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Prediction of Boron Concentrations in Blood from Patients on Boron Neutron Capture Therapy

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Abstract. *Background: In boron neutron capture therapy, blood boron concentration is the key factor to calculate radiation dose, however, blood sampling is difficult during neutron irradiation. Materials and Methods: The prediction of blood boron concentrations for BNCT treatment planning has been prospectively investigated using patient data obtained at first craniotomy after the infusion of a low dose of sodium undecahydroclosododecaborate. Results: The boron biodistribution data showed a biexponential pharmacokinetic profile. If the final boron concentration at 6 or 9 hours after the end of the infusion is within the 95% confidence interval of the prediction, direct prediction from biexponential fit will reduce the error of blood boron concentrations during irradiation to around 6%. Conclusion: Actual boron concentrations during BNCT were reasonably and accurately predictable from the test data.*

Glioblastoma is one of the most difficult malignant brain tumors to treat. Although many researchers have attempted different therapeutic modalities for malignant brain tumors, the prognosis for patients with glioblastoma is still extremely poor (1, 2). Boron neutron capture therapy (BNCT) is an experimental radiation therapy with the major target being glioblastoma (3, 4). In this treatment, selective accumulation of the boron compound in tumor cells along with sufficient thermal neutron irradiation are the key factors to the delivery of an effective dose to the tumor cells. Clinical trials of BNCT for patients with glioblastoma are presently in progress, and many reports indicate the need for further clinical trials of BNCT (5-11). At present, nuclear reactors constitute the only source that can provide enough neutron flux for BNCT.

At the Brookhaven National Laboratory, BNCT irradiation is interrupted transiently at approximately the mid-point of irradiation and blood samples taken. The average blood boron concentration during BNCT is calculated by linear extrapolation of the boron concentrations obtained from blood samples collected at the start, in the middle, and at the end of BNCT irradiation (7, 8). In Japan, venous blood is sampled before and after the irradiation (10). The interruption of irradiation may be time-consuming and costly. Moreover, it may make it difficult to accurately calculate neutron fluence and simple linear extrapolation of the boron concentrations might not represent the exact boron dynamics.

In the Harvard-MIT clinical BNCT trial, blood samples were drawn from the long central venous line during neutron irradiation (12). Sampling blood from the long central venous line is not easy because of the risk of coagulation in the line, which might cause distal embolism. In order to prevent blood from coagulating in the long central venous line, the researchers used heparin in the venous catheter. This clinical BNCT trial for patients with brain tumors did not include a craniotomy during the neutron irradiation, so it is possible that the local use of heparin did not constitute any risk. The protocol at the University of Tsukuba, Japan, and the Japan Atomic Energy Research Institute (JAERI) involves the intra-operative use of thermal neutron irradiation. Thus, even if the amount of heparin used was small, the risk of hemorrhagic complications should be taken into consideration.

Nine patients with either glioblastoma or anaplastic astrocytoma have already been treated in this study using BNCT. In the protocol, each patient was first subjected to an open craniotomy to remove as much of the tumor as possible and to establish the pathological diagnosis. After

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Table I. *Details of patients*

No.	Age/Sex	Histology	BNCT	Test dose(g)	Final dose(g)
1	45/M	Glioblastoma	JRR2	1	5
2	55/F	Glioblastoma	JRR4	1	5
3	48/F	Glioblastoma	JRR4	1	5
4	66/M	Anaplastic astrocytoma	JRR4	1	5
5	38/F	Glioblastoma	JRR4	1	8
6	64/F	Glioblastoma	JRR4	1	5
7	58/F	Anaplastic astrocytoma	JRR4	1	5

BNCT: boron neutron capture therapy
JRR: Japan Research Reactor

the tumor was pathologically diagnosed as glioblastoma or anaplastic astrocytoma, the patient was considered eligible for the BNCT protocol. Just prior to the BNCT irradiation procedure, all the patients were placed under general anesthesia for a second open craniotomy in the operating room at JAERI. Patients were transported to a neutron irradiation room that was tightly sealed and had a full life monitoring system (5). Neutron irradiation usually lasted for 2 hours and, during this time, general anesthesia and life monitoring were maintained from outside the irradiation room. The irradiation time was determined by the boron concentration in the venous blood drawn from the patient just prior to neutron irradiation and by the neutron fluence measured using activation analysis of gold wires that were drawn from the irradiated area during neutron irradiation.

