Boron neutron capture therapy (BNCT) for glioblastoma multiforme: A phase II study evaluating a prolonged high-dose of boronophenylalanine (BPA)[☆]

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Abstract

Background and purpose: To evaluate the efficacy and safety of boron neutron capture therapy (BNCT) for glioblastoma multiforme (GBM) using a novel protocol for the boronophenylalanine—fructose (BPA-F) infusion.

Patient and methods: This phase II study included 30 patients, 26–69 years old, with a good performance status of which 27 have undergone debulking surgery. BPA-F (900 mg BPA/kg body weight) was given i.v. over 6 h. Neutron irradiation started 2 h after the completion of the infusion. Follow-up reports were monitored by an independent clinical research institute.

Results: The boron-blood concentration during irradiation was 15.2–33.7 µg/g. The average weighted absorbed dose to normal brain was 3.2–6.1 Gy (W). The minimum dose to the tumour volume ranged from 15.4 to 54.3 Gy (W). Seven patients suffered from seizures, 8 from skin/mucous problem, 5 patients were stricken by thromboembolism and 4 from abdominal disturbances in close relation to BNCT. Four patients displayed 9 episodes of grade 3–4 events (WHO). At the time for follow-up, minimum ten months, 23 out of the 29 evaluable patients were dead. The median time from BNCT treatment to tumour progression was 5.8 months and the median survival time after BNCT was 14.2 months. Following progression, 13 patients were given temozolomide, two patients were re-irradiated, and two were re-operated. Patients treated with temozolomide lived considerably longer (17.7 vs. 11.6 months). The quality of life analysis demonstrated a progressive deterioration after BNCT.

Conclusion: Although, the efficacy of BNCT in the present protocol seems to be comparable with conventional radiotherapy and the treatment time is shorter, the observed side effects and the requirement of complex infrastructure and higher resources emphasize the need of further phase I and II studies, especially directed to improve the accumulation of ^{10}B in tumour cells.
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New approaches for treatment of glioblastoma multiforme (GBM) are urgently needed. Boron neutron capture therapy (BNCT) represents an interesting modality for selective irradiation of tumour tissue including infiltrating glioma cells. Following improvements in neutron beams and boron carriers, clinical trials of closed-skull BNCT using BPA-F (boronphenylalanine—fructose) and epithermal neutrons were initiated at several centers. The development of the BNCT concept and the present knowledge have carefully been reviewed by R. Barth in 2003 [2]. The BNCT therapy is seemingly well tolerated [1,9]. The clinical outcome of almost 150 patients treated in non-randomized studies seems to compare with conventional and more prolonged radiotherapy [13]. It is noteworthy that the results obtained so far showed no correlation between the nominal radiation

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doses delivered to target volume and survival. One possible explanation of this unexpected outcome might be that the administration of BPA-F as a 2-h intravenous infusion at a dose of 250–330 mg BPA/kg body weight was effective in delivery of boron to only a subpopulation of tumour cells. This conclusion was supported by electron spectroscopy measurements of boron concentration in tumour cells dispersed in the normal brain obtained after debulking surgery [22]. After a 2-h infusion of BPA, the boron concentration in invading tumour cells was only 37% of that in the bulk of the tumour, while the ratio increased to 71% and 100% when the infusion time was increased to 6 and 24 h, respectively. The advantage of longer infusion times was also supported by pre-clinical studies demonstrating advantages of 6-h infusion compared to 2 h [16,24]. The higher boron concentration provides additional advantages, such as shorter irradiation time and lower neutron fluency to become needed to deliver the prescribed doses, which, in turn, reduce the background radiation dose from the proton recoil and the secondary radiation produced by neutron capture in hydrogen and in nitrogen. However, the potential risk that a longer infusion time results in a higher accumulation in normal cells and greater radiation toxicity must also be evaluated. These observations found the rationale to increase the infusion time to 6 h and the total dose of BPA to 900 mg/kg body weight in the present clinical trials at the Studsvik facility in Sweden (for details see [8]).

