REVIEW

Boron neutron capture therapy (BNCT) for newly-diagnosed glioblastoma : Comparison of clinical results obtained with BNCT and conventional treatment

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Abstract : The purpose of this study was to evaluate the clinical outcome of boron neutron capture therapy (BNCT) and conventional treatment in patients with newly diagnosed glioblastoma. Since 1998 we treated 23 newly-diagosed GBM patients with BNCT without any additional chemotherapy. Their median survival time was 19.5 months ; the 2-, 3-, and 5-year survival rates were 31.8%, 22.7%, and 9.1%, respectively. The clinical results of BNCT in patients with GBM are similar to those of recent conventional treatments based on radiotherapy with concomitant and adjuvant temozolomide. J. Med. Invest. 61 : 254-263, August, 2014
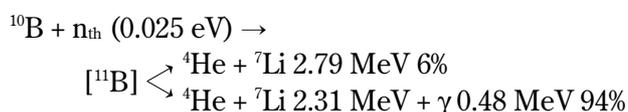
INTRODUCTION

Glioblastoma multiforme (GBM) tumor cells infiltrate deeply into surrounding brain tissue and may even reach the contralateral hemisphere. After a decade of intensive research, these cells remain extremely resistant to all current forms of therapy including surgery, chemo-, radio-, immuno-, and gene therapy. The new anti-cancer drug temozolomide (TMZ) improved clinical outcomes. Randomized clinical trials of TMZ and radiotherapy (RT) vs. RT alone showed that the median survival was 14.6 months with combined therapy and 12.1 months in GBM patients receiving radiotherapy alone (1, 2). Overall survival was 27.2% at 2-, 16.0% at 3-, 12.1% at 4-, and 9.8% at 5 years in patients treated with TMZ ; it was 10.9%, 4.4%, 3.0%, and 1.9%, respectively, in GBM patients subjected to radiotherapy alone (3).

Boron neutron capture therapy (BNCT) is based on the nuclear capture and fission reactions that occur when boron-10, a non-radioactive constituent of the natural elemental boron, is irradiated with low-energy (0.025 eV) thermal neutrons. This results in the production of high linear energy transfer (LET) alpha particles (^{4}He) and the recoiling of lithium-7 (^{7}Li) nuclei as shown below and in Fig. 1.

$$^{10}B + n_{th} \ (0.025 \ eV) \rightarrow$$

$$[^{11}B] < \begin{array}{l} ^4He + {}^7Li \ 2.79 \ MeV \ 6\% \\ ^4He + {}^7Li \ 2.31 \ MeV + \gamma \ 0.48 \ MeV \ 94\% \end{array}$$
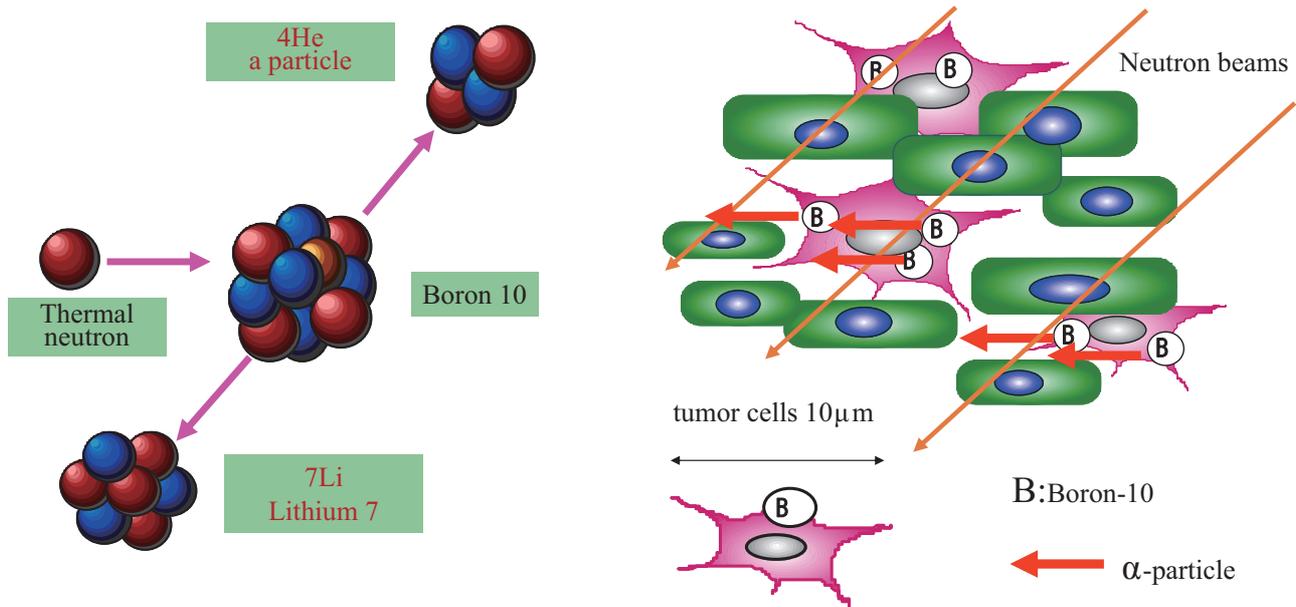
Figure 1   Principles of boron neutron capture therapy (BNCT).
Left : BNCT is based on the nuclear capture and fission reactions that occur whenboron-10, a non-radioactive constituent of the natural elemental boron, is irradiated with low-energy (0.025 eV) thermal neutrons. This result in the production of high linear energy transfer (LET) alpha particles (4He) and the recoiling of lithium-7 (7Li) nuclei.
Right : The destructive effects of these high-energy particles are limited to boron-containing cells. Since they have a very short path-length in tissues (5-9 μm), in theory, BNCT provides a way to selectively destroy malignant cells and spare adjacent normal cells.