During neutron irradiation, it was difficult to measure boron concentration in the blood because the patient was in the irradiation room and entry was not possible for blood sampling. Therefore, we took a blood sample just prior to the neutron irradiation and measured the blood boron concentration by prompt gamma ray analysis (PGA). If the decline of the blood boron concentration during treatment could be predicted prior to neutron irradiation, we would be able to set the irradiation time and doses more effectively. Based on the data collected from these patients, we prospectively investigated boron pharmacokinetics in a candidate for BNCT at the first craniotomy after infusion of a low dose of boron and analyzed the possibility of predicting the final boron concentration in blood at the time of the actual BNCT procedure.

Materials and Methods

Two patients were treated with BNCT at the Japan Research Reactor 2(JRR2) in 1995/1996, and 7 at the Japan Research Reactor 4(JRR4) in 1999-2001. Of these 9 patients, seven were investigated in this study. The other 2 patients were excluded because the first operation had been performed at other institutions. The details of the patients are summarized in Table I. All patients had normal renal function.

Sodium undecahydroclosododecaborate (BSH) was purchased from Boron Biologicals Inc. (Mt Airy, NC, USA), and Katchem Ltd. (Praha, Czech Republic). According to the certificate of analysis provided from Boron Biologicals Inc. and the Institute of Inorganic Chemistry, Academy of Sciences of the Czech Republic, B10 enrichment was 92.0% and 99.7%, respectively. One gram of BSH dissolved in 100 ml physiological saline was infused over 1 hour at 12 hours before the first surgery in the seven patients. Of the 100ml, an aliquot of 2.5ml was reserved and used for a boron concentration check in four cases. Venous blood was sampled 1, 3, 6, 9 and 12 hours after the infusion in all cases and 24 hours in the 5 most recent cases. As for case 1, we failed to obtain the data for the 9-hour time-point after the infusion. At the time of the first operation, tumor tissue was assayed for the boron concentration. Boron concentrations in the BSH solution, blood and tumor were examined using PGA or inductively coupled plasma atomic emission spectroscopy (ICP-AES). In this study we used only PGA data, because we believed PGA data were more reliable than ICP-AES data which do not consider B10 enrichment of the boron compounds. All PGA data presented in this paper are the mean value of several measurements of each sample. All boron concentration data in blood were corrected using their respective B10 enrichment calculated as the ratio of the actual and expected boron concentrations.

BNCT was scheduled for about 1 month after the first operation. The amount of infused BSH was determined based on the dose of 100 mg of BSH/ kg body weight; thus 5g of BSH was infused in all cases, except for case 5 where 8g of BSH was infused, 12 hours prior to BNCT. BSH was dissolved in 500 ml physiological saline and infused over 1 hour. Of the 500 ml solution, an aliquot of 2.5 ml was reserved and used for the boron concentration check, except in 2 cases. Venous blood was sampled 1, 3, 6, 9 and 24 hours after the end of the infusion and just before and after neutron irradiation. Boron concentrations in venous blood were examined using PGA and ICP-AES.

All these procedures complied with the principles laid down in the Declaration of Helsinki, and were approved by the Ethical Committee of the University of Tsukuba and JAERI. A written informed consent was obtained from all the patients and their family in this study.

To compare the data from test dose infusion and final dose infusion, the test data were adjusted by simple multiplication. If the final dose of BSH was 5g, the figure from the test dose infusion was multiplied by 5, assuming pharmacological dose *vs.* blood concentration linearity. Four-parameter biexponential equations were fitted using the least squares fit through points. This regression analysis was carried out using Sigma Plot 2000 software (SPSS Science, Chicago, IL, USA). The errors between real and predicted values of blood boron concentration were evaluated.

