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L-phenylalanine preloading reduces the $^{10}B(n, \alpha)^{7}Li$ dose to the normal brain by inhibiting the uptake of boronophenylalanine in boron neutron capture therapy for brain tumours

Tsubasa Watanabe [a,b], Hiroki Tanaka [a], Satoshi Fukutani [c], Minoru Suzuki [a], Masahiro Hiraoka [b], Koji Ono [c,*]

[a] Particle Radiation Oncology Research Center, Kyoto University Research Reactor Institute, Osaka 590-0494, Japan
[b] Department of Radiation Oncology and Image-Applied Therapy, Kyoto University, Kyoto 606-8501, Japan
[c] Department of Nuclear Science and Engineering, Kyoto University Research Reactor Institute, Osaka 590-0494, Japan

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ABSTRACT

Boron neutron capture therapy (BNCT) is a cellular-level particle radiation therapy that combines the selective delivery of boron compounds to tumour tissue with neutron irradiation. Previously, high doses of one of the boron compounds used for BNCT, L-BPA, were found to reduce the boron-derived irradiation dose to the central nervous system. However, injection with a high dose of L-BPA is not feasible in clinical settings. We aimed to find an alternative method to improve the therapeutic efficacy of this therapy. We examined the effects of oral preloading with various analogues of L-BPA in a xenograft tumour model and found that high-dose L-phenylalanine reduced the accumulation of L-BPA in the normal brain relative to tumour tissue. As a result, the maximum irradiation dose in the normal brain was 19.2% lower in the L-phenylalanine group relative to the control group. This study provides a simple strategy to improve the therapeutic efficacy of conventional boron compounds for BNCT for brain tumours and the possibility to widen the indication of BNCT to various kinds of other tumours.

Introduction

Boron neutron capture therapy (BNCT) is based on the principle that ^{10}B nuclei capture thermal neutrons with high propensity, which leads to the production of two high linear energy transfer particles (^{4}He, 163 keV/μm and ^{7}Li, 210 keV/μm) whose range is limited to the diameter of a single cell (5–9 μm). Theoretically, therefore, BNCT offers the possibility of targeting single tumour cells with less normal tissue damage than conventional therapy if ^{10}B atoms are selectively concentrated in each tumour cell.

The boron compounds commonly used for BNCT exhibit incomplete tumour selectivity. Two boron compounds are currently used in clinical studies of BNCT: disodium mercaptoundecahydro-closo-dodecaborate and L-4-dihydroxy-borylphenylalanine (L-BPA) [1,2]. L-BPA is a derivative of the neutral amino acid phenylalanine, and previous studies have reported that L-BPA transport is mainly undertaken by system L amino acid transporters (LAT) [3,4]. However, the tumour tissue to normal tissue boron concentration ratio (T/N ratio) of L-BPA is not ideal to eliminate tumour tissue in all patients.

Several BNCT studies have described ways to enhance tumour uptake of L-BPA or to decrease the relative accumulation of L-BPA in normal tissue, such as the concomitant use of other substances with L-BPA [5,6] and the optimisation of the L-BPA prescription dose [7]. Morris and colleagues examined the effect of the L-BPA prescription dose on the central nervous system using a rat spinal cord model [7]. The authors reported that 1600 mg L-BPA/kg can increase the blood boron concentration while maintaining a relatively lower boron level in the central nervous system, thereby increasing the normal tissue to blood ratio of boron concentration (N/B ratio). The authors claimed that higher radiation doses can be delivered to the tumour without increasing the radiation-induced damage to the brain through the use of high-dose L-BPA. From a clinical standpoint, however, high-dose L-BPA infusion is not feasible because the renal excretion capacity is limited and because high-dose L-BPA infusion corresponds to high-dose volume infusion, which leads to increases in cardiac afterload and the risk of heart failure. The maximum L-BPA dose ever administered to a human being was 900 mg/kg given over 6 hours for high-grade glioma in Sweden [8].

Abbreviations: BNCT, boron neutron capture therapy; L-BPA, L-4-dihydroxy-borylphenylalanine; LAT, system L amino acid transporters; T/N ratio, tumour to normal tissue boron concentration ratio; N/B ratio, normal tissue to blood ratio of boron concentration; RBE, relative biological effectiveness; CBE, compound biological effectiveness; T/B ratio, tumour to blood ratio of boron concentration.