For successful therapy, a sufficient amount of ^{10}B must be selectively delivered to all tumor cells and enough thermal neutrons must be absorbed to produce lethal damage from the ^{10}B$(n,\alpha)^7$Li capture reaction. The destructive effects of these high-energy particles are limited to boron-containing cells and since their path-length in tissues is very short (5-9 μm), theoretically, BNCT provides a way to selectively destroy malignant cells while sparing adjacent normal cells (Fig. 1). As BNCT offers the possibility of selective tumor-cell killing without damaging adjacent normal brain tissue, it may be an optimal treatment for GBM, which is highly invasive to healthy normal tissue (4-6). In 1968, Hatanaka introduced sodium borocaptate (BSH) as a boron carrier in Japan ; this started the treatment of GBM patients with BNCT combined with BSH and pure thermal neutrons, and established BSH-based intraoperative BNCT (IO-BNCT) (7). Because thermal neutron beams have a limited depth of penetration in tissue, it is necessary to reflect the skin and to raise the bone flap to irradiate the exposed brain directly. This eliminates radiation damage to the scalp and permits treatment of deep-seated residual brain tumors.

The clinical outcomes of IO-BNCT were unsatisfactory in patients whose brain tumor was situated in deeper regions because neutron fluence delivery into the deep regions was inadequate (7-11). Therefore, epithelial neutron beams were developed to improve neutron delivery (11, 12) and a new dose-evaluation system for BNCT, the Japan Atomic Energy Research Institute (JAERI) Computational Dosimetry System (JCDS) was created. It allows evaluation of the BNCT radiation dose on computed tomography- and magnetic resonance imaging (MRI) scans (13, 14). In addition, it facilitates achieving the appropriate head position and -angle with respect to the neutron beam port during irradiation. In 2004, boronophenylalanine (BPA), a new boron compound that is actively taken up by tumor cells (15), was introduced for the treatment of GBM with BNCT. The introduction of the epithermal neutron beam, the clinical use of BPA, and the dose planning system of JCDS made the clinical use of nonoperative BNCT (NO-BNCT) combined with BSH and BPA a reality. We changed from IO-BNCT to NO-BNCT in 2005.

Recent clinical studies on NO-BNCT have focused on high-grade gliomas, malignant meningiomas, head and neck cancers, cutaneous melanomas, and lung- and liver metastasis as potential candidates for BNCT.