Results

Biexponential equation. Each patient showed a biexponential blood clearance pharmacokinetic profile composed of an initial rapid decline followed by a slow wash out (Figure 1). The correlation indexes between the original data and the fitted curves were >0.99 in all cases. From this biexponential

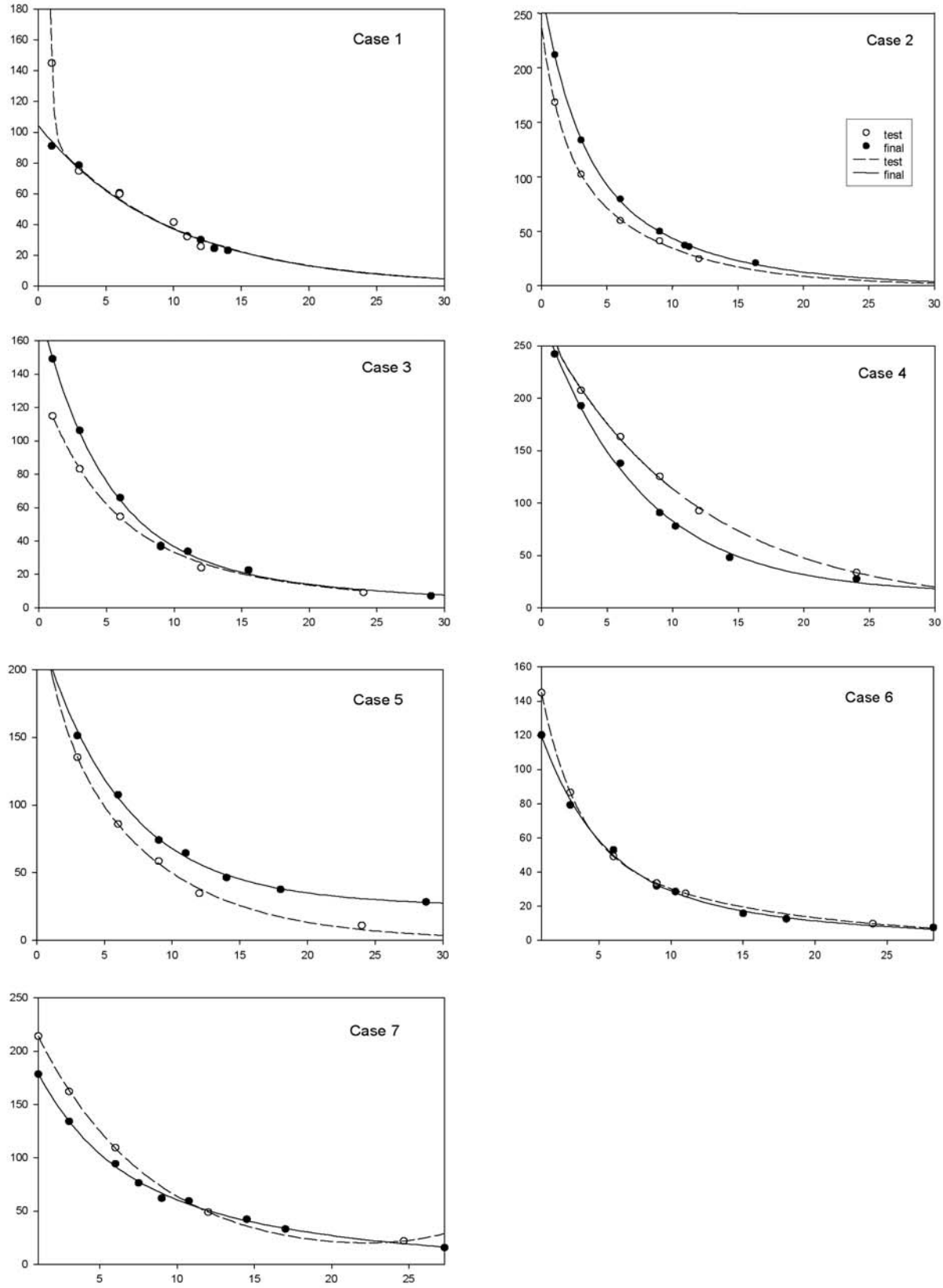

Figure 1. *The predicted and actual blood concentration of boron for each case.*

equation, the 95% confidence intervals of the prediction were calculated. Most final data of boron concentration between 1 and 9 hours after the end of infusion were within the 95% confidence interval of the prediction. However, the final data of boron concentrations of case 4 between 6 and 9 hours after the end of the infusion, and those of case 5 between 3 and 9 hours after the end of the infusion were outside the 95% confidence interval of the prediction.

Errors of predicted values. In our protocol, neutron irradiation is carried out about 12 hours after the end of BSH infusion. This time window was selected because the highest tumor-to-blood ratios are obtained at this time-point (13, 14), therefore boron concentrations within this time period should be predicted accurately. Because the data from the test dose infusion can be used to predict the boron concentration during neutron irradiation, these data were used to evaluate the errors in predicting the final boron concentrations.

