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Boron Neutron Capture Therapy for Newly Diagnosed Glioblastoma

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Boron neutron capture therapy/Boronophenylalanine-PET/Glioblastoma/X-ray radiation therapy.

We evaluate the clinical results of a form of tumor selective particle radiation known as boron neutron capture therapy (BNCT) for newly-diagnosed glioblastoma (NDGB) patients, especially in combination with X-ray treatment (XRT). Between 2002 and 2006, we treated 21 patients of NDGB with BNCT utilizing sodium borocaptate and boronophenylalanine simultaneously. The first 10 were treated with only BNCT (protocol 1), and the last 11 were treated with BNCT followed by XRT of 20 to 30 Gy (protocol 2) to reduce the possibility of local tumor recurrence. No chemotherapy was applied until tumor progression was observed. The patients treated with BNCT (protocol 1 plus 2) showed a significant survival prolongation compared with the institutional historical controls. BNCT also showed favorable results in correspondence with the RTOG- and EORTC-RPA subclasses. The median survival time (MST) was 15.6 months for protocols 1 and 2 together. For protocol 2, the MST was 23.5 months. The main causes of death were cerebrospinal fluid dissemination as well as local recurrence. Our modified BNCT protocol showed favorable results of patients with NDGB not only for those with good prognoses but also for those with poor prognoses.

INTRODUCTION

Surgery followed by radiation therapy is still the standard treatment for glioblastoma (GB). The addition of temozolomide (TMZ) chemotherapy to the standard treatment has significantly increased the proportion of patients who survive longer than 2 years.[1)] However, additional progress is needed, as almost half of GB patients do not survive the first year after diagnosis.

Boron neutron capture therapy (BNCT) has been developed in the hope of achieving a breakthrough in GB treatment.[2,3)] BNCT, a form of tumor-selective particle radiation, comprises a binary approach. First, a boron-10 (^{10}B)-labeled compound delivers high concentrations of ^{10}B to the target tumor relative to the surrounding normal tissues. This is followed by thermal neutron irradiation. When neutrons collide with ^{10}B atoms, the ^{10}B (n, alpha) ^{7}Li neutron capture reaction releases alpha and ^{7}Li particles. These particles have the characteristics of high relative biological effectiveness and high linear energy transfer. In addition, the particles have extremely short tracks (5–9 micrometers), which results in relatively selective tumor cell kill without significant adjacent normal brain tissue damage. Therefore, if sufficient concentrations of boron compounds can be made to accumulate selectively in tumor tissues, BNCT would become an ideal radiotherapy.

Since the 1950s, BNCT has been used to treat high-grade gliomas, although the results have not been satisfactory.[4)] We modified the therapy in several ways to resolve problems previously existing, and applied this modified BNCT to malignant gliomas beginning in January, 2002[2,3)] by using Kyoto University Research Reactor (KUR).

First, we utilized an epithermal rather than a thermal beam to improve the distribution of thermal neutrons in deep sites.[5)] Second, we used both of the boron compounds that are currently available worldwide for BNCT: sodium borocaptate (BSH) and boronophenylalanine (BPA). These compounds reach different subpopulations of tumor cells and

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accumulate in them in a different fashion.[6] BSH is not delivered into the normal brain through the blood-brain barrier, and the concentration of this compound in tumor tissue is related to both its vasculature and its concentration in the blood. BPA accumulates preferentially in the actively proliferating subpopulation. However, some of the compound inevitably accumulates in normal tissue. Therefore, the simultaneous use of both compounds cancels out the disadvantages of each.[7] Third, we used ^{18}F-BPA-positron emission tomography (PET) to estimate the BPA concentrations in the tissues.[8,9]

With these improvements, we were able to apply BNCT without craniotomy and with an accurate estimation of the absorbed dose. By implementing these modifications, we can rapidly shrink malignant gliomas on neuro-images, as reported elsewhere.[2,3]

Five years have passed since we first used this modified BNCT. Therefore, in the present manuscript, we can apply survival analysis to newly diagnosed glioblastoma (NDGB) patients who were treated with BNCT at our institute. To reduce the heterogeneous anti-tumor effects of BNCT and consequently improve patient survival, we combined BNCT with non-selective X-ray irradiation therapy (XRT) for the latter half of NDGB patients. We evaluated the survival results of BNCT, especially in combination with XRT.

METHODS

Patient enrollment

This study was approved by the ethics committee of Osaka Medical College, Takatsuki, Japan, and the Kyoto University Committee for Radiation Therapeutics, Kyoto, Japan. In addition, a written informed consent was obtained from each patient. From 2002 to 2006, we treated a total of 42 patients of malignant glioma using BNCT. Here, we report the results only for NDGB (WHO grade IV, n = 21) patients. Our eligibility criteria for this trial were as follows: 1) supratentorial NDGB (no history of radiation or chemotherapy); 2) no cerebrospinal fluid (CSF) dissemination upon diagnosis; 3) no tumor extension to the opposite hemisphere.

With protocol 1, we treated 10 patients from 2002 to 2004. With protocol 2, we treated 11 patients from 2004 to 2006. None of the patients underwent chemotherapy until tumor progression was confirmed histologically or by BPA-PET, as described below.