METHODS AND MATERIALS

• *Dose planning and evaluation*

The BNCT radiation dose was evaluated based on the physical boron dose (Gy) and the weighted dose (Gy(w)) using JCDS. Based on the BNCT radiation dose we applied a new concept of BNCT to the physical radiation dose of the boron n-α reaction. To compare the radiation effect of the two heavy particles and to evaluate the efficacy of BNCT we determined the physical radiation dose of the boron n-α reaction (11). The weighted dose was calculated by multiplying the weighting factors to account for the increased biological effectiveness of the high-LET dose components, α and ^{7}Li particles, through the boron neutron capture reaction.

• *Patients and protocols*

The ethics committee of the Graduate School of Health Biosciences, the University of Tokushima, approved this study ; prior informed consent was obtained from all participating patients.

Between 1998 and 2005 we treated 23 newly diagosed GBM patients with BNCT ; they included 17 patients who underwent BSH-based IO-BNCT, and 6 patients subjected to BSH and BPA-based NO-BNCT. To be enrolled in this study, patients had to satisfy all of the following criteria : their glioma was diagnosed as glioblastoma (grade IV), they had no serious systemic diseases, and their general condition was good according to the Karnofsky Performance Scale (KPS> 70). No patient subjected to BNCT received additional radiotherapy or chemotherapy after BNCT. Our institutional controls were 34 newly diagnosed GBM patients treated by external conventional radiotherapy (RT) with concomitant and adjuvant temozolomide (TMZ) between 2006 and 2009 at Tokushima University Hospital.

• *BNCT procedure and JCDS measurements*

For IO-BNCT, 12-15 hours before neutron irradiation we delivered 100 mg/kg BSH via intravenous (iv) infusion within 60 min. On the day of BNCT we performed craniotomy under general anesthesia to target the neutron beam directly on the tumor tissue. For NO-BNCT we used a combination of 100 mg/kg BSH and 250 mg/kg BPA. BSH and BPA were administered iv within 60 min 12 hours and 1 hour before irradiation, respectively. The neutron beam was irradiated directly through the skin under local anesthesia. The boron concentration in blood and tumor tissue was measured immediately using gamma-ray spectroscopy.

• *Survival analysis*

We compared the median survival time (MST) from the initial surgery between BNCT patients and our institutional historical controls, i.e. patients treated with debulking surgery followed by external conventional RT and chemotherapy. Estimates of survival propability were calculated using the Kaplan-Meier method.

We also compared the survival time of our 23 BNCT patients with the survival of international historical controls, i.e. corresponding recursive partitioning analysis (RPA) subclasses as defined by the European Organization of Research and Treatment of Cancer (EORTC) (16) (RPA class III : age< 50, GBM, WHO performance status 0, class IV : age< 50, GBM, WHO performace status 1-2 or age$\geq$ 50, GBM, complete/partial surgery, Mini-Mental Status Examination (MMSE)$\geq$ 27, class V : age$\geq$ 50, MMSE< 27, biospy only).

RESULTS

• *Patient profiles*

IO-BNCT was performed in 17 GBM patients (1998, n=6 ; 2001, n=11), NO-BNCT in 6. The patient age and the results of RPA for BNCT alone and for RT+TMZ obtained at Tokushima University Hospital are shown in Table 1.

The mean post-diagnosis follow-up period for all 23 patients was 30 months (range 5-111 months). All but one patient died from cerebrospinal fluid (CSF) dissemination (n=4), tumor invasion to the brain stem (central nervous system (CNS) dissemination, n=2), both CSF and CNS dissemination (n= 1), local recurrence and CSF dissemination (n=1), suspected local recurrence and/or radiation necrosis (no histopathological verification, n=4), wound infection (n=2), distinct metastasis (n=1), local recurrence (n=5), unknown causes (n=1), or acute myocardial infarction (n=1). CSF and/or CNS dissemination without local recurrence at the primary site was the cause of death in 7 of 21 patients (33%).

