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Boron neutron capture therapy for glioblastoma multiforme: clinical studies in Sweden

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Summary

A boron neutron capture therapy (BNCT) facility has been constructed at Studsvik, Sweden. It includes two filter/moderator configurations. One of the resulting neutron beams has been optimized for clinical irradiations with a filter/moderator system that allows easy variation of the neutron spectrum from the thermal to the epithermal energy range. The other beam has been designed to produce a large uniform field of thermal neutrons for radiobiological research. Scientific operations of the Studsvik BNCT project are overseen by the Scientific Advisory Board comprised of representatives of major universities in Sweden. Furthermore, special task groups for clinical and preclinical studies have been formed to facilitate collaboration with academia. The clinical Phase II trials for glioblastoma are sponsored by the Swedish National Neuro-Oncology Group and, presently, involve a protocol for BNCT treatment of glioblastoma patients who have not received any therapy other than surgery. In this protocol, *p*-boronophenylalanine (BPA), administered as a 6-h intravenous infusion, is used as the boron delivery agent. As of January 2002, 17 patients were treated. The 6-h infusion of 900 mg BPA/kg body weight was shown to be safe and resulted in the average blood–boron concentration of 24 μg/g (range: 15–32 μg/g) at the time of irradiation (approximately 2–3 h post-infusion). Peak and average weighted radiation doses to the brain were in the ranges of 8.0–15.5 Gy(W) and 3.3–6.1 Gy(W), respectively. So far, no severe BNCT-related acute toxicities have been observed. Due to the short follow-up time, it is too early to evaluate the efficacy of these studies.

Introduction

A new comprehensive boron neutron capture therapy (BNCT) center has been constructed at the R2-0 research reactor at Studsvik (100 km south of Stockholm), Sweden. The facility provides excellent conditions for both preclinical and clinical studies. A cavity in the biological shield of the reactor extends all the way to the pool-liner and the open reactor core, which is mobile in the pool, can easily be positioned at the pool-liner directly facing the cavity. It was, therefore, possible to install the appropriate materials for fully optimized filter/moderator assemblies between the reactor fuel and the irradiation position. Furthermore, the cavity is large enough for installation of two adjacent filter configurations, one providing a variable neutron energy distribution and equipped with a flexible, extended collimator-aperture system for clinical irradiations, and the other with a pure field of well thermalized neutrons flooding a large experimental

cavity for radiobiological studies. The reactor can be positioned in front of one or the other of the beam lines as appropriate. The facility also includes a clinical room, a mock-up room for patient positioning and an analytical laboratory with an inductively coupled plasma atomic emission spectrometer (ICP-AES) for measurement of boron concentrations in the blood and in other tissues.

The Studsvik BNCT project enjoys a strong support from the medical-research community in Sweden. In fact, representatives of major universities and of all university hospitals are in one way or another involved in the project and particularly in the implementation of the proposed clinical trials. These trials, initially involving a Phase II protocol for treatment of primary glioblastoma multiforme (GBM), should provide a solid base for thorough clinical evaluation including comparative studies with conventional photon therapy.

This work is an overview of the facility and the current clinical studies. Therefore, the presentation is by no means comprehensive and many aspects such as, for example, the clinical outcome and the beam dosimetry will be covered in detail in follow-up publications.

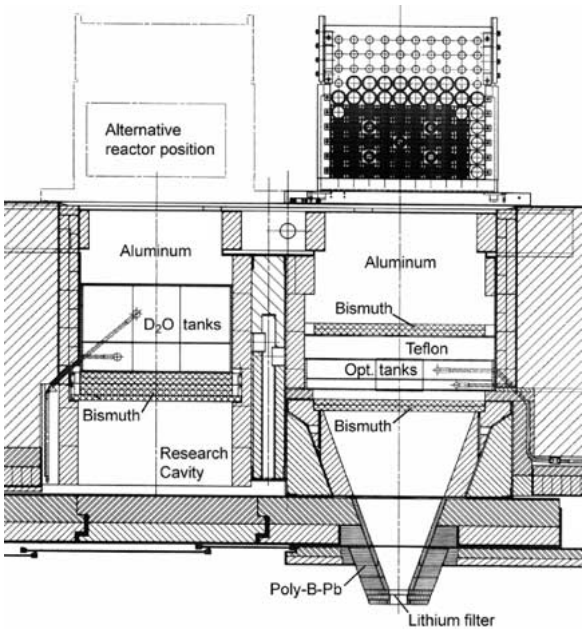

Figure 1. Horizontal cross-section of the beam configurations at the Studsvik BNCT facility.