The objective of this phase II study at the Studsvik BNCT facility was to assess the degree of tumour control, survival, the safety of BNCT using a 6-h infusion of BPA-F, and the evaluation of the quality of life in patients with glioblastoma multiforme.

Patients and methods
Patients characteristics

Between March 2001 and February 2003, 30 patients with verified glioblastoma multiforme and a good performance status were included in this phase II protocol, designed according to the Geehan two-step procedure. One patient was not eligible since he received only 4% of the prescribed BNCT dose. The median age of the 29 evaluable patients (16 male and 13 female, was 53 years (range 26–69 years). Seven patients had grade 0 of the WHO Performance Status; 19 were of grade 1 and 3 of grade 2. Twenty-seven patients were subjected to debulking surgery, while three patients not eligible for debulking surgery had only a minimally invasive diagnostic biopsy. No other therapies in the primary setting were allowed. The aim was to deliver BNCT no later than 6 weeks following the surgery/biopsy. The study was approved by ethics committees at the participating hospitals. One patient was excluded from the per protocol analysis since she was only given 4% of the planned BNCT dose due to bad compliance. At relapses the patients were given treatment at the discretion of each responsible physician.

Tumour volume (defined as the contrast-enhancing volume) and target (defined as the volume corresponding to the pre-operative tumour volume, plus oedema, plus a 2-cm margin) volumes were in the ranges of 14–306 cm^3

(median 45 cm^3) and 154–885 cm^3 (median 352 cm^3), respectively.

Immediately after BPA-infusion and after neutron treatment, all patients were given high-dose betamethasone. As corticosteroids are known to interfere with the amino acid transport through the blood–brain barrier [21], the goal was to limit their use to a minimum before BPA-infusion. The high-dose betamethasone treatment was continued for a few more days and thereafter gradually decreased and adjusted to the clinical status of each patient by the discretion of the responsible physicians.

BNCT procedure

The treatment procedure has been described in detail elsewhere [8]. The standard BNCT procedure used at Studsvik included two days of preparation, the day of BNCT and an overnight observation at the affiliated hospital. During the first day a CT scan was carried out with and without contrast. Fiducial triangulation points, marked on the patient's scalp and identified by radiographic markers, were used for treatment-planning and patient positioning. The treatment position simulation to realize the optimal irradiation geometry resulting from the treatment-planning was carried out at a geometrical replica of the epithermal beam port usually on the day before the scheduled neutron irradiation.

Two hours after completion of the BPA-F infusion, the patient was transferred to the Studsvik BNCT facility for neutron irradiation and put in the irradiation position as was previously determined during the treatment position simulation. All patients were irradiated with two fields using a 10×14 cm^2 collimator. The duration of irradiation was adjusted to deliver the prescribed peak brain dose, which in turn depended upon the reactor power and the average blood ^{10}B concentration during irradiation. Intercom was used for communication with the patient during irradiation and patient's status was monitored using a closed-circuit TV system and a pulse-oxymeter.

Approximately 1 h after neutron irradiation the patient was transported back to the hospital for an overnight observation.

Boronophenylalanine–fructose

Solutions of the BPA-F complex for infusion were prepared at a concentration of 30 mg BPA/ml (0.14 M) using a modification of previously published procedures (see [8,9]). Briefly, BPA (95% atom ^{10}B-enriched, L-isomer, obtained from Glyconic, NY, USA) was combined in water with a 10% molar excess of fructose. The pH was adjusted to 9.5–10.0 with NaOH, the mixture was stirred until all solids dissolved, and the pH was then readjusted to 7.4 with HCl. The concentration was attuned with water to 0.14 M. The solution was passed through a 0.22 μm-pore sterilization filter (Nalge Company, Rochester, NY) and was transferred to sterile infusion bags. A fresh solution of BPA-F was prepared for each patient and was used within 48 h of preparation. Pyrogenicity and sterility tests were done for each batch.

