\circ$, $C_1(t)$ of the normal brain based on actual PET study (normal brain $^{18}$F level on PET); $\bullet$, the estimated $C_1(t)$ (estimated normal brain $^{18}$F level).
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over 20 min. It shows a time-activity curve for l-¹⁸F-¹⁰B-FBPA obtained under conditions similar to those used for BNCT. In BNCT, a large amount of L-¹⁰B-BPA-fructose solution is infused over 60 min. Segmental convolution using Equations C–H therefore seems to be appropriate for slow i.v. infusion.

Pharmacokinetics of l-¹⁸F-¹⁰B-FBPA Determined by PET. Based on the results of dynamic studies, we calculated the rate constants (K₁, k₂, k₃, and k₄) for the three-compartment model in Fig. 1A. Radioactivity in tumor tissue increased rapidly for 20 min after bolus injection and increased gradually thereafter (Fig. 2, A and B). The rate constants obtained are shown in Table 1. When BNCT is performed clinically, L-¹⁰B-BPA is infused at 170–280 mg/kg body weight, and the tumor ¹⁰B level during BNCT is 20–35 µg/ml (in ppm). In this case, estimation of the ¹⁰B level based on Ur* and Ic* is often inappropriate, but segmental convolution of the serially determined plasma ¹⁰B concentrations in Equation D yields accurate estimations (Fig. 4). To use Equation E, K₁, k₂, k₃, and k₄ should be obtained beforehand by PET using l-¹⁸F-¹⁰B-FBPA for each patient, or the mean values shown in Table 1 can be used. The input function of L-¹⁰B-BPA in plasma, Cᵢ*(t), was obtained by the prompt γ measurement connected with the reactor.

Fig. 5, A and B, shows examples of a PET study to assess the suitability of the segmental convolution method. Both images are of patients with glioblastoma. These two patients underwent slow infusions of L-¹⁸F-¹⁰B-FBPA, and we performed a continual measurement by PET and plotted Cᵢ*(t). In this PET measurement, slow infusions of l-¹⁸F-¹⁰B-FBPA were performed under conditions of administration quite similar to those of clinical BNCT. The closed squares show values of Cᵢ*(t) for the tumor obtained from the PET study, and the open squares show the estimated curves, which were plotted by convolution of the input function [Cᵢ*(t)] of ¹⁸F radioactivity obtained by continual arterial blood specimen collection at the same time, with the mean values of K₁–k₄ shown in Table 1 substituted into the weight function. As shown, the values estimated by the segmental convolution method corresponded well with the PET measurements in each case, confirming the suitability of the segmental convolution method.

Therefore, as shown in Table 2, we administered subtherapeutic doses of L-¹⁰B-BPA to seven patients and plotted the estimated curves of the ¹⁰B levels using the method of calculation described above. The estimated curves were calculated by the input function of the ¹⁰B level obtained by continuous arterial blood sampling. Typical examples are shown in Fig. 6, A and B. In the seven cases shown in Table 2, we were able to substitute the proper rate constants determined by PET in Equation C. We compared the estimated values with the ¹⁰B levels in surgical specimens for these seven cases. As shown in Table 2, the estimated values tended to be higher than those for surgical specimens but were similar to them, except in cases 1 and 2. On PET, the highest radioactivity area can be set as the concerned area. As a result, the highest value will be the representative value. On the other hand, in the case of the surgical sample, selection of only a high area of ¹⁰B is impossible. For this simple reason, a discrepancy develops between them. However, in patients from whom a homogenous tumor sample was obtained, the surgical sample is close to the estimated value, and the data are considered as validating the adequacy of the present method.

Discussion

In Vivo l-¹⁰B-BPA Pharmacokinetics Determined with l-¹⁸F-¹⁰B-FBPA PET. In the treatment of gliomas, l-¹⁸F-¹⁰B-FBPA uptake permits clear visualization of the main part of the tumor and helps to determine the extent of tumor resection required. Infiltrating cells are present around the main part of the tumor, and treatment of this area with BNCT is considered to be the most reasonable approach. We assumed that infiltrating cells have the same biochemical properties as cells in the main part of the tumor, which could be
macroscopically observed by PET, and planned the use of thermal neutron irradiation in BNCT. With this concept for PET-based BNCT, clinical application of BNCT using L-\(^{10}\)B-BPA was successful. L-\(^{10}\)B-BPA is cleared rapidly from the blood but is retained in tumor tissue and actively taken up by proliferating cells. Its accumulation in tumors was demonstrated by dynamic PET using L-\(^{18}\)F-\(^{10}\)B-FBPA (6, 9). An important factor in BNCT is the determination of the \(^{10}\)B concentration in both the tumor tissue and normal brain. An increase in the tumor:normal ratio increases the efficacy of BNCT, because it allows a greater tumor dose to be delivered per dose administered to normal tissue, and the tumor dose is limited by normal tissue tolerance (4). Appropriate indications for BNCT include a tumor:normal ratio above 2.5 (21). We studied the factors contributing to accumulation. An increase in \(K_1\) is the principal factor affecting the accumulation of L-\(^{18}\)F-\(^{10}\)B-FBPA (6, 9). As described above, L-\(^{18}\)F-\(^{10}\)B-FBPA accumulation is accomplished within 42 min after bolus i.v. injection in dynamic PET studies. The rapid achievement of equilibrium (within 42 min) was attributed to \(K_1\). When PET scans were performed in patients with high-grade gliomas during 1–2 h after injection, we found a decrease in radioactivity in the tumor region after a while (Fig. 7). This seemed to be due to catabolism, as suggested by the action of \(k_4\) in the tumors. X axis, time (minutes); Y axis, \(^{18}\)F activity.