For a historical control, we used NDGB patients who were treated by surgical removal followed by XRT and chemotherapy (mainly ACNU, n = 27; 3 out of 27 were treated with TMZ) from 1990 to 2006 at Osaka Medical College, and in accordance with above criteria for BNCT. For the control group, all patients were operated on to achieve maximum tumor removal, as with the patients in the BNCT group, and patients with biopsy only were excluded from the group, as were the patients treated with BNCT at recurrence. From 2002 to 2006, we routinely recommended BNCT as the primary treatment for NDGB patients, however, approximately 4 months every year of the study, atomic reactors were not available for BNCT due to periodic maintenance. During these periods, all NDGB patients were enrolled in the control group.

Clinical regimen of BNCT

An approximate flowchart of our clinical BNCT regimen is depicted in Fig. 1. In both protocols 1 and 2, the patients received a BPA-PET to assess the distribution of BPA and to estimate the boron concentration in the tumors. The lesion/normal brain (L/N) ratio of BPA uptake can be estimated by using the data obtained from those assessments, and was the basis for dose planning as described previously.[2,3] Before BNCT we applied craniotomy to remove as much of the tumor as possible. Within a month after the craniotomy, BNCT was performed. In protocol 1, the patients were administered 100 mg/kg of BSH and 250 mg/kg of BPA for one hour intravenously 12 hours prior and just prior to neutron irradiation, respectively. Blood was sampled every 2 hours after BSH administration until neutron irradiation was completed, to monitor the boron concentration in the blood. The boron concentration from BSH in the blood during neutron irradiation was estimated from the measured ^{10}B concentration -time relationship. From the previous BNCT experience, which was performed with craniotomy, we hypothesized that the boron concentrations in tumor and blood contributed from BSH were equal just prior to neutron irradiation. The boron concentrations from BPA in the tumor

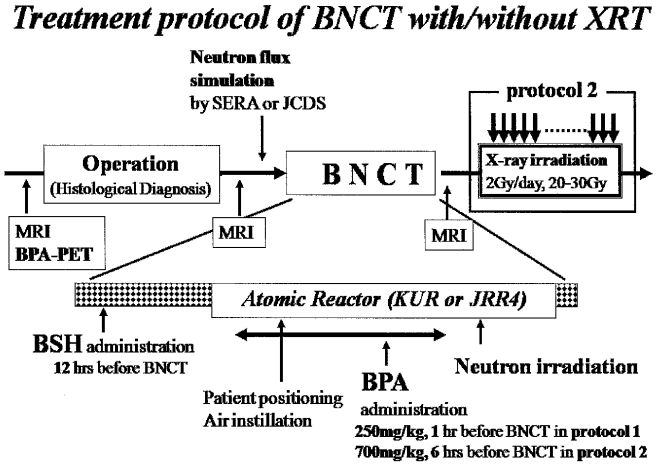

Fig. 1. A flow chart showing the treatment regimen of modified BNCT combined with external beam X-ray irradiation (protocol 2). BPA and BSH were simultaneously used in our BNCT, and the treatment was followed with conventional XRT 2 Gy daily fractionation. The total dose of XRT was determined based on the irradiated dose for the normal brain at the time of BNCT. In protocol 1, BPA was administered at 250mg/kg for one hour, and XRT was omitted. BNCT: boron neutron capture therapy, BPA: boronophenylalanine, BSH: sodium borocaptate, XRT: X-ray radiation therapy.

and normal brain were also estimated by the L/N ratio of BPA-PET. Judging from these boron concentrations contributed from each boron compound, neutron fluence rate simulated by dose-planning program (SERA or JCDS) and the factors of relative biological effectiveness of neutron beam and compound as shown in Table 1, total dose to tumor and normal brain could be estimated, as following formula.

Equivalent dose (Gy-Eq) = $D_B \times CBE_B + D_N \times RBE_N + D_\gamma \times$ hour

D_B: Boron dose (Gy) = $7.43 \times 10^{-14} \times$ boron concentration ($\mu g^{10}B/g$) $\times \Phi$ thermal neutron fluence

D_N: Nitrogen dose (Gy) = $6.78 \times 10^{-14} \times$ nitrogen concentration (weight %) $\times \Phi$ thermal neutron fluence

D_γ: Gamma-ray dose: = 0.83 Gy/hour

(These parameters are used in KUR)

Φ thermal neutron fluence = thermal neutron fluence rate ($n/cm^2/sec$) $\times$ radiation time

Here, Gy-Eq (Gy: Gray) corresponds to a biologically equivalent X-ray dose that can have equivalent effects on tumors and on the normal brain. To compare the effects of the $^{10}B(n, \alpha)^7Li$ reaction by different boron compounds relative to photons, the term compound biological effectiveness (CBE, below) has been defined as an alternative to the relative biological effectiveness (RBE).[11,12] The microdistribution of ^{10}B varies depending upon the pair of boron compounds and normal tissue. Therefore, this value is determined experimentally by using pure thermal neutron beam on each pair. The formula to calculate the value is,

CBE = {X-ray Dose – (Thermal Neutron Dose × RBE)} / $^{10}B(n, \alpha)^7Li$ Dose.