Facility

The design goal for the clinical beam was to cover the whole range of potential applications, including treatment of deeply seated tumors, which requires a beam of neutrons with energies in the epithermal range, as well as treatment of superficial tumors, which requires a beam of neutrons at lower energies. Extensive radiation transport calculations using the general Monte Carlo N-particle transport code, MCNP, version 4B [1], and the discrete ordinates neutron/photon transport code, DORT, version 3.2 [2], resulted in the filter/moderator composition shown in Figure 1. The filter/moderator components are all quadratic and the collimator has the shape of a truncated pyramid.

The aluminum and the Teflon components of the beam filtration system slow down (moderate) the fast neutrons from the reactor by scattering, while the ^{6}Li filter effectively removes neutrons at lower energies by absorption. In conjunction, these components serve to enhance the relative intensity of neutrons in the epithermal energy range. ^{6}Li has relatively low cross-section for scattering and also does not emit undesired secondary radiation. It can, therefore, be positioned at the downstream end of the collimator, where it is easily accessible for change of filter thickness. The Bi photon shield is divided into two sections with one section positioned before the Teflon compartment to minimize the radiation degradation of the material and with the other section positioned after the D_2O compartment to attenuate the gamma radiation produced by absorption of neutrons in the Al walls of the D_2O containers. The collimator lining in the shutter region and in the extended part of the collimator is made from a composite material consisting of lead (80%), polyethylene (19%) and boron (1%). The aperture of the truncated-pyramid shaped collimator can easily be adjusted in size and shape to optimize the contours of the neutron field for an individual patient.

Different thicknesses of heavy water and lithium in the clinical beam can be combined to tailor the neutron source so that it produces a thermal neutron flux peak at any desired depth in tissue between 0 and 3 cm. This unique flexibility of the beam will allow for the treatment of both superficial and deeply seated tumors under optimal conditions. Calculated beam parameters in air at the exit of the collimator aperture of the clinical beam using the configuration with no D_2O and with 9-mm thick ^{6}Li filter are listed in Tables 1 and 2.

This configuration results in a relatively hard spectrum suitable for irradiation of deeply located tumors. Figure 2 shows the dose rates to the tumor and the brain tissue as a function of depth. The dose distributions

Table 1. Physical beam parameters in air at the exit of the collimator aperture of the clinical beam calculated for the reactor power of 1 MW

Epithermal range	Φ_{epth} (n cm^{-2} s^{-1})	K_{fast}/Φ_{epth} (Gy cm^{-2} n^{-1})	K_{γ}/Φ_{epth} (Gy cm^{-2} n^{-1})
0.4 eV–10 keV	3.2×10^{9}	5.6×10^{-13}	7.1×10^{-13}

Table 2. Beam parameters at 3 cm depth in a $20 \times 20 \times 15$ cm^3 PMMA phantom calculated for the reactor power of 1 MW

Φ_{th} (n cm^{-2} s^{-1})	D_B (Gy h^{-1} ppm^{-1})	D_{γ} (Gy h^{-1})	D_N (Gy h^{-1})	D_{fast} (Gy h^{-1})
6.3	1.7	21.2	3.4	1.3

have been calculated assuming boron concentrations and biological effectiveness factors similar to those used for treatment planning in the clinical trials with *p*-boronophenylalanine (BPA) [3].

The thermal neutron research beam has been designed to produce a pure, large (50×50 cm^2) and homogenous field of thermal neutrons. The lateral dimension of the irradiation port is 70×70 cm^2 and the depth is 50 cm. With both D_2O compartments filled (45 cm) the resulting neutron energy spectrum is well thermalized. Other configurations with 15 or 30 cm of D_2O allow variation of the neutron spectrum for radiobiological studies.

Project organization

The organization of the Studsvik BNCT program involves several closely interacting groups. The Scientific Advisory Board oversees scientific and ethical aspects of the entire program and, in particular, approves trial protocols before submission to authorities. The Clinical Studies Task Group is directly responsible for the planning and the execution of the trials. The treatment team includes the responsible physician at the BNCT facility, the responsible medical physicist, and an experienced nurse. Patient care during BNCT treatment is supplied by a local medical centre in Nyköping, with backup, as needed, from the collaborating oncology clinics. Experienced neuropathologists and neuroradiologists are involved in the evaluation of the outcome of the treatment.