• *MST and survival rate in patients treated by BNCT or RT + TMZ*

The MST in patients treated by BNCT (n=23) was 19.5 months ; the 2-, 3-, and 5-year survival rate was 31.8%, 22.7%, and 9.1%, respectively. The MST in patients receiving RT+TMZ (n=34) was

Table 1 : Summary of patients treated by BNCT alone and by RT+TMZ at Tokushima University Hospital between 1998 and 2009

	BNCT alone group	RT+TMZ group
Number of patients	23	34
age	47±21	59±14
Above 70	2/23 (9%)	11/34 (32%)
Below 15	2/23 (9%)	0 (0%)
Surgical radicality		
GTR	1 (4%)	1 (3%)
STR	7 (30%)	15 (44%)
PR	15 (65%)	8 (24%)
Biopsy	0 (0%)	8 (24%)
No surgery	0 (0%)	2 (6%)
RPA classification		
III	8 (35%)	2 (6%)
IV	8 (35%)	13 (38%)
V	7 (30%)	19 (56%)

BNCT : boron neutron capture therapy, RPA : recursive partitioning analysis, RT : radiotherapy,
TMZ : temozolomide
GTR : gross tumor removal, STR : subtotal tumor removal, PR : partial tumor removal

13.5 months ; the 2- and 3-year survival rate was 27.5% and 16.5%, respectively. There was no statistically significant difference (p=0.25) between the two groups with respect to the survival probability estimates (Fig. 2).

The MST in patients subjected to IO-BNCT or NO-BNCT was 17.4 and 24.2 months, respectively ; the 2-, 3-, and 5-year survival rates were 23.5% and 50.0%, 23.5% and 16.7%, and 5.9% and 16.7%, respectively. There was no statistically significant difference
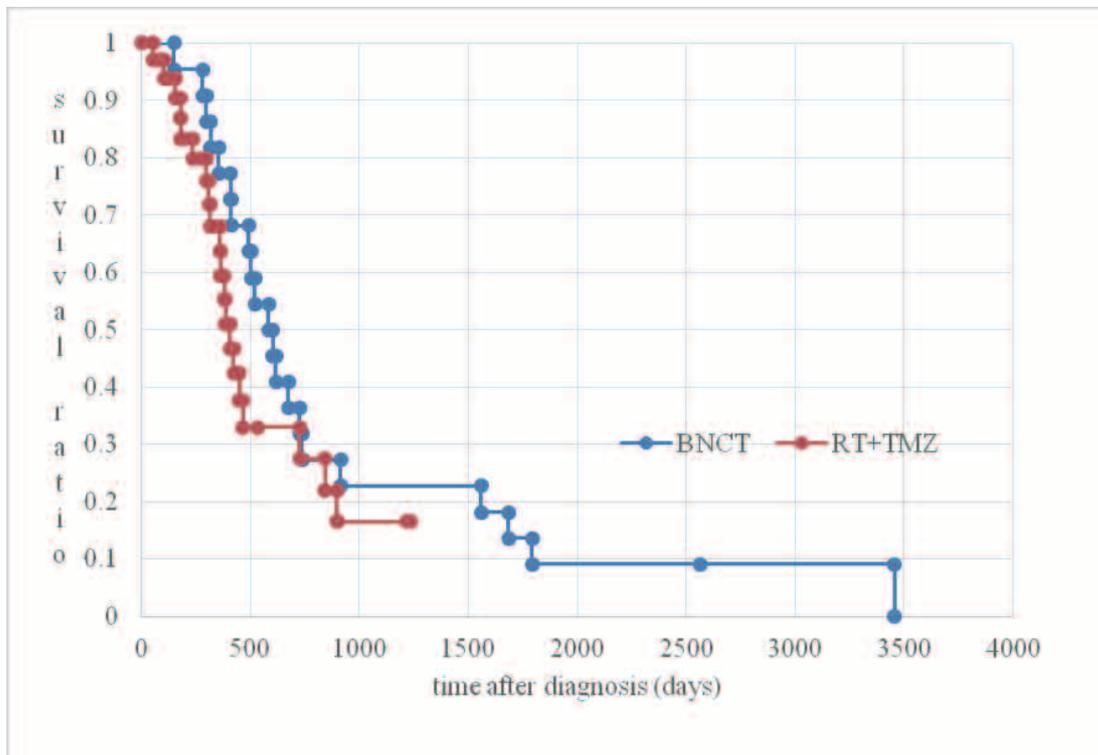

Figure 2   Kaplan Meier curves of patients treated with BNCT alone (n=23) or with RT+TMZ (n=34).
There was no statistically significant difference between patients who underwent BNCT alone and patients treated with RT+TMZ in the survival probability estimates (p=0.25).
BNCT, boron neutron capture therapy ; RPA, recursive partitioning analysis ; RT, radiotherapy ; TMZ, temozolomide.

