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Survival benefit from boron neutron capture therapy for the newly diagnosed glioblastoma patients

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ABSTRACT

Objective: Since 2002–2007, we applied boron neutron capture therapy (BNCT) to >50 cases of malignant gliomas (MGs) with epithermal neutron irradiations. Recently, we showed the early radiographical improvement of malignant glioma patients by our modified BNCT, with simultaneous use of BPA (borono-phenylalanine) and BSH (sodium borocaptate). In this time, we focused on the survival benefit from BNCT for the newly diagnosed glioblastoma patients.

Methods: BNCT group including 21 newly histological confirmed glioblastoma patients treated with surgical removal followed by BNCT in Osaka Medical College during 2002–2006 period. Ten patients were treated with BNCT only, and in the other 11 patients, 20–30 Gy fractionated external beam X-ray irradiation therapy (XRT) was performed after BNCT. No chemotherapy was administered until tumor progression was observed.

Results: Treatments were well tolerated. Any kind of acute systemic or local severe toxicity were not demonstrated. Mean over all survival of the patients treated by BNCT was 20.7 and the median was 15.6 months with 2-years survival of 25%. Stratification by RPA criteria showed 6, 6, 8 and 1 patients, respectively, in classes III–VI. Three patients out of six in class III and one out of eight in class V are alive at the end point of this study. All the patients in classes IV and VI died. Median survival time for the BNCT group compared to the RTOG database was as follows: 20.6 months vs. 17.9 months for class III; 16.9 months vs. 11.1 months for class IV; 13.2 months vs. 8.9 months for class V.

Conclusion: The RTOG RPA prognostic criteria were helpful in establishing which class of glioma patients could potentially benefit from BNCT. BNCT showed a survival benefit in all of the RPA classes of the RTOG database not only for the good prognosis group.

1. Introduction

To create a breakthrough in the treatment for GB, we have been developing boron neutron capture therapy (BNCT) (Kawabata et al., 2003; Miyatake et al., 2005).

Numerous varieties of boron delivery agents have been developed and tested in experimental studies (Doi et al., 2008; Barth et al., 2005), but only two boron-containing drugs have been used clinically, sodium undecahydro-mercapto-*closo*-dodecaborate ($Na_2B_{12}H_{11}SH$ or sodium borocaptate [BSH]) and 4-dihydroxy-boryl-phenylalanine (or borono-phenylalanine [BPA]) (Barth et al., 2005). Each boron compound has defects as a BNCT agent. BSH dose not actively accumulate in GB, but passively accumulates by the destruction of blood brain barrier (BBB). On the other hand, BPA actively accumulates in tumors but its accumulation is significantly weak in the quiescent cell population of a tumor. Therefore, the simultaneous use of both compounds can increase the boron level in tumors while compensating for each other's faults. The effectiveness of the combined use of BSH and BPA was demonstrated in mouse tumor studies (Ono et al., 1999). Based on these findings in the experiments, we performed, for the first time ever, a new BNCT, in

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which BSH and BPA were simultaneously combined, obtaining good tumor response on MRI, not only for the newly diagnosed malignant gliomas but also for the recurrent cases which had been initially treated by X-ray irradiation therapy (XRT). In our initial protocol, all of the patients received a combination of BSH (100 mg/kg) and BPA (250 mg/kg body weight) administered intravenously.

BNCT was carried out at the Kyoto University Research Reactor Institute (KURRI) using an epithermal neutron beam 12 and 1 h after the administration of BSH and BPA, respectively. This BNCT showed impressive radiographical shrinkage of the tumor mass, and improved the quality of life for even those patients with recurrent malignant gliomas, as described above and reported previously (Kawabata et al., 2003; Miyatake et al., 2005). We achieved a favorable survival benefit for newly diagnosed GB patients with this BNCT protocol, as described below. In the current modified protocol, we applied this BNCT followed by XRT to obtain a more favorable survival benefit for newly diagnosed GB (NDGB) patients. This study was based on experimental animal data showing that a significant therapeutic gain could be obtained when BNCT was combined with an X-ray boost (Barth et al., 2004).