Table 1. RBE (relative biological effectiveness) and CBE (compound biological effectiveness) factor

Radiation			Tumor	Brain	Skin
Thermal Neutron		RBE	3.0	3.0	3.0
Epithermal Neutron		RBE	3.0	3.0	3.0
$^{10}B(n, \alpha)^7Li$	: BPA	CBE	3.8	1.35	2.5
	: BSH	CBE	2.5	0.37	0.8
γ-ray Dose		RBE	1.0	1.0	1.0

BPA: boronophenylalanine; BSH: sodium borocapate.

Dose response relationship of $^{10}B(n,alpha)^7Li$ reaction to tumor or normal tissue depends on the microdistribution of the ^{10}B which is different in each compound. But we can know only macroconcentration of ^{10}B (mg/g tissue) for dose calculation, and "RBE" is determined using this dose. Apparently this "RBE" is different from real RBE of alpha particle of $^{10}B(n,alpha)^7Li$ reaction and varies depending on compound and tissue. In BNCT, this "RBE" for each boron compound is termed as CBE (compound biological effectiveness) values. These RBE and CBE values are determined by human and experimental animal studies.

In protocol 2, 12 hours prior to neutron irradiation the patients were administered 100 mg/kg of BSH intravenously for one hour; later, for the 6 hours just prior to irradiation, they also received 700 mg/kg of BPA continuously. The neutron irradiation time was determined not to exceed 13 and 15 Gy-Eq to the normal brain in protocols 1 and 2, respectively. Within 2 weeks after neutron irradiation, a 2 Gy daily fraction of XRT was applied, for a total of 20 to 30 Gy, as shown in Fig. 1. The purpose of this boost XRT was to decrease the possibility of local recurrence, depending on 2 issues. One is to compensate possible heterogeneous distribution of boron compounds and the other is to compliment the lack of neutron fluence, especially in the deep part. The dose of XRT, therefore, total dose of XRT + BNCT was determined based on the BNCT dose for the normal brain, i.e., not exceeding biologically equivalent dose to 45Gy in the daily fractionation XRT. Radiation field of boost XRT was determined to cover the T2-high lesion in the MRI just before BNCT. The X-ray beam was delivered through anterior-posterior or bilateral opposing fields.

After treatment, all patients were carefully followed up with physical, neurological and neuroradiological examinations, and the toxicity and effectiveness of the treatment were evaluated at 1- to 3-month intervals. When MRI showed a new gadolinium (Gd)-enhanced lesion or increased perilesional brain edema, BPA-PET was again applied to assess the lesion for radiation necrosis or tumor progression.[10] If the lesion showed radiation necrosis, steroids, anticoagulants (chiefly warfarin) and vitamin E were administered. If the lesion indicated tumor progression, supplementary treatment such as chemotherapy or additional surgery was applied if possible. Actually, 11 cases were applied recraniotomy, as described in detail in the Results. Also 7 out of 21 BNCT cases were treated with TMZ, as mentioned in the Discussion. In the historical control group, additional treatments were also applied in case of tumor progression.

Survival analysis

The survival time from initial debulking surgery in BNCT patients was compared with that of the institutional historical controls that were treated with debulking surgery followed by XRT and chemotherapy, as described above. Estimates of the survival probability were calculated using the Kaplan-Meier method, and differences in survival curves were compared using the log-rank test. Data were analyzed using the JMP7 statistical software package (SAS Institute Inc., Cary, NC, USA). P values less than 0.05 were judged as statistical significant.

For the 21 patients who received BNCT, survival time was compared not only with that of the institutional historical controls but also with that of the corresponding recursive partitioning analysis (RPA) subclasses as defined by the Radiation Therapy Oncology Group (RTOG)[11] and the

European Organization of Research and Treatment of Cancer (EORTC)[12] as international historical controls. Based on this RTOG-RPA, GB was classified into 4 prognostic subgroups (classes III to VI), and the median survival time (MST) for Classes III, IV, V, and VI were 17.9, 11.1, 8.9, and 4.6 months, respectively.[11] Each patient treated with BNCT was stratified into his or her respective RPA class, and each patient's survival was introduced with special reference to this historical control. We could not apply any statistical analyses between our BNCT results and these international historical controls because raw data of the latter were not available.

We chose to use overall survival, not progression-free survival, as the primary endpoint. Our reasoning for this decision was as follows. Intensive treatments, such as chemoradiotherapy with TMZ, caused a high incidence of pseudoprogression (psPD) in the early phase of the treatments. It is impossible to distinguish between true tumor progression and pseudoprogression by Gd-MRI alone.[13,14] We experienced the same phenomenon, also with high frequency, in the patients treated with BNCT.[15] In addition, radiation necrosis is difficult to be distinguished from local tumor progression as stated above. Thus, progression-free survival was not suitable as the primary endpoint.