On the day of irradiation, BPA-F was infused intravenously (i.v.) over 6 h to deliver 900 mg BPA/kg body weight. To assess the boron concentration in the blood, blood samples were intravenously taken just before the start of irradi-

ation, during the break between irradiations at different patient positions, and immediately following the irradiation were used for calculating the average boron concentration during the irradiation.

Additional samples were collected at 12, 15 and 24 h after the start of the infusion. Boron concentration in all samples was measured using induced current plasma atomic emission spectroscopy, for details see [5].

Treatment-planning

The tumour was delineated as the contrast-enhanced zone based on the pre- and post-operative brain scans, and the clinical target volume was defined as a pre-operative tumour volume plus oedema plus a two-centimetre margin. The BNCT treatment-planning software SERA [20] uses CT or MRI images to render the three-dimensional patient geometry, and generate both isodose contours for each beam component and the total BNCT dose. The software requires the input of the boron concentration in the blood and tumour as well as the biological effectiveness factors (RBE and C-RBE) [12], to be used. To be emphasized, in order to improve our evaluation of the tumour border we also performed a MRT/CT within 72 h after surgery to be able to exclude post-surgical reactions which in most studies can hamper a correct later evaluation.

The measured average blood–boron concentration of ^{10}B during BNCT was used to calculate the dose to the normal brain structures. Although the results obtained from stereological morphometry [11] suggests that the average ratio of tumour to blood ^{10}B concentrations is 3.8:1.0, it is prudent to assume that some parts of the tumour that were not perfused as well as the average will contain somewhat less ^{10}B. The 3.5:1 tumour: blood ^{10}B ratio was used to estimate the radiation doses delivered to tumour cells. The RBE-weighted doses were calculated using the following weighting factors: 1.3 and 3.8 for the dose from the boron neutron capture reaction in brain and tumour tissue, respectively; 3.2 for the dose from secondary protons and 1.0 for the gamma dose component (see [9]). For treatment-planning, the duration of irradiation was adjusted to limit the peak and average brain dose to 15.0 Gy(W) and 6.0 Gy(W), respectively.

Post-BNCT management and follow-up

Following the completion of the BNCT procedure, the patients were transferred back to the collaborating hospital where they remained, initially, for 48 h and then overnight for observation. At the completion of the in-hospital observation the patients were discharged to the care of the designated follow-up physicians. The post-BNCT information according to the study protocol was collected and controlled by an independent CRO (Clinical Research Organisation) according to GCP (Good Clinical Practice). Clinical evaluation, including CT/MRT, was performed 6 weeks after BNCT and thereafter every third month.

Time to progression and survival were calculated from the date of BNCT treatment. Survival from radiological diagnosis was also calculated. All adverse effects were graded according to the WHO grading system of toxicity and reported in the patient's medical records and on the case record forms. Quality of life was evaluated using the EORTC

brain cancer module (BCM 20) combined with the EORTC core quality of life questionnaire (QLQ-C30).

Treatment following recurrences was at the discretion of each responsible physician. Thirteen of the 29 evaluable patients were treated with temozolomide at varying time intervals after a progressive disease was evident. Two patients underwent additional surgical resection at relapse, and two patients received additional radiotherapy.

Statistical analysis

The Kaplan–Meier method was used for the survival analysis and the differences between different groups were tested with the log rank test.

Results

Boron pharmacokinetics

The 6-h infusion of 900 mg BPA per kg body weight resulted in an average blood–boron concentration of 24.7 μg/g (range 15.2–33.7 μg/g) at the time of irradiation (approximately 2–3 h post-infusion). The detailed results regarding the pharmacokinetics of boron concentration in the blood and tissues have been discussed previously [6,8]. The maximum boron concentration in the blood was observed at the end of infusion and ranged from 23 to 53 μg/g. Mean blood–boron concentration at 6 and 18 h post-infusion was 18 μg/g (range 12–25 μg/g) and 7 μg/g (range 3–11 μg/g), respectively.