**Fig. 7** Differences in the courses of time-activity curves between tumor lesion and normal brain tissue. The time-activity curves of \(^{18}\)F (in cps/ml) were real data obtained in a patient with GBM. When PET scans were performed 1–2 h after the injection, we found a decrease in radioactivity in the tumor region after a while. This seemed to be due to the catabolic process, as suggested by the action of \(k_4\) in the tumors. X axis, time (minutes); Y axis, \(^{18}\)F activity.

level is maintained by \(k_1\) and decreased by \(k_4\) in tumor tissue after a while. Although a similar process occurs in normal tissue, normal tissue has a higher \(k_3\) (0.033 ± 0.015) than does tumor tissue (GBM, 0.018 ± 0.007; AIII, 0.025 ± 0.014). Fig. 7 shows that differences between tumor and normal tissue in time course changes decreased with time in the L-\(^{18}\)F-\(^{10}\)B-FBPA study. This suggests that \(^{10}\)B levels in normal tissue gradually approach the tumor \(^{10}\)B level as a result of the higher \(k_3\) value in normal tissue. It may be appropriate to start BNCT when the difference in \(^{10}\)B concentration between normal tissue and tumor is marked.

**Pathological Features and Pharmacokinetics.** There are some important problems regarding pathological features and pharmacokinetics in gliomas. One of them is whether the cellularity of the tumor sample relates to the boron content. In general, the cellularity of tumors is the standard of malignancy. The detailed comparison of malignancy and L-\(^{18}\)F-\(^{10}\)B-FBPA uptake was described in our previous report (9). Elowitz et al. (23) also referred the correlation. However, because microscopic heterogeneity is observed in tumor tissues, a numerical determination of the tumor cellularity using a part of the tumor tissues is generally difficult, although the cellularity can be classified into various stages based on the evaluation of pathologists. Therefore, we did not compare the cellularity with the boron contents. We also recognize that classifying the cellularity by certain numerical indices is an important subject to understand the detailed mechanism of \(^{10}\)B-BPA uptake and the protection of the brain. Regarding these subjects, future experiments should be performed to solve this problem, including the administration of a compound, a cell population marker as a positron tracer, and a simultaneous scan by L-\(^{18}\)F-\(^{10}\)B-FBPA. Then, discussion comparing the results of positron tracer administration with scanning data is thought to be necessary.

Another problem is that if only a relatively small percentage of the tumor cells are undergoing mitosis at any one time, then the uptake of L-\(^{18}\)F-\(^{10}\)B-FBPA would significantly underestimate the true size of the tumor. When we investigated the relationship between the malignancy of the tumor and L-\(^{18}\)F-
10B-FBPA uptake, it was clinically found that the malignancy is greatly dependent on the capacity of amino acid transport by tumors. However, we have encountered cases of low-grade tumors with marked amino acid uptake. It was considered that these low-grade tumors might correspond to metabolically active nonproliferating cells. Furthermore, although these tumors were pathohistologically classified as low grade, the prognoses of the patients were unsatisfactory (9). In general, however, macroscopic analysis is the objective level for the methodology described here, and it is difficult to differentiate the small percentage of metabolically active cells included in the entire tumor mass. Because there is the possibility of underestimating regions with the proliferating potential, treatment of this area with BNCT should be considered as a concept of the target area.

Conditions for Quantitative Measurement of Tissue 10B Levels in Clinical BNCT. We found that the segmental convolution method is appropriate for clinical BNCT. This method uses two different modalities. Equation E involves data from PET and the prompt γ method. The rate constants obtained by PET are used in the weight function in Equation C. The input function describing changes over time in 10B levels, \( C_{p}(t) \), is also involved in Equation C. In the present study, when we compared the 10B values estimated by PET with those of surgical specimens, the estimated values were found to be very close to the 10B levels in the surgical specimens, as shown in Table 2. The similarity between L-18F-10B-FBPA and L-10B-FBPA in their pharmacokinetics was thus verified. Therefore, the proper rate constants for L-10B-FBPA in each subject were regarded as similar to those for L-18F-10B-FBPA obtained by PET (Fig. 1, A and B).