* Corresponding author. Tel.: +81 75 451 2390; fax: +81 75 451 2627.
E-mail address: onokoji@rri.kyoto-u.ac.jp (K. Ono).

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Considering the tissue structure of tumour and the brain, the advantageous effects of high-dose L-BPA are attributed to the difference in the rate of uptake/clearance of L-BPA through LAT between tumour tissue and the blood–brain barrier. With this perspective, we examined the effects of LAT substrates on L-BPA distribution in vivo and investigated an alternative method of high-dose L-BPA to enhance T/N ratio and to decrease the N/B ratio for BNCT, thereby decreasing normal tissue damage.

Materials and methods

Materials

L-BPA enriched with more than 95.0% ^{10}B isotope was kindly supplied by the Stella Pharma Corporation (Osaka, Japan). SCC-VII cells ($3.0 * 10^5$) were inoculated subcutaneously into the left hind legs of four-week-old female C3H/He mice (CLEA Japan, Tokyo, Japan). The experiments were performed two weeks after inoculation, when each tumour had reached approximately 1 cm in diameter. The mice were handled according to the recommendations for the Handling of Laboratory Animals for Biomedical Research, compiled by the Committee on Ethical Handling Regulations for Laboratory Animal Experiments, Kyoto University. All animal experiments were conducted in accordance with the institutional laboratory animal handling guidelines.

The L-BPA and amino acid administration protocol and measurements of boron concentration

L-BPA was used in the solution as a fructose complex, the preparation of which has been previously described [9]. Each amino acid solution used in this study was dissolved in distilled water before administration. Hydrophobic amino acids were dissolved in distilled water prior to administration by gently heating to less than 80 °C to solubilise the compounds. One millilitre of each concentration of amino acid solution (1000 mg/kg in experiment 1; 50, 100, 250, 500, 1250, and 2500 mg/kg in experiment 2) was administered orally after a 3-hour fast. Thirty minutes later, the mice were injected with L-BPA–fructose solution subcutaneously into nuchal sites. One hour after L-BPA injection, a blood sample was collected by cardiac puncture, and the mice were euthanised by cervical dislocation. Tissue samples were excised immediately and placed in test tubes. Three mice were used at each dose point.

The blood and tissue samples were digested with perchloric acid (60%) and hydrogen peroxide (30%) for 24 h at 75 °C. The boron concentrations in each sample were measured by inductive coupled plasma atomic emission spectrometry with iCAP 6000 (Thermo Fisher Scientific Inc., Massachusetts, USA) and were normalised as μg/g.

Experiment 1: screening

According to the protocol, 500 mg L-BPA/kg and 1000 mg/kg of various substrates for LAT were administered [5]. The N/B ratios of the normal tissues were compared with those of the control group.

Experiment 2: an examination of the dose-dependent effects of L-phenylalanine on the uptake of boron compounds

The effect of preloading with various concentrations of L-phenylalanine before L-BPA injection (250 mg/kg) on L-BPA accumulation in tissues was examined. Aqueous solutions of L-phenylalanine were prepared at 50, 100, 250, 500, 1250, and 2500 mg/kg in 1 mL of water.

Radiation dose calculation

The total physical radiation dose is given by the equation:

$$\text{Physical dose (Gy)} = D(^{10}B) + D(^{14}N) + D(H) + D(\gamma)$$

$$D(^{10}B) = 7.43 * 10^{-14} * (\text{boron concentration } (\mu g/g)) * \varphi(th)$$

$$D(^{14}N) = 6.78 * 10^{-14} * (\text{nitrogen concentration (weight \%)}) * \varphi(th),$$

where B and N stand for boron and nitrogen. D(^{10}B), D(^{14}N), and D(H) are the physical doses from the reactions of ^{10}B(n, α)^{7}Li, ^{14}N(n, p)^{14}C, and ^{1}H(n, n')^{1}H, respectively. D(γ) comes from the induced absorbed gamma dose and the background gamma dose from the beam source. φ(th) is the thermal neutron fluence rate. The weight fraction of nitrogen was estimated to be 2.2%. The values $7.43 * 10^{-14}$ and $6.78 * 10^{-14}$ represent the karma factors for ^{10}B and for ^{14}N, respectively [10].