Current studies

Based on the results of the previous BNCT studies [3–5], a Phase II protocol has been designed to carry out clinical BNCT Phase II trials for GBM at Studsvik. The studies are sponsored by The Swedish National Neuro-Oncology Group, which consists of one neurosurgeon and one oncologist from each university hospital in Sweden and additional members particularly active in research and development in the field of neuro-oncology. The protocol was approved by the Swedish Medical Products Agency, the Swedish Radiation Protection Authority and ethics committees of participating institutions.

In this first protocol, BNCT is offered to patients who have had gross total or partial debulking but received no other therapies. Also patients for whom, because of the location of the tumor, the neurosurgeon considered

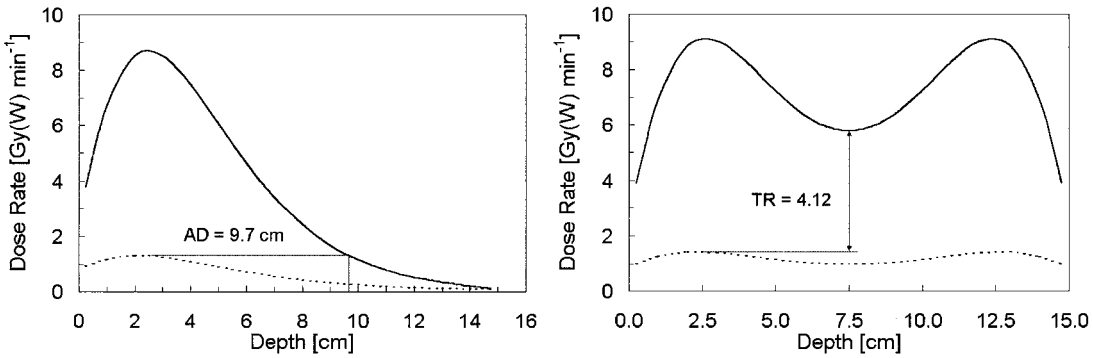

Figure 2. Depth-dose distributions for the Studsvik most penetrating epithermal neutron beam using a single-field (left panel), or two-field, parallel-opposite irradiation (right panel). Solid and dashed lines represent doses delivered to the tumor and normal tissues, respectively. The dose rates were calculated for the reactor power of 1 MW using the same RBE factors and tumor to brain boron concentration ratios as those assumed for treatment planning calculations. AD = advantage depth, TR = therapeutic ratio.

a gross tumor debulking to be particularly hazardous and who have had only a minimally invasive diagnostic biopsy of GBM are eligible. Other inclusion and exclusion criteria are listed in Table 3. As it is important to minimize the delay between the first debulking craniotomy and BNCT, the aim is to deliver BNCT no later than 6 weeks following the surgery/biopsy. The primary objective of the current protocol is to evaluate tumor response defined as lack of tumor progression according to McDonald criteria [6] at 3 and 6 months after BNCT. Secondary objectives include: (1) Evaluation of the safety of BNCT following surgery or biopsy. (2) Assessment of time to clinical or radiological progressive disease. (3) Evaluation of quality of life, symptom control and side effects of patients subjected to BNCT. (4) Evaluation of the overall survival time. (5) Estimation of health resource utilization as compared to conventional treatment of glioblastoma.

The neutron radiation is carried out at 2–3 h following a 6-h infusion of BPA-fructose complex (BPA-F) to the total dose of 900 mg BPA/kg body weight. The prescribed normal brain peak and average weighted radiation dose does not exceed 15 Gy(W) and 6 Gy(W), respectively [7,8]. The Gehan two-step procedure will be used to evaluate the outcome of the studies. The lowest limit of therapeutic efficacy considered to be significant is a response rate of 20%. Response is defined as lack of disease progression, i.e. stable disease, partial or complete response according to McDonald criteria evaluated within 3 and 6 months post-BNCT. In addition, survival time, time to progression, side effects and quality of life will be evaluated. When possible, treatment effects on the tissues and the tumor will also be evaluated by a neuropathologist. The pattern of tumor recurrence (if any) and radiation damage (if any) will be compared with the treatment plan and the radiation doses delivered during BNCT.

Treatment planning

Based on the pre- and post-operative brain scans, the gross tumor volume (GTV) is defined as the contrast-enhanced zone and the clinical target volume (CTV) as well as the planning target volume (PTV) are identified. The BNCT treatment planning software SERA [9] 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 tumor as well as the biological effectiveness factors (RBE and C-RBE) [7], to be used.