RESULTS

Patients' profiles and BNCT parameters

The patients' profiles and BNCT parameters are listed in Table 2. Cases 1 to 10 were treated using protocol 1 and cases 11 to 21 were treated using protocol 2. The L/N ratios of BPA uptake judged by BPA-PET ranged from 2.1 to 7.1. The minimal tumor doses for GTV in protocols 1 and 2 were 16.3 to 63.0 Gy-Eq and 26.9 to 65.4 Gy-Eq, respectively. In protocol 2, XRT of a total dose of 20–30Gy was started within 2 weeks after BNCT, as described above.

Survival

Patients treated with BNCT (n = 21) had a MST of 15.6 months (95% confidence interval (CI): 12.2–23.9) after diagnosis (Fig. 2A and Table 3). Here the date of diagnosis is the initial debulking surgery date, as descried above. This was significantly longer than the MST for the historical controls at our institute who were treated with surgical removal followed by XRT and chemotherapy (n = 27, MST was 10.3 months (95% CI: 7.4–13.2), log-rank test p = 0.0035). The RPA class distribution of 21 patients treated with BNCT at the initial diagnosis was as follows: Class III = 6 (29%); Class IV = 6 (29%); Class V = 8 (38%); Class VI = 1 (5%). The MSTs of the patients in classes III, IV, V, and VI were 23.5, 16.9, 13.2, and 9.8 months, respectively (Table 3). Of the 21 patients, 4 are still alive. In historical control, the RPA class distribution was as follows: Class III = 3 (11%); Class IV = 14 (52%); Class V = 8 (30%); Class VI = 2 (7%). The distributions of each RPA class in BNCT group and institutional historical control group are a little bit different. We compare the survival of both groups in low risk RPA (class III and IV) and in high risk RPA (class V and VI) separately. The MST of BNCT group in low risk group was 18.5 months (n = 12, 95% CI: 13.7–36.1) and that of historical control was 13.0 months (n = 17, 95% CI: 8.6–18.0). There is statistical significance in log-rank test (p = 0.028). The MST of BNCT group in high risk group was 12.2 months (n = 9, 95% CI: 9.8-undetermined) and that of historical control was 7.4 months (n = 10, 95% CI: 2.7–10.3). There is also statistical significance in log-rank test (p = 0.0083).

Table 2. Patient profile and parameters of BNCT in 21 cases with newlydiagnosed glioblastoma

Case	age, sex	BPA-PET	absorbed dose (Gy-Eq)[a] tumor[b]		XRT (dose(Gy))[c]	RTOG RPA class	Survival (months)
		(L/N)	max	min			
1	51, F	3.5*	50.6	23.8	–	5	9.9
2	73, M	7.1	57.3	27.0	–	5	10.4
3	56, F	3.5*	64.8	32.6	–	4	14.1
4	44, F	3.5*	47.5	46.2	–	3	62.2**
5	61, F	5.5	79.9	26.7	–	4	36.1
6	65, F	5.1	71.4	21.7	–	5	12.2
7	69, F	5.4	58.7	28.7	–	5	14.1***
8	57, F	3.2	37.7	16.3	–	4	13.7
9	61, M	3.7	57.6	23.2	–	5	15.6
10	49, F	3.2	37.7	16.3	–	4	18.5
11	62, F	4.8	115.0	63.0	30	6	9.8
12	16, F	6.6	149.0	39.7	24	3	17.4
13	69, F	3.5	89.5	65.4	20	4	23.9
14	36, F	4.3	96.4	42.3	30	3	23.5
15	63, F	3.5	60.6	26.9	20	5	41.5**
16	29, F	3.7	72.0	36.5	20	4	15.3
17	18, F	4.5	84.2	57.1	30	3	34.5**
18	59, M	3.5*	90.6	61.4	30	5	10.2***
19	15, M	3.3	122.0	43.1	30	3	11.0
20	69, F	2.1	52.0	26.9	30	5	22.2
21	46, F	2.1	64.0	44.6	20	3	17.7**

BPA: boronophenylalanine, PET: positron emission tomography, L/N: lesion to normal brain ratio, Gy-Eq: gray equivalent, XRT: X-ray radiation therapy, RN: radiation necrosis, rec.: recurrence

Cases 1 to 10 were treated by protocol 1 and cases 11 to 21 were treated by protocol 2.

[a]: Absorbed doses include contributions from gamma photons, ^{14}N (n, p) ^{14}C and ^{10}B(n, a) ^{7}Li reactions. A spot region of irradiated dose calculated by a SERA workstation is listed above.

[b]: Tumor was identified as a contrast-enhanced lesion by Gd on MRI.

[c]: XRT dose was identified as a total dose of 2 Gy daily fractionated external beam X-ray irradiation.

*: For these cases, BPA-PETs were not applicable and an L/N ratio of 3.5 was applied using the mean value from the literature (*Int J Rad Oncol Biol Phys* 40: 829–34, 1998).