The relative biological effectiveness (RBE) factor is the multiplier of the physical dose from a particular radiation source to produce the same biological effect relative to X-ray as a reference radiation. The compound biological effectiveness (CBE) factor is a parameter that is calculated in a similar way to the RBE and is defined experimentally as the multiplier of the physical dose from ^{10}B(n, α)^{7}Li as follows [11]:

$$\text{CBE factor} = \{\text{X-ray } ED_{50} - (\text{Thermal beam } ED_{50} * RBE)\} / {}^{10}B(n, \alpha)^7 \text{ Li } ED_{50}$$

ED_{50} is the median effective dose calculated from the dose–effect curves. The CBE used in this study was 3.8 for tumour tissue [12]. The CBE for the central nervous system was taken from a report of the CBE values at each variable dose of L-BPA with correction for the RBE value from the X-ray [7]. The RBE of nitrogen, hydrogen, and γ-ray are 3.0, 3.0, and 1.0, respectively. Finally, the biologically equivalent dose for BNCT (Gy-eq) is calculated as follows:

$$\text{Total dose (Gy-eq)} = D(^{10}B) * CBE + D(^{14}N) * RBE(\text{nitrogen}) + D(H) * RBE(\text{hydrogen}) + D(\gamma) * RBE(\gamma\text{-ray})$$

The differences between the brain dose and the tumour dose among the control and the L-phenylalanine groups were calculated under two conditions. In condition 1, the peak dose in the brain was calculated assuming that the same point dose on the axis was set to the tumour tissue. This approach reflects the amount of irradiated dose in the brain that can be reduced from the L-phenylalanine prescription compared to the control group. In condition 2, the limitation dose was equally set in the brain at 12 Gy-eq, and the advance depth, which is defined as the depth where the tumour dose equals 20 Gy-eq, was calculated in the control and L-phenylalanine groups.

Statistical analysis

The data are expressed as the mean ± standard deviation. The differences between the experimental and control groups were analysed by Dunnett's test to correct for multiple comparisons. P values less than 0.01 were considered statistically significant. All of the statistical analyses were performed with JMP Pro 11 software (SAS Institute Inc., Cary, NC, USA).

Results

Experiment 1: L-phenylalanine antagonise the uptake of L-BPA in the brain

Table 1 presents the screening results of various amino acids. L-phenylalanine exhibited inhibitory effects on the uptake of L-BPA, especially in the brain. The N/B ratio of the brain in the L-phenylalanine group decreased to 41.0% relative to that in the control group. Other amino acids did not exhibit any remarkable effect on the N/B ratio.

Experiment 2: the dose-dependent effects of L-phenylalanine on L-BPA distribution

Fig. 1 presents the dose-dependent effects of L-phenylalanine on the N/B ratio and the tumour to normal tissue boron concentration ratio (T/N ratio). Low-dose L-phenylalanine exhibited no effect on L-BPA uptake in normal tissues or in the tumour tissues. However, high-dose L-phenylalanine dramatically inhibited L-BPA uptake in the brain relative to the tumour tissue. Therefore, the T/N ratios of the 1250 mg/kg and 2500 mg/kg L-phenylalanine groups were significantly increased relative to that of the control group ($p < 0.01$). No apparent change was observed with respect to the T/N ratio in the liver and tongue despite the significant decrease of boron concentrations in these organs. This result was due to the similar responses to high-dose L-phenylalanine preloading between tumour tissue and these organs regarding the uptake of L-BPA. Therefore, the reduction in the boron concentration in the liver and tongue was proportional to that in the tumour tissue and reduction rate of boron concentrations.

Radiation dose calculations using the change in the T/N and N/B ratios by L-phenylalanine

Fig. 2 presents radiation dose components in the control group and high-dose L-phenylalanine group. The maximum brain dose of the L-phenylalanine group decreased below that of the control group

Table 1
The percentage decrease in the effects of preloading amino acids prior to L-BPA administration.