Radiation dosimetry

The radiation doses delivered to the tumour and normal tissue are summarized in Table 1. Radiation doses delivered to the tumour cells within the contrast-enhancing tumour volume and to the tumour cells infiltrating normal brain beyond the contrast-enhancing volume were calculated assuming blood-to-tumour ^{10}B concentration ratio of 3.5 and a uniform distribution of boron within the residual tumour. Peak and average weighted absorbed doses to the brain were in the ranges of 7.0–15.5 Gy (W) and 3.3–6.1 Gy(W), respectively. The minimal weighted absorbed dose delivered to the tumour and target volumes ranged from 15.5 to 54.3 Gy and from 8.8 to 30.5 Gy, respectively.

Adverse effects

An overview of the reported adverse events from all 29 patients is presented in Table 2. Mild and transient side effects such as tiredness and diarrhoea occurred during the infusion in some of the patients. Skin reaction (erythema) was evident in 8 patients. In one patient itchy erythema of grade 3 was seen, most likely related to the anti-epileptic medication with carbamezapin. The patient also developed similar symptoms later on when he was on treatment with phenytoin. The symptoms disappeared completely in a couple of weeks after the treatment was changed. One patient suffered from severe macroscopic haematuria during and following the BNCT procedure, which was completely resolved within 2 weeks. This was assumed to be related to the infusion of a high concentration of BPA-F.

Table 1
Nominal radiation doses delivered to the tumour and normal tissues

	Absorbed doses to the brain		Absorbed doses to the tumour	
	Weighted [Gy(W)]	Physical [Gy]	Weighted [Gy(W)]	Physical [Gy]
Peak	11.9 (8.1—15.4)	9.1 (6.2—12)	69.0 (49—99)	21.0 (15—29)
Average	4.6 (3.2—6.1)	3.7 (2.5—4.9)	58.0 (34—81)	17.9 (11—25)
Minimum	<1	<1	35.0 (15.4—54.3)	11.1 (3.7—13.4)

Mean and range are given.

Table 2
Adverse events obtained during the study period in 19 of 29 patients

Type of AE	No. of events	No. of patients
Skin/mucosa	13	8
Seizures (epilepsies)	12	7
Thrombosis	8	6
Abdominal	5	4
Depression	3	3
Aphasia	2	2
CVS	2	2

Other WHO grades 1—2 toxicities reported include transient lymphocytopenia, granulocytosis, skin pigmentation, patchy atrophy, altered taste, alteration of saliva, otitis media, external otitis, tiredness, psychosis, haematuria, alopecia, dry mouth, conjunctivitis, thyroid dysfunction. CVS, cerebrovascular insult.

Fig. 1. Survival outlined for each individual patient, and status at the time for analysis. T, patients treated with temozolomide at relapse.

In seven patients, 12 epileptic seizures (grades 1—3) in close relationship to the delivered BNCT were reported. Three of the patients have had seizures also at the time of diagnosis, but were free from seizures after the start of anti-epileptic treatment.

Abdominal disturbances, constipation and flatulence with pain (grades 1—2), which could not be excluded to be associated with BNCT, were reported by 4 patients. Venous thromboembolism although most likely not directly related to the BNCT was seen in 6 patients at different time intervals after the BNCT. In addition, a general impression expressed by most investigators was the need for higher and extended treatment with corticosteroids compared to what is required following conventional radiotherapy.

To summarize, the total number of adverse events reported were 61 in 19 out of the 29 evaluated patients. Nine grades 3—4 adverse events were reported in 4 of the 29 patients (epileptic seizures, haematuria, thrombosis, erythema) in close proximity to the BNCT procedure.