**: alive

***: Cases 7 and 18 died from concomitant thyroid cancer and cerebrovascular disease, respectively.

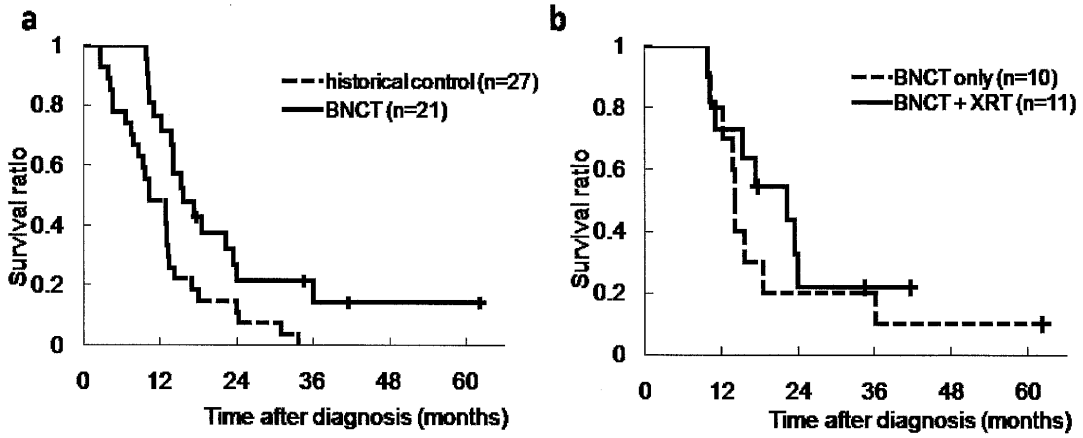

Fig. 2. Kaplan-Meier survival curves of newly diagnosed glioblastoma patients treated with BNCT. A: A continuous line represents the survival times of the patients treated with BNCT (protocols 1 plus 2, n = 21), and show an MST of 15.6 months. Four out of 21 cases are still alive. A broken line represents the survival times of our institutional historical controls (surgical removal, XRT and chemotherapy) (n = 27) and show an MST of 10.3 months (log-rank test, p = 0.0035). B: A continuous line represents the survival times of the patients treated with BNCT followed by XRT boost (protocol 2, n = 11), and show an MST of 23.5 months. Three out of 11 cases in protocol 2 are still alive. A broken line represents the survival times of the patients treated by protocol 1(n = 10), and show an MST of 14.1. There is no statistical significance in the difference in MSTs between these groups.

Table 3. Comparison of survival data among RPA class in the RTOG database[a], EORTC (RT/TMZ) trial[b] and in our cases treated with BNCT[c]

RTOG RPA class	RTOG original (1463 cases)[a]		EORTC (RT/TMZ)[b]		BNCT group (21 cases)[c]	
	case	Median (mo)	case	Median (mo)	Case[d]	Median (mo)
III	175	17.9	42	21.4	6	23.5
IV	457	11.1	152	16.3	6	16.9
V	395	8.9	93	10.3	8	13.2
VI	263	4.6	NR[e]		1	9.8

RPA: recursive partitioning analysis, RTOG: Radiation Therapy Oncology Group, EORTC: European Organization for Research and Treatment of Cancer, RT: radiation therapy, TMZ: Temozolomide, BNCT: boron neutron capture therapy

[a]: Curran W., *et al.* Recursive partitioning analysis of prognostic factors in three radiation therapy oncology group malignant glioma trials. *J Natl Cancer Inst* 1993;85:704–710.

[b]: Mirimanoff R.O., *et al.* Radiotherapy and temozolomide for newly diagnosed glioblastoma: Recursive partitioning analysis of the EORTC 26981/22981-NCIC CE3 phase III randomized trial. *J Clin Oncol* 2006, 24: 2563–2569

[c]: BNCT group including 21 newly histologically confirmed glioblastoma patients treated with BNCTat Osaka Medical College between 2002 and 2006.

[d]: Three patients out of 8 in class III and 1 of 4 in class V were alive at the end point of this study. All of the patients in class IV had died.

[e]: not reported.

Therefore, it can be concluded that BNCT group shows the long survival in comparison with historical control not mainly by the difference of distribution of each RPA class in both groups. Our BNCT results for survival among the NDGB cases were favorable in comparison with those obtained from the corresponding RTOG- and EORTC- RPA subclasses (Table 3).

All patients receiving protocol 2 tolerated this treatment well. Of the 11 patients in protocol 2, 3 are still alive. The survival time from the date of diagnosis was calculated using the Kaplan-Meier method (Fig. 2B). The MST of the protocol 2 was 23.5 months (95% CI: 10. 2 – undetermined) after diagnosis (n = 11), and that of the protocol 1 patients (n = 10) was 14.1 months (95% CI: 9.9–18.5), although the difference was not statistically significant.

Reoperation after BNCT

Eleven cases were applied recraniotomy when the enhanced lesion on MRI increased in size, as stated above. Surgical specimen at recraniotomy in cases 3, 8, 13, 14 showed tumor progression. In these cases, only partial tumor removal could be done. Also surgical specimen in cases 1, 2, 4, 6, 14, 15, 20 showed mainly necrosis. Three (cases 1, 2, 6) out of these 7 treatment-related necrosis cases were considered as psPD because the lesions increased in size within 3 months after BNCT and the lesions were stable or decreased in size during the observation period after the recraniotomy.