(p=0.41) between the two groups with respect to the survival probability estimates.

• *MST and survival rate in RPA-subclassified patients treated by BNCT or RT+TMZ*

Of the 23 patients treated by BNCT, 8 each were in RPA subclass 3 and 4 ; the other 7 were in RPA subclass 5. MST in RPA 3-, 4-, and 5 patients was 17.4-, 20.6-, and 11.9 months, respectively (Table 2). The 2-, 3-, and 5-year survival rates were 37.5%, 37.5%, and 16.7%, (RPA 3), 37.5%, 12.5%, and 0% (RPA 4), and 18.8%, 0% and 0% (RPA 5).

In our series, of the 34 patients treated with RT+TMZ, 2 were subclassified as RPA 3, 13 as RPA 4, and 19 as RPA 5. The MST for RPA 4 and RPA 5 patients was 24.2 and 12.8 months, respectively (Table 2). The 2- and 3-year survival rate in RPA 4 and RPA 5 patients was 29.5% and 17.1%, and 29.5% and 9.0%, respectively. There was no statistically significant difference between patients subjected to BNCT or RT+TMZ with respect to the survival probability estimate of patients in subclasses RPA 4 (Fig. 3) (p=0.91) and RPA 5 (p=0.84) (Fig. 4).

Table 2 : Comparison of the median survival time in patients enrolled in the EORTC-NCIC trial and at Tokushima University Hospital

EORTC RPA class[a]	EORTC-NCIC trial[b] RT+TMZ		Our study[c]			
			RT+TMZ group		BNCT alone group	
	n	months	n	months	n	months
RPA 3	42	18.7	2	NE	8	17.4
RPA 4	152	16.3	13	24.2	8	20.6
RPA 5	93	10.7	19	12.8	7	11.9
overall	287	14.6	34	13.5	23	19.5

BNCT, boron neutron capture therapy ; RPA, recursive partitioning analysis ; RT, radiotherapy ;
TMZ, temozolomide ; NE, not evaluated ; n, number of patients

[a]Mirimanoff RO *et al.* Radiotherapy and temozolomide for newly diagnosed glioblastoma : Recursive partitioning analysis of the EORTC26981/22981-NCIC CE3 phase III randomized trial. J Clin Oncol. 24 : 2563-2569, 2006
[b]Stupp R *et al.* Effect of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomized phase III study : 5-year analysis of the EORTC-NCIC trial. Lancet Oncol. 10 : 459-466, 2009
[c]Our study of 23 newly diagnosed GBM patients treated with BNCT. It included 17 patients treated with IO-BNCT and 6 patients treated with NO-BNCT between 1998 and 2005. It also included 34 newly diagnosed GBM patients who were treated by external conventional radiotherapy and temozolomide (TMZ) between 2006 and 2009 at Tokushima University Hospital.
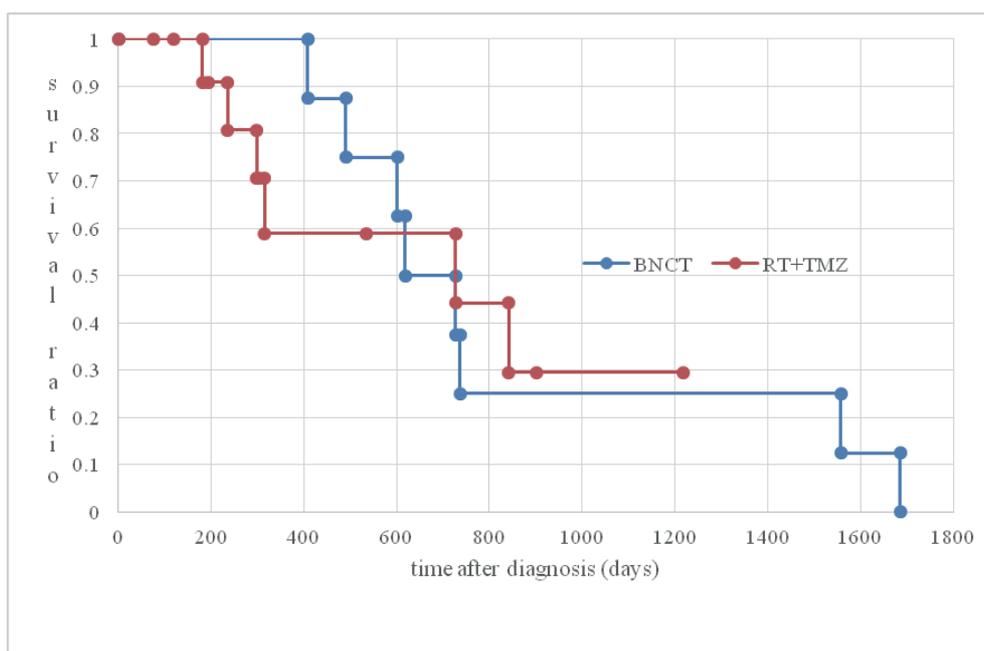