Survival

All patients had a follow-up of at least ten months with regard to survival. The survival and progression-free survival are seen in Figs. 1 and 2. The median progression-free survival (PFS) was 5.8 months defined as the time from the start of BNCT treatment and until the detection of recurrence. The diagnosis of recurrences was based on CT/MRI and/or clinical deterioration. In 4 patients a PET-evaluation verified the occurrence of relapses with metabolic active tumours. In one patient a re-operation verified the presence
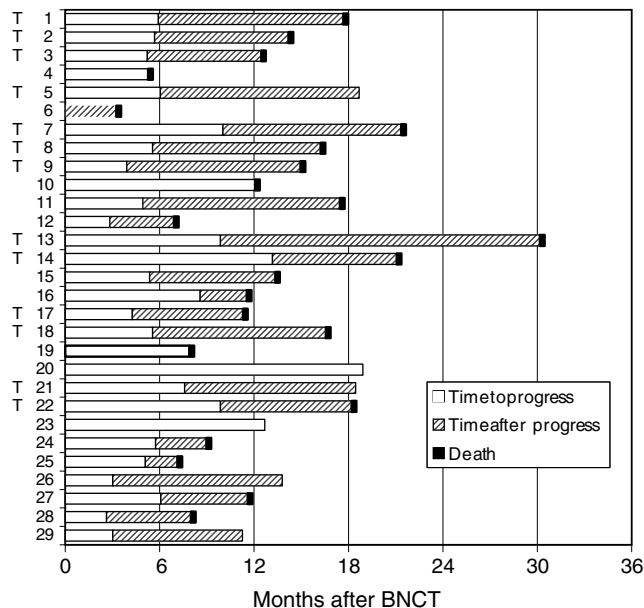
of viable tumour cells. Neurological deterioration was progressively seen in almost all patients during the study period (Fig. 2).

Twenty-three of the 29 evaluable patients were dead at the time for follow-up, performed at least 10 months after treatment. Twenty of them died from progressive GBM, while one died due to pulmonary embolism 3 months after BNCT. In this patient an autopsy could not detect any sign of viable tumour. One patient died from haemorrhage in the tumour and pulmonary embolism, however, with progressive brain tumour disease. One patient died after 8 months without any verified progressive disease, but no other clear explanation could be detected. The overall median survival was 14.2 months calculated from BNCT treatment and the median time from histological diagnosis to BNCT treatment was 40 (1—75) days. The median survival time from radiological diagnosis was 16 months. The patient excluded from the analysis, given only 4% of the prescribed neutron dose, died after 4 months and was not included in this survival analysis. At recurrence 13 of the evaluable patients received treatment with temozolomide, at the discretion of each responsible physician. The median survival of the patients that received temozolomide after tumour
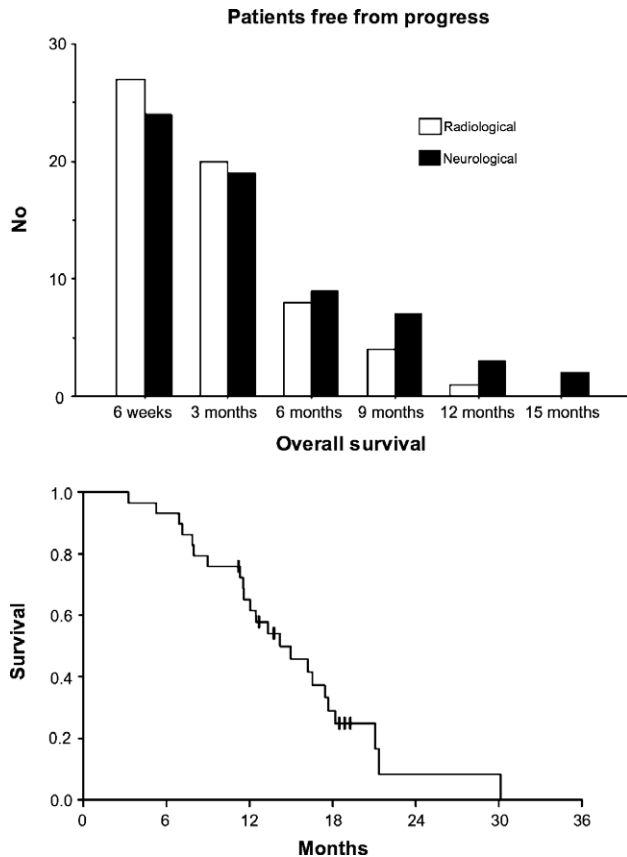
Fig. 2. Patients free from radiological and neurological progress after BNCT treatment (median progression-free survival 5.8 months). No, number of patients. *Inset*: Kaplan—Meier overall survival curve after BNCT treatment (median survival 14.2 months).