The mean and median error of the blood boron concentrations determined between 10 and 14 hours after the BSH infusion were 15.77 and 11.76%. Errors of more than 20% were observed only in Cases 4 and 5. In these 2 cases the final boron concentrations at 6 and 9 hours after the end of the infusion were out of the 95% confidence interval of the prediction. The mean and median error of the blood boron concentrations determined between 10 and 14 hours after the BSH infusion in the other five cases were 8.54 and 6.38%.

In order to reduce the error of prediction, we attempted a proportional adjustment of the predicted value to fit the final value by multiplying the ratio of the predicted and final values at the 9-hour determination point. After this adjustment, the mean and median error of the blood boron concentrations determined between 10 and 14 hours after the BSH infusion were 10.50 and 11.54% for all cases, and 17.73 and 11.99% for case 4 and case 5.

From these results, the following strategies are recommended to predict boron concentration in blood. If the final boron concentration at 6 or 9 hours after the end of the infusion is within the 95% confidence interval of the prediction, direct prediction from biexponential fit will bring the error to around 6%. If the final boron concentration at 6 or 9 hours after the end of the infusion is out of the 95% confidence interval of the prediction, adjustment will decrease the error and the expected error will be between 10 to 17%.

Following is an illustrative case report showing that our prediction method using test infusion data was useful to determine irradiation time and doses. We usually set the maximum reactor power to 2MW. Case 4 showed a relatively slow wash out of BSH in a test biodistribution study, even though this patient had normal renal function. We therefore decreased the maximum reactor power from the usual 2MW to 1.5MW. As a result, the neutron flux on the brain surface of this patient was 1.84E9 $cm^{-2}sec^{-1}$. The mean brain surface neutron flux of the other 4 patients who were irradiated at 2MW atomic reactor power in JRR4 was 2.38E9±2.33E8 $cm^{-2}sec^{-1}$. Using this low neutron flux, we could safely complete the BNCT procedure for this patient with a relatively high boron concentration in blood, in the usual irradiation time.

Tumor boron concentration and dose calculation. Several tumor samples were taken to determine the boron concentration during the first operation. Usually the boron concentration in the tumor varies because of tumor heterogeneity. There are many discussions regarding tumor sampling and tumor dose calculations. We calculated the $^{10}B(n,\alpha)^{7}Li$, $^{14}N(n,p)^{14}C$, fast neutron and gamma dose for both normal tissue and tumor in every case; however, these values depend, in part, on the methods of measurement and calculation. Because tumor boron concentration and dose calculation are beyond the scope of the present study, we have only discussed blood boron concentration in this paper.

Discussion

In our study, the single parameter biexponential equations and the approximate curves fit well for all data. The correlation indexes between the original data and the approximate curves were greater than 0.99 in all cases. These findings suggest that the blood clearance of BSH is biexponential and biphasic, and that actual measurement at some time-points is sufficient for drawing these curves. All previous reports have found that the blood clearance of BSH is biphasic (11, 13-19) or triphasic (20, 21).

Gabel *et al.* reported that the blood boron concentration showed a linear correlation with the BSH dose infused (16). The present results support their findings. Using the proposed prediction method, the median error of boron concentration was 11.76% up to 14 hours after the BSH infusion. Thus, we were able to predict the boron concentration after the infusion of a full dose of BSH from the boron concentrations measured after infusion of 1 g of BSH with an estimated accuracy of about 90%. The final boron concentration at 6 or 9 hours after the end of infusion was within the 95% confidence intervals of the prediction for 5 out of 7 cases. For these cases, the prediction error from low-dose infusion was 6.38%. There must be many causes for the discrepancy between the test and final data. Many factors, such as renal function, the volume of drip infusion, the usage of diuretics, *etc.*, can influence the clearance of blood boron. These factors might have varied significantly in the 2 cases in which the prediction errors were large. Although it is impossible to control all physiological factors in a clinical setting, 5 of the 7 cases studied here showed a

good correlation between the test and final boron pharmacokinetics. Further investigations should be performed to determine the factors influencing the errors seen in the present study. These factors should be controlled in the same manner in future studies. Even though PGA measurement appears to be reliable, reproducible and sensitive, the measurement error of PGA should be clarified in the future and the measurement method of boron concentration needs to be improved to reduce errors.

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