Figure 3   Kaplan Meier curves of patients treated with BNCT alone (n=8) or with RT+TMZ (n=13) who were subclassified as RPA 4. There was no statistically significant difference between the two patient groups in the survival probability estimates (p=0.91). BNCT, boron neutron capture therapy ; RPA, recursive partitioning analysis ; RT, radiotherapy ; TMZ, temozolomide.
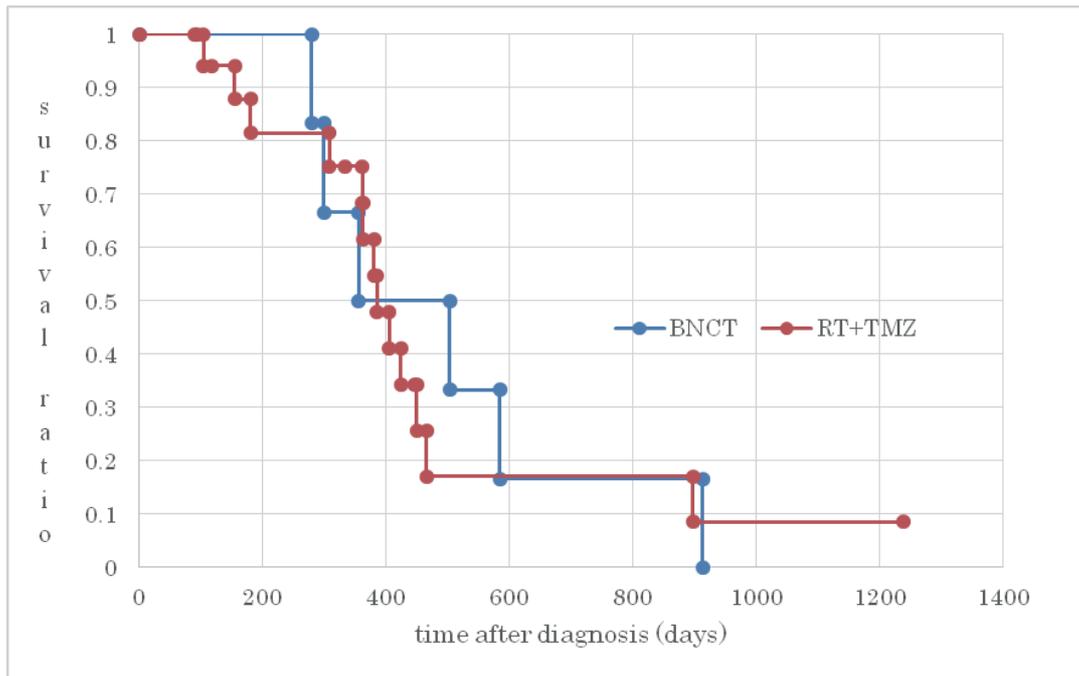
Figure 4   Kaplan Meier curves of patients treated with BNCT alone (n=7) or with RT+TMZ (n=19) who were subclassified as RPA 5. There was no statistically significant difference between the two patient groups in the survival probability estimates (p=0.84). BNCT, boron neutron capture therapy ; RPA, recursive partitioning analysis ; RT, radiotherapy ; TMZ, temozolomide.