	Blood	Liver	Stomach	Jejunum	Skin	Tongue	Brain
Control (L-BPA only) (μg/g)	16.99 ± 0.85	14.00 ± 1.75	24.73 ± 3.16	22.16 ± 3.59	9.03 ± 0.30	36.93 ± 2.26	6.55 ± 0.26
N/B ratio	–	0.82	1.46	1.30	0.53	2.17	0.39
L-Phe + L-BPA (μg/g)	14.26 ± 1.25	10.83 ± 1.23	10.98 ± 0.30	17.83 ± 3.17	9.54 ± 3.71	36.43 ± 17.09	2.30 ± 0.24
N/B ratio (percentage decrease)	–	0.76 (92.7%)	0.77 (52.7%)	1.25 (96.2%)	0.67 (126.4%)	2.55 (117.5%)	0.16 (41.0%)
L-Leu + L-BPA (μg/g)	15.12 ± 2.28	9.52 ± 0.06	20.85 ± 1.08	15.87 ± 1.11	10.47 ± 0.34	32.41 ± 4.02	5.58 ± 0.34
N/B ratio (percentage decrease)	–	0.63 (76.8%)	1.38 (94.5%)	1.05 (80.8%)	0.69 (130.2%)	2.14 (98.6%)	0.37 (94.9%)
L-Gln + L-BPA (μg/g)	14.06 ± 2.53	11.63 ± 1.76	19.76 ± 3.33	24.05 ± 7.35	8.15 ± 0.66	32.83 ± 6.73	6.83 ± 0.45
N/B ratio (percentage decrease)	–	0.83 (101.2%)	1.41 (96.6%)	1.71 (131.5%)	0.58 (109.4%)	2.33 (107.4%)	0.49 (125.6%)
L-Gly + L-BPA (μg/g)	14.93 ± 0.28	11.52 ± 0.37	19.47 ± 0.94	15.17 ± 0.40	10.2 ± 0.54	31.86 ± 2.03	6.73 ± 0.60
N/B ratio (percentage decrease)	–	0.77 (93.9%)	1.30 (89.0%)	1.02 (78.5%)	0.68 (128.3%)	2.13 (98.2%)	0.45 (115.4%)
L-Ala + L-BPA (μg/g)	18.16 ± 1.07	15.42 ± 0.91	21.71 ± 1.24	19.90 ± 0.03	8.43 ± 0.80	37.40 ± 2.80	6.27 ± 0.13
N/B ratio (percentage decrease)	–	0.85 (103.7%)	1.20 (82.2%)	1.10 (84.6%)	0.42 (79.2%)	2.06 (94.9%)	0.35 (89.7%)
L-Thr + L-BPA (μg/g)	19.51 ± 2.51	14.75 ± 0.53	20.89 ± 2.48	21.10 ± 2.15	8.57 ± 0.70	36.89 ± 1.34	5.55 ± 0.18
N/B ratio (percentage decrease)	–	0.76 (92.7%)	1.07 (73.3%)	1.08 (83.1%)	0.44 (83.0%)	1.89 (87.1%)	0.28 (71.8%)

Abbreviations: L-BPA = L-4-dihydroxy-borylphenylalanine; N/B ratio = normal tissue to blood boron concentration ratio; L-Phe = L-phenylalanine; L-Leu = L-leucine; L-Gln = L-glutamine; L-Gly = L-glycine; L-Ala = L-alanine; L-Thr = L-threonine.

when the same dose was delivered to the tumour tissue (Condition 1 in Table 2, Fig. 3). The peak dose in the brain was reduced from 12 Gy-eq to 10.94 Gy-eq and 9.70 Gy-eq at the blood boron concentrations of 25 and 40 μg/g, respectively. When the same limitation dose was used in the brain (12 Gy-eq), the change in the T/N ratio increased the advance depth (Condition 2 in Table 2, Fig. 3). The advance depth increased from 7.85 cm and 8.52 cm to 8.12 cm and 9.12 cm with blood boron concentrations of 25 and 40 μg/g, respectively. In this simulation, we used the values of 25 and 40 μg/g because these values are commonly observed in clinical situations as the maximum boron concentrations in the blood when patients received 500 mg/kg L-BPA in 2 hours or 900 mg/kg L-BPA in 6 hours, respectively [8].

Discussion

High-dose L-phenylalanine preloading enhance the BNCT effects

This study demonstrated that preloading with high-dose L-phenylalanine in L-BPA BNCT reduced the brain dose and increased the tumour dose. The N/B ratio of the brain in the 1250 mg L-phenylalanine/kg group was 0.11, which was consistent with a previous report of the administration of 1600 mg L-BPA/kg [7]. Thus, oral high-dose L-phenylalanine preloading prior to the administration of conventional L-BPA doses showed the potential to produce the same advantageous effects as a high-dose L-BPA injection. In a previous report, the authors emphasised the importance of lowering the N/B ratio due to the advantageous effects on CBE in the brain, which is indisputably agreeable [7]. Furthermore, the blood boron concentration of 1600 mg L-BPA/kg reached 93 μg/g, which corresponded to 9300 μmol/L. Assuming that the boron concentration in the tumour tissue increased proportionally according to the blood boron concentration without a change in the tumour to blood ratio of boron concentration (T/B ratio), the boron concentration in the tumour tissue could reach 186–279 μg/g, or 18,600–27,900 μmol/kg, under conditions in which the T/B ratio was 2–3. However, given the excretion of L-BPA from tumour cells via transporters and the fact that the average plasma amino acid concentrations are several dozen to hundreds of μmol/L, these boron concentrations in the tumour tissue do not seem feasible. When a high dose of L-BPA is administered, the actual boron concentration in the tumour tissue would be saturated. From this perspective, high-dose L-phenylalanine is an acceptable alternative to high-dose L-BPA injection to improve the therapeutic efficacy of BNCT for brain tumours because L-BPA dose can be set to a conventional dose in clinical situations.