progression was 17.7 months as compared to 11.5 months ($p < 0.05$) in those that had not received (Fig. 1).

As shown in Fig. 3, no correlation between the delivered radiation doses and survival times, adverse effects, or quality of life were detected.

Quality of life

EORTC QLQ 30 evaluation forms used in order to get information of the patients self estimated quality of life before and after BNCT. Fig. 4A—C illustrates some of the parameters and show that the patients well-being progressively declined.

Discussion

The present phase II study in patients with glioblastoma multiforme and a good performance status suggest that a single session of BNCT is feasible and that the survival time seems to be comparable to that following multifractionated conventional photon irradiation. However, the effects on survival using BNCT alone is still limited and most of the patients had progress of their disease already within 6 months. BNCT, thus, still must be considered as an experimental therapy and needs to be further improved before it can be adopted in the routine management. It is also of importance to emphasize recently obtained data from controlled clinical studies demonstrating that chemotherapy in addition to conventional irradiation displays beneficial effects [23]. Although not part of the present protocol, it was interesting to find that this observation was also evident in the present evaluation showing a clear survival advantage for those patients who were treated with temozolomide after recurrence.
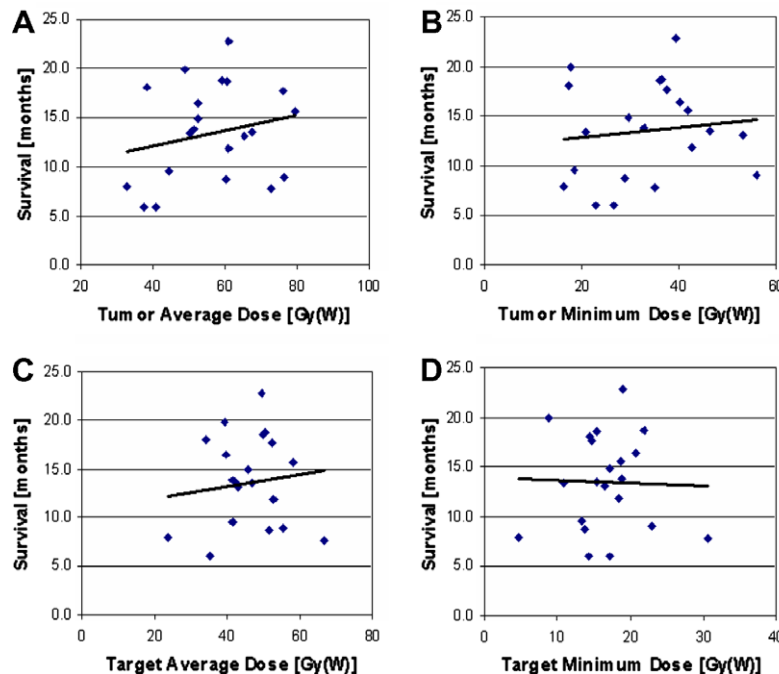

Fig. 3. Survival time versus nominal average and minimum doses delivered to tumour and target volumes.

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