DISCUSSION

The mechanism of selective boron uptake in tumor cells was reported as follows : BSH cam pass through the disrupted blood-brain-barrier easily and boron can be internalized into cells in endocytic pathways after binding to the plasma membrane (17). BPA is incorporated into tumor cells via a metabolism pathways of amino acids (18). The destructive effects of these high-energy particles are limited to boron-containing cells and since they have very short path-lengths in tissues (5-9 µm), theoretically, BNCT provides a way to selectively destroy malignant cells while sparing adjacent normal cells (4-6). As BNCT may facilitate the selective killing of tumor cells without damaging adjacent normal brain tissue, it may be an optimal treatment for GBM, which is highly invasive to healthy normal tissue.

The first clinical trials were carried out in 1951 by Sweet at Massachusetts General Hospital, by Brownell at the Massachusetts Institute of Technology, and by Farr at the Brookhaven National Laboratory in New York. They used sodium tetraborate (borax), sodium pentaborate, p-carboxyphenylboroic acid, or sodium decahydrodecaborate as the sole boron delivery agent and thermal neutron beams as the neutron. However, their results were discouraging because none of their patients survived for one year. Hatanaka (5) and Barth *et al.* (6) reported that serious complications such as acute brain swelling and delayed cerebral necrosis arose due to the high boron content in blood and in normal brain tissue at the site of neutron irradiation. In 1968 Hatanaka introduced BSH as a boron carrier in Japan ; GMB patients were subsequently treated with BNCT combined with BSH and pure thermal neutrons, and this was followed by the establishment of BSH-based IO-BNCT which achieved good clinical results (7-9). Laramore and Spence who analyzed the survival data of a subset of 12 patients who had been treated by Hatanaka between 1987 and 1994 found that there was no differences in the survival times between that subset and patients in the RTOG-RPA classification (19). Elsewhere we presented our clinical results of IO-BNCT using BSH ; our MST was 19.5 months and the 1- and 2-year survival rate was 60.6% and 37.9%, respectively (12).

Stupp *et al.* (2) reported that an oral alkylating agent, TMZ, given concomitantly with RT followed by six 28-day cycles of TMZ alone, significantly prolonged the survival of GBM patients. Consequently, the delivery of concurrent RT and TMZ became the new standard of care for patients with newly diagnosed GBM. Stupp *et al.* (3) also reported a 5-year analysis of their randomized RPA-subclassified phase III EORTC-NCIC trial (RT plus concomitant

TMZ chemotherapy followed by the periodic use of TMZ chemotherapy). Their overall MST was 14.6 months; MST was 18.7-, 16.3-, and 10.7 months for patients subclassified as RPA 3, RPA 4, and RPA 5 (Table 2). Overall their 2-, 3-, and 5-year survival rates where 27.2%, 16.0% and 9.8%, respectively (Table 3).

We compared the clinical results we obtained in our RPA-subclassified patients treated with RT+TMZ or with BNCT alone and compared our outcomes with the results of the international EORTC-NCIC trial. Although our study population was smaller, our results in patients who received RT+TMZ were similar to those reported by Stupp *et al.* (2). Our patients treated with BNCT alone underwent no additional chemotherapy; their overall MST was 19.5 months (Table 2); their 2-, 3-, and 5-year survival rate was 31.8, 22.7 and 9.1% (Table 3). Analysis of the clinical outcomes revealed no statistically significant difference in our RPA 4 and RPA 5 patients. Furthermore, MST and the survival rate in our patients treated with BNCT alone were comparable to the findings of the EORTC-NCIC trial.

The literature contains several reports on the clinical results of BNCT. Kankaanranta *et al.* (20) at Helsinki University Central Hospital in Finland reported 22 GBM patients who suffered recurrence after receiving standard therapy. They subsequently underwent BNCT with BPA. Their overall MST was 7 months, and the median time to disease progression was 3 months. The aim of a phase I clinical trial performed by the EORTC to evaluate BSH as a boron delivery agent (21) was to investigate the systemic toxicity of BSH, the tolerated radiation dose, and the dose-limiting toxicity of BNCT. The delivery of BNCT was in 4 fractions on 4 consecutive days. In that trial the MST was 10.4-13.2 months for newly diagnosed GBM patients. In a Swedish clinical trial

29 newly diagnosed GBM patients received an infusion of 900 mg/kg BPA in the course of 6 hours (22-25). The MST was 17.7 months compared to 15.5 months in patients who received standard therapy comprised of surgery followed by RT and TMZ.