The potential application of L-phenylalanine as a T/N ratio enhancing agent

The results of this study can be applicable in two clinical situations. First, the administration of L-phenylalanine before L-BPA injection resulted in a 19.2% decrease in the brain dose relative to the brain dose in the control group with a blood boron concentration of 40 μg/g (Table 2, Condition 1). One of the severe adverse effects of BNCT for malignant brain tumours is radiation necrosis because patients have received as much as 60 Gy of X-ray to the brain near the primary tumour lesion prior to BNCT [13]. When the brain dose of BNCT becomes approximately 20% lower with L-phenylalanine, the risk of radiation-induced brain necrosis decreases considerably. Second, the result of this study showed that under conditions in which the irradiated dose in the brain of the L-phenylalanine group was the same as that of the control group, the advance depth increased in length (Table 2, Condition 2). In clinical situations, a previous study reported the high incidence of both out-of-field recurrence and cerebrospinal fluid dissemination after BNCT [14]. These cases, therefore, would benefit from increasing the advance depth by L-phenylalanine.

The relationship between the CBE value and the N/B ratio

In the dose calculation for BNCT, it is necessary to account for the fact that the value of CBE varies with the N/B ratio. We used

Table 2
The difference between the normal brain dose and the tumour dose in the control and L-phenylalanine groups.

		T/B ratio	N/B ratio	Condition 1		Condition 2	
				Peak dose of brain (Gy-eq)	Irradiation time (min)	Peak dose of brain (Gy-eq)	Irradiation time (min)
Control group	40	1.76	0.46	12.00	81.1	8.52	81.1
	25				68.7	7.85	68.7
L-Phe group	40	1.36	0.11	9.70	85.9	9.12	106.3
	25			10.94	100.0	8.12	109.7

Abbreviations: T/B ratio = tumour to blood boron concentration ratio; N/B ratio = normal tissue to blood boron concentration ratio; L-Phe = L-phenylalanine.