When actually performing BNCT, we must reconfirm the tumor 10B level by measurement of L-10B-BPA in arterial blood. As mentioned above, the input function of L-10B-BPA can be determined by blood sampling during this 1–2 h. The tumor 10B level can be more precisely determined by convoluting the input function of \( C_{p}(t) \) to Equations B–E using \( K_{1}, k_{2}, k_{3}, \) and \( k_{4} \). In evaluating indications for BNCT, \( I_{c^{*}} \) and \( U_{r^{*}} \) are useful for estimating the dose of L-10B-BPA required (6), but the tumor 10B level calculated by the segmental convolution method based on the prompt γ measurement is more reliable for the performance of BNCT.

In the former (6) and the present studies, we evaluated two different methods of estimating 10B concentration. The first method permits estimation by PET alone and is useful for determining the indications for BNCT. In the second method, the proper rate constant for brain tumors is used, and the 10B concentration in tumor tissue is obtained using the input function for plasma 10B concentration. This method is useful for the performance of clinical BNCT, and with it, tissue concentration can be measured even after slow infusion. Systematic PET-based BNCT is possible using one or the other of these two methods according to the purpose. With the first method, the administered dose of L-10B-BPA can be estimated for individual patients by PET, and patients can be selected for future BNCT. With the second method, the concentration in the tumor can be accurately determined at the time of neutron irradiation using L-10B-BPA, and the method is widely suitable for clinical BNCT, because the averaged PET data as shown in Table 1 are enough to use in future patients without individual PET study. The development of this PET-based BNCT system has made it possible for us to perform BNCT accurately using reliable objective data. Using this system, we have performed BNCT with thermal neutrons on patients with high-grade gliomas (24, 25).

In conclusion, tumor 10B levels can be more accurately determined by convoluting the input function to the weight function using rate constants. The similarity in pharmacokinetics between L-18F-10B-FBPA and L-10B-FBPA was also confirmed. Using the PET-based BNCT system described here, clinical performance of BNCT using L-10B-FBPA is possible here.

Acknowledgments

We acknowledge the technical support and effort of Kazuo Wakita and Hitoshi Horii (Cyclotron Unit, Nishinjih Hospital, Kyoto, Japan). We gratefully thank Dr. Kiichi Ishiwata (PET Center, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan) for helpful advice regarding L-18F-10B-FBPA synthesis and its biological properties.

Appendix

\[ C_{p}(t) = \sum_{i=1}^{3} a_{i}e^{-\lambda_{i}t} \]  
\[ C_{i}(t) = \frac{K_{1}}{(\alpha_{2} - \alpha_{1})} \left[ (k_{3} + k_{4} - \alpha_{1})e^{-\lambda_{1}t} \right] \]  
\[ + (\alpha_{2} - k_{3} - k_{4})e^{-\lambda_{4}t} \]  
\[ \oplus C_{p}(t) \]

with

\[ \alpha_{1} = \left[ \frac{k_{2} + k_{4} - \sqrt{(k_{2} + k_{4})^{2} - 4k_{2}k_{4}}}{2} \right] \]
\[ \alpha_{2} = \left[ \frac{k_{2} + k_{4} + \sqrt{(k_{2} + k_{4})^{2} - 4k_{2}k_{4}}}{2} \right] \]  
\[ C_{i}(t) = \left( A e^{-\alpha_{1}t} + B e^{-\alpha_{2}t} \right) \oplus C_{p}(t) \]

with

\[ A = \frac{K_{1}}{(\alpha_{2} - \alpha_{1})} (k_{2} + k_{4} - \alpha_{1}) \]
\[ B = \frac{K_{1}}{(\alpha_{2} - \alpha_{1})} (\alpha_{2} - k_{3} - k_{4}) \]  
\[ t_{j} - 1 < t < t_{j} \]
\[ C_{p}(t) = G_{j} + K_{j} \]  
\[ C_{i}(t) = \int_{0}^{t} (A e^{-\alpha_{1}t} + B e^{-\alpha_{2}t} \times (G_{j} + K_{j}) dt \]

\[ C_{i}(t) = \frac{AG_{j}}{\alpha_{1}} (e^{-\alpha_{1}t} + \alpha_{1}t - 1) + \frac{BG_{j}}{\alpha_{2}} (e^{-\alpha_{2}t} + \alpha_{2}t - 1) \]
\[ - \frac{AK_{j}}{\alpha_{1}} (e^{-\alpha_{1}t} - 1) - \frac{BK_{j}}{\alpha_{2}} (e^{-\alpha_{2}t} - 1) \]
\[ \Delta C_{i}(t) = C_{i}(t) - C_{i-1}(t) \]  
\[ \Delta C_{i}(t) = C_{i}(t) - C_{i-1}(t) \]
\[ C(t) = \sum_{i=1}^{n} \Delta C_i(t) \]  

\[ \text{References} \]

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