Side effects of BNCT

All of the BNCT patients showed alopecia. Also, in the early period of this study, some patients showed transient

oliguria and fever during the first 24 hours after BNCT. We concluded these side effects were caused by recrystallization of BPA in urine. Thereafter, we overhydrated the remaining patients after BNCT, and no such side effects were observed again. Cases 11, 17, 18 other than above 7 histologically verified cases were considered as radiation necrosis judging from PET study. Four cases were symptomatic and other 6 cases were asymptomatic. We described radiation necrosis in the Discussion.

Representative case: Case 17

An 18-year-old female had a right parietal tumor partially removed in a hospital in May 2005 (Fig. 3, Column A). The histopathological diagnosis was GB. She was transferred to our hospital for BNCT for the remaining lesion. Prior to BNCT, we applied BPA-PET to confirm the BPA accumulation and simulation of the absorbed dose. The L/N ratio in the BPA-PET image was 4.5, as shown in Fig. 3, Row A. We performed re-craniotomy to remove the additional tumor (Fig. 3, Row B) and settled the Ommaya's reservoir to fill the cavity with air before the neutron irradiation, in order to increase the amount of neutrons reaching the bottom of the tumor. As a BNCT simulation, the minimum tumor dose and maximum normal brain dose were estimated to be 57.1 Gy-Eq (5.4 cm beneath the parietal scalp) and 10.8 Gy-Eq (2.5 cm beneath the scalp), respectively. An additional 30 Gy XRT (2 Gy × 15 Fr) was applied for the deep part of the tumor. The patient was followed-up with periodic MRI without any newly appearing lesions. Twenty-four months after BNCT, a small enhanced lesion was found. The patient returned to our clinic so that we could determine whether or not the lesion represented tumor progression. We applied BPA-PET again, and found no tracer uptake (Fig. 3, Row C). The lesion identified on MRI was considered to show radiation necrosis but not tumor progression. The MRI taken 26 months after BNCT is also shown in Fig. 3, Row C. A white arrow shows the absence of enlargement of the enhanced lesion on MRI. The patient was neurologically free and