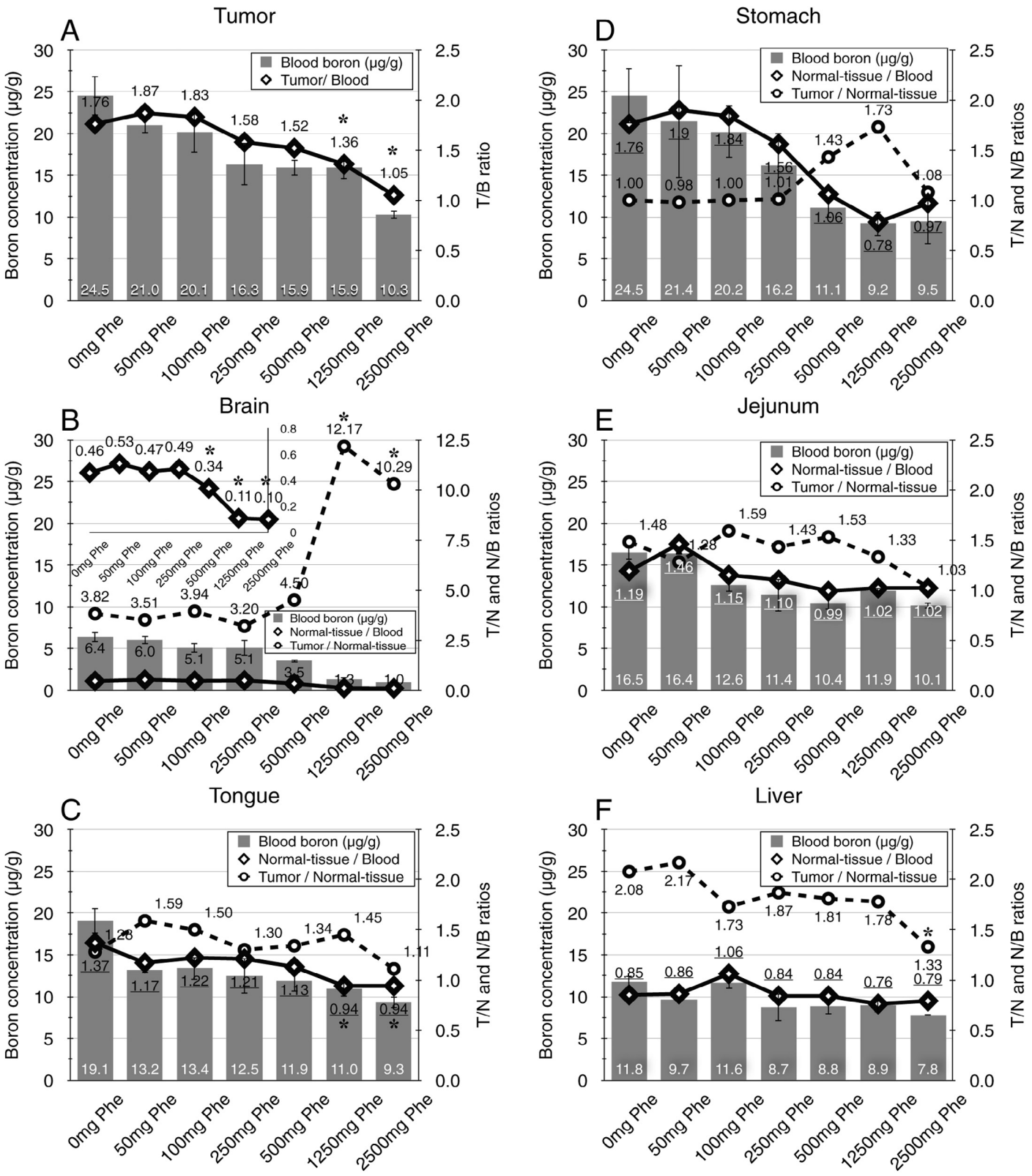

Fig. 1. Each figure presents the blood boron concentration, tumour to normal tissue boron concentration ratio (T/N ratio), and normal tissue to blood boron concentration ratio (N/B ratio). The high-dose L-phenylalanine (L-Phe) groups (1250 mg/kg and 2500 mg/kg) exhibited significant decreases in the N/B ratio in the brain (*$p < 0.01$).

CBE values of 0.88 and 0.48 for the control group and the high-dose L-phenylalanine group, respectively, according to a previous report [8]. The value of 0.48 was applied to the high-dose L-phenylalanine group because the N/B ratio in the L-phenylalanine group was equal to that of the high-dose L-BPA group in the previous report. We used 0.88 as the CBE factor for our control group because this was the CBE factor determined in the conventional L-BPA dose group in the previous report and because no alternative