In Japan, Miyatake *et al.* (15) and Kawabata *et al.* (26, 27) performed studies in which either BPA alone or in combination with BSH was administered as BNCT. They reported that patients treated with surgery and BNCT using 100 mg/kg BSH and 700 mg/kg BPA infused over 6 hours, followed by 20-30 Gy of fractionated X-rays had an MST of 23.5 months. Yamamoto *et al.* (28, 29) used either BPA or BSH alone or in combination as boron delivery agents. MST in their IO-BNCT patients who received 100 mg/kg BSH alone was 23.3 months; it was 27.1 months when they administered NO-BNCT using 100 mg/kg BSH plus 250 mg/kg BPA followed by 30 Gy of fractionated X-rays.

Elsewhere (30) we reported our clinical results obtained with IO-BNCT and NO-BNCT; MST was 19.5 months and the 2-, 3-, and 5-year survival rate was 26.1%, 17.4% and 5.8%, respectively. The data reviewed here show that the clinical BNCT outcome of newly diagnosed GBM patients tended to be better in Japan than in European series. We attribute this to two factors in recent Japanese BNCT procedure, i.e. combined use of BSH and BPA as the boron delivery agents to obtain homogeneous accumulation in tumor cells, and the delivery of additional conventional radiotherapy of 20-30 Gy after BNCT to irradiate tumor cells that infiltrated areas away from the tumor center.

We did not use TMZ in our patients treated with BNCT because at the time covered by this study it was not available in Japan. Based on our results we expect that combination treatment of GBM patients with BNCT and adjuvant TMZ will improve

Table 3 : Comparison of the GBM survival rate in the EORTC-NCIC trial and in our patients

	2 years (%)			3 years (%)			5 years (%)		
	EORTC-NCIC trial[a] RT+TMZ	Our study[b]		EORTC-NCIC trial[a] RT+TMZ	Our study[b]		EORTC-NCIC trial[a] RT+TMZ	Our study[b]	
		RT+TMZ	BNCT alone		RT+TMZ	BNCT alone		RT+TMZ	BNCT alone
Overall (months)	27.2	27.5	31.8	16.0	16.5	22.7	9.8	NE	9.1

BNCT : boron neutron capture therapy, RPA : recursive partitioning analysis, RT : radiotherapy,
TMZ : temozolomide, NE : not evaluated

[a]Stupp R *et al.* Effect of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomized phase III study : 5-year analysis of the EORTC-NCIC trial. Lancet Oncol. 10 : 459-466, 2009
[b]Our study of 23 newly diagnosed GBM patients treated with BNCT. It included 17 patients treated with IO-BNCT and 6 patients treated with NO-BNCT between 1998 and 2005. It also included 34 newly diagnosed GBM patients who were treated by external conventional radiotherapy and temozolomide (TMZ) between 2006 and 2009 at Tokushima University Hospital.

the outcomes of our previous institutional- and the reported international clinical results for RT plus TMZ.

FUTURE PERSPECTIVES

The current status of BNCT is based on reactor-based neutron sources. It requires neutron sources that can be installed in the hospital environment. Low-energy particle accelerators are more appropriate for this purpose. The availability of this instrumentation in specialized health-care institutions may determine the future of BNCT. The major advantages of accelerator-based BNCT over reactor-based neutron sources are the possibility of their installation in hospitals, lower radiation hazards, and simple licensing, installation, and maintenance. At the Kyoto University Research Reactor Institute in Japan, a cyclotron-based neutron source has been developed for a phase I clinical trial to treat patients with recurrent GBM (31). We expect that in the near future, accelerator-based BNCT may replace treatments using reactor-based neutron sources.

CONCLUSION

Our findings show that favorable results can be obtained in newly diagnosed GBM patients treated by BNCT. Furthermore, patients may further benefit when BNCT is combined with chemotherapeutic agents such as TMZ. Combination therapy must be further evaluated and definite results regarding the survival benefits of BNCT in GBM patients require a strictly designed phase III study.

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