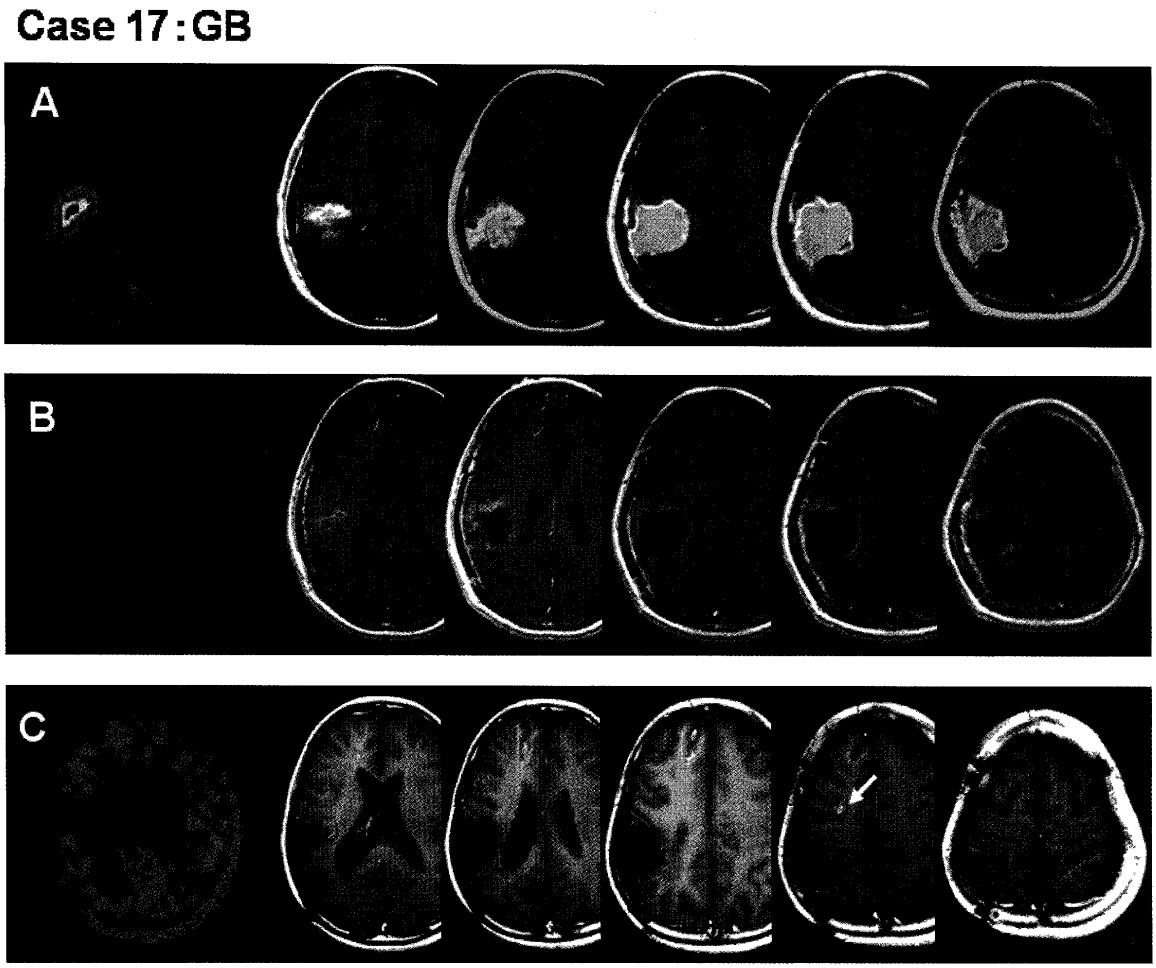

Fig. 3. Case 17: An 18-year-old female had a right parietal glioblastoma partially removed in a hospital in May 2005 (A). We performed re-craniotomy to remove the additional tumor and settled the Ommaya's reservoir to fill the cavity with air before neutron irradiation (B). MRI taken 26 months after BNCT is shown in C. The white arrow shows a newly appearing Gd-enhanced lesion, which was judged to be radiation necrosis. BPA-PETs taken prior to BNCT and 2 years after BNCT are listed in the left panel in rows A and C, respectively.

100% on KPS at the time this manuscript was prepared.

DISCUSSION

Comparisons of BNCT patients with institutional historical control and RTOG- and EORTC- RPA databases

BNCT has been applied to a limited extent for the treatment of malignant gliomas. So far, several clinical studies of BNCT have been reported.[16–19] In each of those studies, the MST was approximately 13 months. Although these survival times were similar to those obtained with surgery followed by XRT, no firm conclusions can be made as to whether the clinical results of BNCT are equivalent or superior to those of XRT. To improve the clinical effectiveness of BNCT for malignant gliomas, we have made several modifications, as described in the Introduction. With these modifications, it is likely that we can achieve more favorable results for BNCT on NDGB than were obtained in the previous trials. In our series (protocols 1 and 2, n = 21), the patients treated with BNCT had an MST of 15.6 months (95% CI: 12.2–23.9) after diagnosis. That of our institutional historical control (n = 27, MST: 10.3 months (95% CI: 7.4–13.2)) was significantly shorter (p = 0.0035, by log-rank test). However our historical control was obtained from 1990 to 2006. Since the BNCT series data were collected from 2002 to 2006, recent advancements in surgical procedure or chemotherapy may have influenced our BNCT series data. On the other hand, it is accepted that the extensive removal of NDGB showed a limited benefit for the survival of NDGB patients with large series study. Lacroix, *et al.*[20] reported that more than 98% removal of NDGB showed moderate benefit of the prolongation of MST such as 4 months or so, in comparison of less than 98% removal.[20] In BNCT group and institutional historical control group, 4 out of 21 patients and 5 out of 27 patients were received more than 98% removal of the tumor, respectively. Probably, advancement in chemotherapy, especially the advent of TMZ, may have improved the results of our BNCT cases in comparison with our historical control. Our discussion of the effects of TMZ in our BNCT series appears under the subheading *Further improvements* below.

Also, to apply a more objective comparison, we made reference to the RTOG- and EORTC-RPA databases. Previously, Hatanaka *et al.* reported good clinical results with BNCT.[21] However, Laramore *et al.*[22] analyzed the survival data of a subset of 12 patients who had been treated by Hatanaka between 1987 and 1994.[21] They concluded that there were no differences in their survival times compared with the RTOG-RPA classifications. Our patients in RTOG RPA classes III, IV, and V had MSTs of 23.5, 16.9, and 13.2 months compared with MSTs of 17.9, 11.1, and 8.9 months for these respective classes in the original RTOG trials[11] (Table 3). Of course, raw data from RTOG database is not yet available. It is impossible, and in any case would be meaningless to compare our BNCT data to RTOG-RPA data directly with statistics, as described above. Also, the RTOG-RPA database was published in 1993 and the data were collected in the late 1980s. So the same issue of possible data obsolescence arises, as it did with the institutional historical control, in light of recent advancements in surgical procedures and chemotherapy. To avoid the bias introduced by such advances, our results were also compared with the EORTC-RPA database.[12] An EORTC-RPA study was published recently, and all the patients in this study were treated with TMZ. At least, our study showed that the prognosis of BNCT patients was not bad in each RPA subclass of RTOG and EORTC. The response to BNCT was seemed to be favorable, especially in the poorer subclasses (RPA IV-VI).[11]

In our BNCT series, the MST of the patients treated with BNCT followed by XRT boost (protocol 2) was 23.5 months (95% CI: 10.2 – undetermined), while the MST of the patients treated with BNCT without XRT boost (protocol 1) was 14.1 months (95% CI: 9.9–18.5) (Fig. 2B), although the there was no statistical significance in survival between two protocols in log-rank test. We discuss the rationale for this modification in protocol 2 below.

Modifications in protocol 2

To the best of our knowledge, BNCT clinically has never been followed by a photon boost until the time of tumor progression. In the present study, we performed our new BNCT protocol combined with XRT for NDGB patients to diminish the possibility of tumor recurrence. This approach was based on experimental animal data showing that a significant therapeutic gain could be obtained when BNCT was combined with an X-ray boost.[23] Barth *et al.*[2] recently reported that an X-ray boost after BNCT could significantly enhance survival time in an experimental brain tumor model.