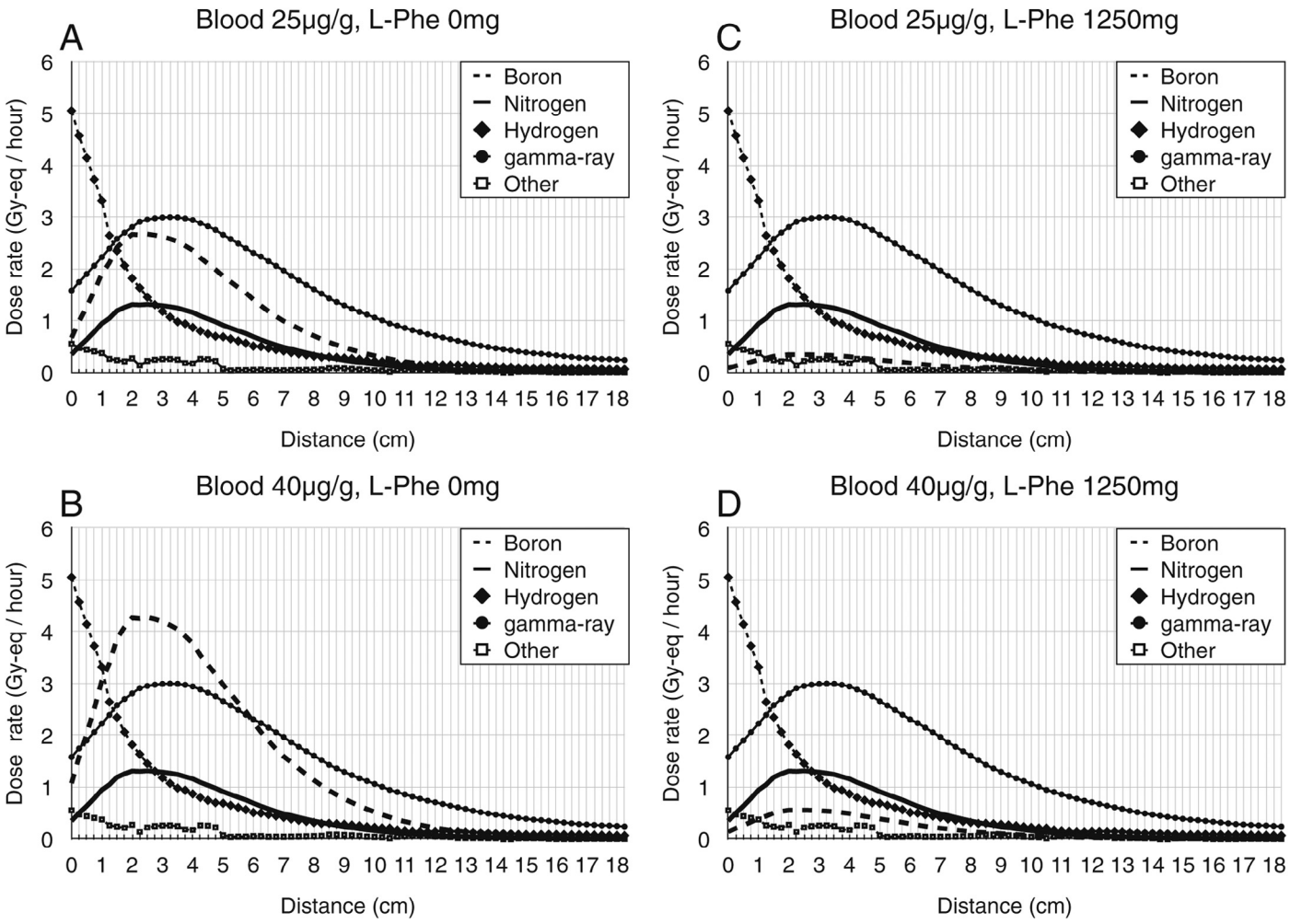

Fig. 2. L-phenylalanine (L-Phe) dramatically suppressed the boron-derived dose. The influence of high-dose L-Phe on the decreased boron dose is greatest at higher blood boron concentrations.

values have been previously determined. However, we observed a difference in the N/B ratio between the control group in the previous report and our control group. The N/B ratio of the control group in the previous report was 0.33, and that of the control group in this study was 0.46. Therefore, the dose calculation using 0.88 overestimated the radiation dose delivered to the control group in this study, as the CBE factor decreased in response to the increased N/B ratio. Taking this overestimation in the control group into account, the advantageous effects of L-phenylalanine preloading relative to the control group would be greater than the dose calculation results described in this study.

Limitations

There are some limitations to this study. First, high-dose L-phenylalanine in this study increased irradiation time because irradiation time was prescribed according to the organs at risk in BNCT. Second, the expression of LAT differs from patient to patient. Therefore, the effect of L-phenylalanine may differ in each clinical case. The effect of L-phenylalanine should be examined individually before the use of L-phenylalanine in clinical situations through imaging methods such as ^{18}F-labelled L-BPA positron emission tomography. Third, to evaluate the possible usefulness of L-phenylalanine, additional animal studies including positron emission tomography imaging studies, in vivo therapy studies and dose–response studies of the normal brain with high-dose L-phenylalanine would be required. We used SCC-VII tumour bearing C3H mice model in this study. Animal studies in an orthotopic brain tumour model and with other tumour cell lines would be also required before this could be evaluated clinically, considering that enhanced uptake of L-BPA by L-DOPA pre-loading in C6 glioma bearing rats previously shown by Capuani et al. [6] failed to be demonstrated in F98 glioma bearing rats [15].