2. Methods

Our BNCT protocol using both BPA and BSH simultaneously has been described previously (Kawabata et al., 2003). Our methods were as follows:

First, we started using epithermal neutrons instead of thermal neutrons to obtain good penetration for deep-seated lesions. Second, we simultaneously used two different boron compounds (BSH and BPA) with different accumulation mechanisms to the tumor cells (Yokoyama et al., 2006; Ono et al., 1999). Third, we utilized a dose simulation work station, the simulation environments for radiotherapy applications (SERA). Fourth, ^{18}F-labeled BPA-positron emission tomography (BPA-PET) was performed for the estimation of the boron compound accumulation prior to neutron irradiation (Imahori et al., 1998). Fifth, we filled the tumor removed cavity with air to obtain enough neutron flux, especially for the bottom of deep-seated tumors (Sakurai et al., 2006). Sixth, we developed a central shielding method with a lithium plate at the center of the irradiation field to obtain uniform neutron distribution and increase the neutron flux relatively at the periphery in the radiation field (Ono et al., 2000).

With these modifications, even patients with deep-seated tumors can be treated by BNCT without craniotomy with a short hospital stay. In the present study, the revised protocol was used as a new protocol as follows.

Twelve hours before the neutron irradiation, the patients were administered 100 mg/kg of BSH intravenously for 1 h. BPA of 700 mg/kg was infused continuously to the patients for 6 h before the irradiation, and they were positioned for neutron irradiation in the reactor (KUR or JRR-4 (Japan Atomic Energy Agency Research Reactor 4)). Just after termination of continuous BPA infusion for 6 h, neutrons were irradiated. We used the dose-planning workstation to calculate the radiation dose for tumors from the ^{18}F-labeled BPA-positron emission tomography data and blood ^{10}B concentrations obtained every 2 h after BSH administration. We used an epithermal neutron beam.

Following this, a 2 Gy daily fraction of XRT was applied, for a total of 20–30 Gy. The total dose of XRT was decided based on the BNCT dose for the normal brain. This protocol was approved by the Ethical Committee of Osaka Medical College and also by the Committee for Reactor Medicine in KURRI. In addition, the indication of BNCT for each candidate was discussed by the latter committee. In Protocol 1, we aimed to apply more than 30 Gy-Eq for gross tumor volume (GTV) and <12 Gy-Eq for normal brain, as BNCT. In Protocol 2, we aimed to apply more than 40 Gy-Eq for GTV and <15 Gy-Eq for normal brain.

Patient enrollment: In the current manuscript, we report the results only for NDGB patients. No chemotherapy was applied for any of the patients until the tumor progression was confirmed histologically or by BPA-PET. Survival time from histologically diagnosed GB was compared with the survival time of the institutional former series of GB patients who were treated by surgical removal followed by XRT and chemotherapy

Table 2

Group	*n*	MST	95% CI (months)	*P*-value (Log-rank test)
Without BNCT	27	10.3	(7.4–13.2)	
With BNCT	21	15.6	(12.2–23.9)	0.0035

See also Fig. 1.

Table 3

	Hazard ratio	95% CI	*P*-value
With BNCT (vs. control)	0.399	(0.206–0.746)	0.0038

See also Fig. 3.

Table 4

Group	*n*	MST	95% CI (months)	*P*-value (Log-rank test)
Historical control	27	10.3	(7.4–13.2)	
With BNCT only	10	14.1	(9.9–18.5)	0.0581
With BNCT plus XRT	11	23.5	(10.2–)	0.0103

See also Fig. 2.

Table 5

	Hazard ratio	95% CI	*P*-value
With BNCT (vs. control)	0.399	(0.206–0.746)	0.0038
BNCT+XRT (vs. control)	0.323	(0.128–0.710)	0.0040
BNCT+XRT (vs. BNCT only)	0.598	(0.0211–1.63)	0.3126

See also Fig. 3.

Table 1

Group	*n*	Mean±SD (months)	Median (MST, months)	1 year (%)	2 years (%)
Without BNCT	27	12.3±8.1	10.3	48.2	14.8
With BNCT	21	20.7±13.1	15.6	76.2	25.0

See also Fig. 1.