Using the solid model descriptions of the regions of interest, a three-dimensional Monte Carlo radiation transport model is applied to calculate the complex radiation fields present in BNCT treatments [9,10]. These radiation fields are then related to radiation doses

Table 3. Inclusion and exclusion criteria of the protocol #1

Inclusion criteria	Exclusion criteria
1. Age $\geq$ 18 years	1. Other primary cancer, with the exception of radically treated squamous or basal cell carcinoma of the skin or 5 years without relapse after diagnosis of other malignancy
2. Performance status 0–2 according to the WHO definition	2. Performance Status WHO grade 3–4, except for patients with a general condition corresponding to WHO 0–1, but due to physical handicap graded as PS 3 or 4
3. Histologically/cytologically confirmed glioblastoma multiforme	3. Any other medical condition that, in the view of the investigator, is a contraindication to inclusion in the study
4. Life expectancy of at least 3 months	4. Chemotherapy, biological therapy, radiotherapy or immunotherapy given previously for brain tumor or within 3 years for other malignancy
5. No other medical condition likely to interfere with treatment or the assessment of its efficacy	5. Radiotherapy to the head, which would interfere with additional radiotherapy treatment for brain tumor
6. No history of phenylketonuria	6. Cardiac pacemaker, metal prostheses or metal implant of any kind (other than titanium microplates and screws) in the head, shoulder, or neck region. However, dental or other prostheses that are readily and harmlessly removable or, if not removable, deemed by us to be irrelevant to BNCT, are exempt
7. Written and verbal informed consent	7. Pregnancy (risk patient must be subjected to urine tests)

delivered to the CTV and surrounding areas. When the planning calculations are complete, the radiation fields are displayed in the original image space as dose contours, and the optimal beam location and treatment time balancing tumor cell kill against healthy tissue sparing is determined. The accuracy of the treatment planning software was verified by in-phantom measurements of neutron fluxes and photon and neutron absorbed doses using, respectively, activation probes and ionization chambers. The measurements were normalized to readings obtained from beam monitors (see Dose monitoring section below).

The measured average blood–boron concentration during BNCT is used to calculate the dose to the normal brain structures. The tumor-to-blood boron concentration ratio used to estimate the tumor and target volume dose is 3.5 : 1 [11]. Although the results obtained from stereological morphometry [12] suggests that the average ratio of tumor-to-blood ^{10}B concentrations is 3.8 : 1.0, it is prudent to assume that zones of the tumor that are not perfused as well as the average will contain somewhat less ^{10}B. The 3.5 : 1 tumor : blood ^{10}B ratio is used to estimate the radiation doses delivered to tumor cells. The RBE-weighted doses are calculated using the following weighting factors: 1.3 and 3.8 for the dose from the boron neutron capture reaction in brain and tumor tissue, respectively; 3.2 for the dose from secondary protons and 1.0 for the photon dose component [3,7]. For treatment planning, the duration of irradiation is adjusted to limit the peak and average brain dose to 15.0 Gy(W) and 6.0 Gy(W), respectively. Whenever possible unilateral irradiation fields are applied in order to spare the contralateral hemisphere (Figure 5).

Dose monitoring

The epithermal neutron flux is monitored by two neutron-sensitive fission chambers located in the wall of the collimator. Pulses from the fission chambers are fed through a single-channel analyzer units into a computer counter interface. Virtual instrumentation software is used for processing and visualization of the data. The monitor units from the fission chambers are correlated to the total dose at the reference depth using data obtained from in-phantom measurements of neutron fluxes and photon and neutron doses determined by gold activation and ionization chambers, respectively. Au/Cu activation wires are used as entrance dosimeters to verify doses delivered by each treatment field.

Patients

Seventeen patients (11 male and 6 female) with histopathology verified GBM or astrocytoma grade 4 were treated within the current protocol between March 2001 and January 2002. Some patient characteristics are listed in Table 4. At the time of BNCT, the median age of these patients was 54 years (range 26–63 years), and 12 of them represented grade 1 of the WHO Performance Status; three were of grade 0 and two of grade 2. GTV (defined as the contrast enhancing volume) and CTV (defined as the volume corresponding to the preoperative tumor volume, plus edema, plus a 2-cm rim) volumes were in the ranges of 14–306 cm^3 (median 71 cm^3) and 154–885 cm^3 (median 347 cm^3), respectively.