In conclusion, we determined that L-phenylalanine preloading improved both the T/N and N/B ratios in the brain in L-BPA BNCT. L-phenylalanine has advantageous effects on both the tumour and brain doses. We believe that T/N ratio enhancers can expand the role of BNCT in cancer therapy by decreasing the normal tissue dose and increasing the tumour advance depth, potentially expanding the indications for BNCT in the future.

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Conflict of interest

The authors declare no conflicts of interest.

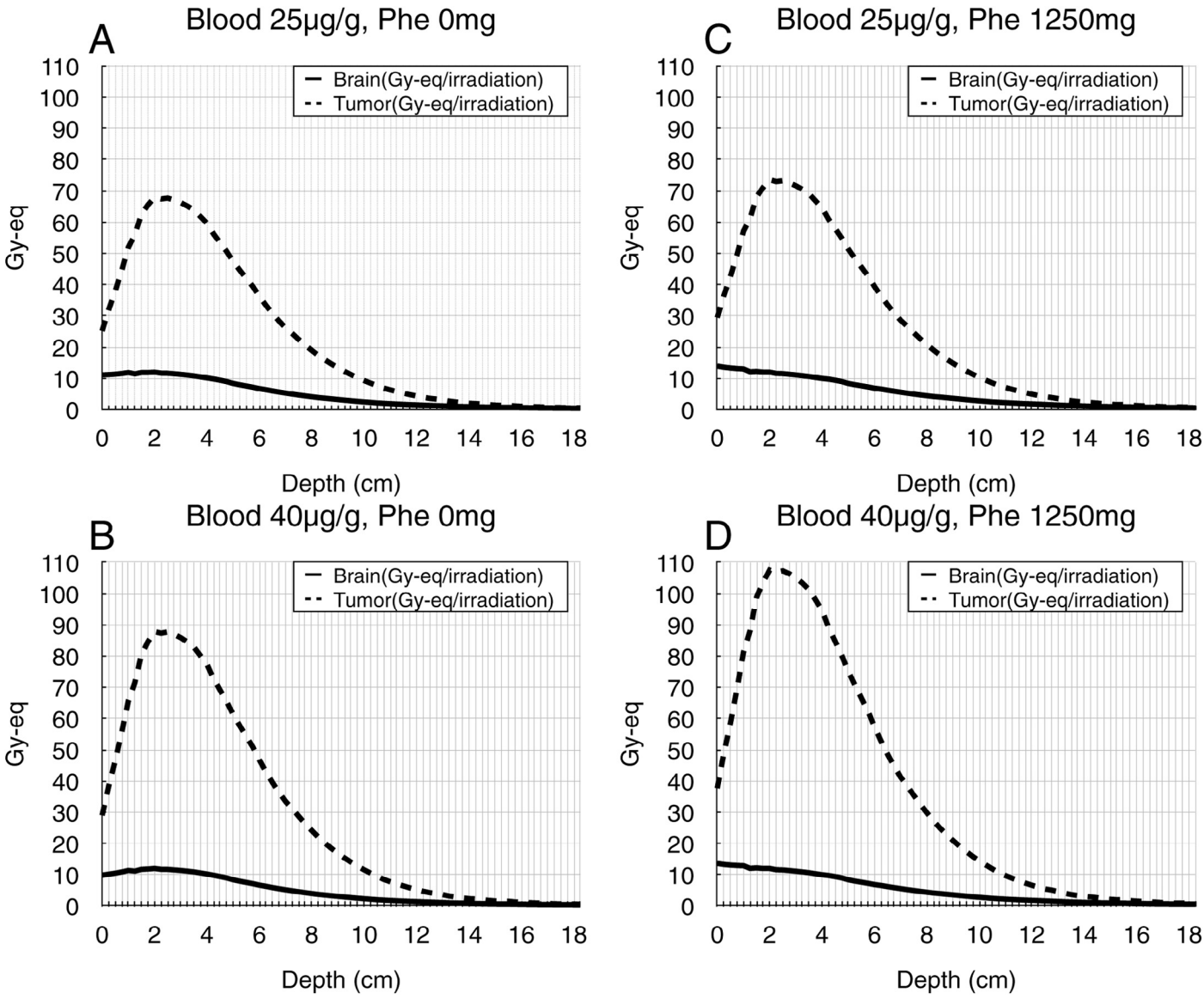

Fig. 3. The depth–dose curves of the tumour tissue and the brain in the 1250 mg/kg L-phenylalanine (L-Phe) group are calculated under the conditions at blood boron concentrations of 25 μg/g (A, B) and 40 μg/g (C, D).

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