In our trial, we used BPA and BSH in combination. Here, the micro-distributions of BSH[24,25] and BPA[26–28] differed at the cellular level, and their simultaneous use could cover this heterogeneous distribution, especially on the tumor bulk.[7,29–31] To augment the absorbed dose of infiltrated tumor cells, where BPA should play an important role, we increased the amount of BPA from 250 mg/kg (protocol 1) to 700 mg/kg (protocol 2) and prolonged the infusion time from 1 hr (protocol 1) to 6 hrs (protocol 2). These changes were based on a BNCT study performed in Sweden[19,32] and on animal experimental data using secondary ion mass spectroscopy.[26,27] The Swedish group carried out a BPA-based trial using an epithermal neutron beam.[32] That study differed significantly from all previous clinical trials in that the total amount of BPA administered was 900 mg/kg, infused intravenously over 6 hours. The longer infusion time should theoretically give a more homogeneous distribution of boron compounds, even in the infiltrating lesion.[26,27,33,34] This approach by the Swedish group was well tolerated, and the MST for the 29 patients in their trial was 14.2 months after BNCT. In the present study, we modified this Swedish

method combining the BPA therapy with BSH. This was the rationale for our protocol 2.

Problems to be confronted

CSF dissemination, along with local progression, was a major cause of death after BNCT. This tendency was also confirmed in both protocols 1 and 2. Also, CSF dissemination was prominent even in the GB patients who had been treated with BNCT on recurrence.[35] In protocols 1 and 2 combined, we lost 7, 5, and 3 patients due to CSF dissemination, local tumor progression and both dissemination and local tumor progression, respectively (data not shown). CSF dissemination can be diagnosed by MRI or CSF cytology. About local tumor progression, we confirmed only 4 cases at recrainiotomy, as stated above. The rest cases were speculated as local tumor progression by follow-up MRI and responsiveness to steroids. It is generally accepted that more than 85% of tumor progression in GB patients arises within 2 cm of the original margin of the contrast-enhancing lesion by XRT.[36–38] These findings indicate that the local control of GB by BNCT is relatively good in comparison with XRT, but the problem of CSF dissemination remains. Some patients showed radiographical and neurological aggravation after BNCT with the XRT boost for NDGB; this tendency was more prominent in recurrent GB patients who had been treated with full-dose XRT and treated again with only BNCT upon recurrence. The lesions were occasionally removed when we could not control them with medication. Histological examination often showed radiation necrosis with no evidence of tumor residues, and these patients were well controlled after surgery. Even some NDGB patients, such as case 17 (protocol 2) showed radiation necrosis. This is probably caused by the elevated absorbed dose for the normal brain with the combination of additional XRT in protocol 2. Management of these pathologies with the correct diagnosis by BPA-PET is also important for patients who receive high-dose irradiation, as case 17 shows.[10] This radiation necrosis in protocol 2 may be diminished by additional XRT with gradation of the absorbed dose, more in the deeper and less in the shallower lesions, using multi-leaf collimators.

Further improvements

Recently, Stupp *et al.*[1] reported that an oral alkylating agent, TMZ, given concomitantly with XRT followed by six 28–day cycles of TMZ alone, significantly extended survival in NDGB. As a result, concurrent XRT and TMZ, followed by 6 monthly cycles of adjuvant TMZ, became the new standard of care for patients with NDGB. It should be pointed out that, in our BNCT patients, no chemotherapy was applied to patients in either protocol until tumor progression was confirmed. In protocols 1 and 2, 2 and 5 patients, respectively, were treated with TMZ when they showed enlargement in Gd-enhanced MRI. In 3 of those cases, BPA-PET and histology proved that there was no tumor progression. In the EORTC study group (XRT plus concomitant TMZ chemotherapy followed by subsequent periodic use of TMZ as chemotherapy), Mirimanoff *et al.*[12] reported an excellent result with RPA sub-classifications for NDGB, as shown in Table 3. Our BNCT group (n = 21) showed almost equal MST in RPA classes III and IV and slightly better MST in RPA class V in comparison with this EORTC study (Table 3), irrespective of the fact that limited numbers of patients were given TMZ only when they were diagnosed with a recurrence, as described above. In addition, TMZ shows a limited benefit when administered for a GB relapse. Brada, *et al.*[39] reported that TMZ showed a modest survival benefit for recurrent GB, with a 5.4 month median prolongation after TMZ administration. Taken together, the results indicate that in our BNCT series, TMZ might show a limited contribution to the prolongation of survival.

In any case, BNCT has not been clinically evaluated when given sequentially or concomitantly with cancer chemotherapy. BNCT is likely to benefit from being combined with chemotherapeutic agents such as TMZ, and such combinations should be further researched. Further study is now under way for this protocol; modified BNCT with XRT boost, followed by chemotherapy. To obtain definitive results of the survival benefit of BNCT for NDGB, a strictly designed phase 3 study is necessary.

CONCLUSIONS

In conclusion, we can achieve favorable results from BNCT in NDGB patients. We applied two major modifications to the current BNCT protocol (protocol 2) in addition to our former protocol (protocol 1). The first modification is a longer-term and larger BPA infusion, and the second is the additional application of XRT.

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