BNCT procedure

A typical BNCT session at Studsvik is summarized in Table 5. During the first day, usually on Monday afternoon, CT scans are carried out with and without contrast. Fiducial triangulation points, marked on the patient's scalp and identified by radiographic markers, provide data on spatial distribution of tumor and normal tissues and help to establish a baseline coordinate system used in the BNCT treatment planning software. The position of the beam entry point in relation to the fiducial markers (patient coordinates) and the positions of the fiducial markers in a system of coordinates with origin at the center of the collimator are identified to facilitate positioning of the patient at the epithermal neutron treatment port.

The treatment position simulation is usually carried out on the day before the scheduled neutron irradiation. For this procedure, a geometrical replica of the epithermal beam port, which provides direct visualization of the beam entry point on the scalp, has been constructed in a radiation-free environment. The simulation room and the epithermal beam treatment room are equipped with four and three alignment lasers, respectively. The aim of the simulation procedure is to realize the optimal irradiation geometry resulting from the treatment planning. A thermoplastic mask is used for fixation of the head in the treatment position (Figure 3). The position of the patient in relation to the collimator is precisely delineated using the lasers and reproduced in the epithermal beam treatment room for the irradiation.

Table 4. Patients characteristics

Patient ID	Age	Volume (cm^3)		Survival time		Alive
		Tumor[a]	Target[b]	Post-BNCT	Post-diagnosis	
CRF1	56	130	468	3.2	5.8	No[c]
CRF2	52	44	188	17.6	18.1	No
CRF3	26	40	301	17.8	19.9	Yes
CRF4	57	306	885	16.9	18.9	Yes
CRF5	62	42	154	6.9	7.7	No
CRF6	48	26	217	15.5	18.0	Yes
CRF7	41	45	521	15.6	14.2	Yes
CRF9	54	112	478	13.1	12.4	No
CRF10	42	94	533	13.5	14.0	Yes
CRF11	54	71	270	12.8	14.3	Yes
CRF12	61	212	465	7.1	8.7	No
CRF13	53	76	398	12.4	14.2	Yes
CRF14	47	127	298	11.7	13.3	Yes
CRF15	58	30	346	10.7	13.0	Yes
CRF16	63	92	513	5.1	6.0	No
CRF17	60	14	236	9.8	11.4	Yes
CRF18	43	22	347	8.5	10.7	Yes

[a]Contrast enhanced volume on a CT scan. [b]Pre-operative tumor + edema + 2-cm rim. [c]Cause of death: pulmonary embolism.

Table 5. Time schedule for a typical BNCT session at Studsvik

Day	Activity	Location
Monday	Patient information	Collaborating hospital
	Treatment planning CT scan	Collaborating hospital
Tuesday	Patient positioning	Studsvik BNCT facility
	Admittance to the hospital	Collaborating hospital
Wednesday	BPA infusion	Collaborating hospital
	Neutron irradiation	Studsvik BNCT facility
	Overnight observation	Collaborating hospital
Thursday	Release from the hospital	Collaborating hospital

On the day of irradiation, BPA-F is infused intravenously (i.v.) over 6 h to deliver 900 mg BPA/kg body weight. Blood samples are drawn from the other i.v. line prior to the start of the infusion, every 60 min during the first 5 h of the infusion and every 30 min thereafter until neutron irradiation. Samples taken just before the start of irradiation, during the break between irradiations at different patient positions, and immediately following the irradiation are used for calculating the average boron concentration during the irradiation. Additional samples are collected at 12, 15 and 24 h after the start of the infusion. Also, the technique of microdialysis was used in three patients to compare intracranial concentrations of boron with the levels in serum. Microdialysis allows sampling of soluble molecules from the interstitial fluid by means of a semi-permeable membrane at the tip of a probe. In those three patients, intracranial probes were located in the tumor region (contrast enhanced volume on CT scans), in the brain adjacent to tumor region, and in the normal brain distant from the tumor. Boron concentration in all samples was measured using ICP-AES [13].

After completion of the infusion at the collaborating hospital, the patient is transported by ambulance to the Studsvik BNCT facility for neutron irradiation and put in the irradiation position as was previously determined during the treatment position simulation. The duration of irradiation is adjusted to deliver the prescribed peak brain dose, which in turn depends upon the reactor power and the average ^{10}B concentration during irradiation. Different levels of reactor power in the range from 300 to 600 kW are used to adjust time of irradiation, so that the irradiation of each field takes not less than 5 min and not more than 20 min. Intercom is used for communication with the patient during irradiation and patient's status is monitored using a closed-circuit TV system and a pulse-oxymeter.

After irradiation, patients are transferred back to the collaborating hospital where they remain overnight for

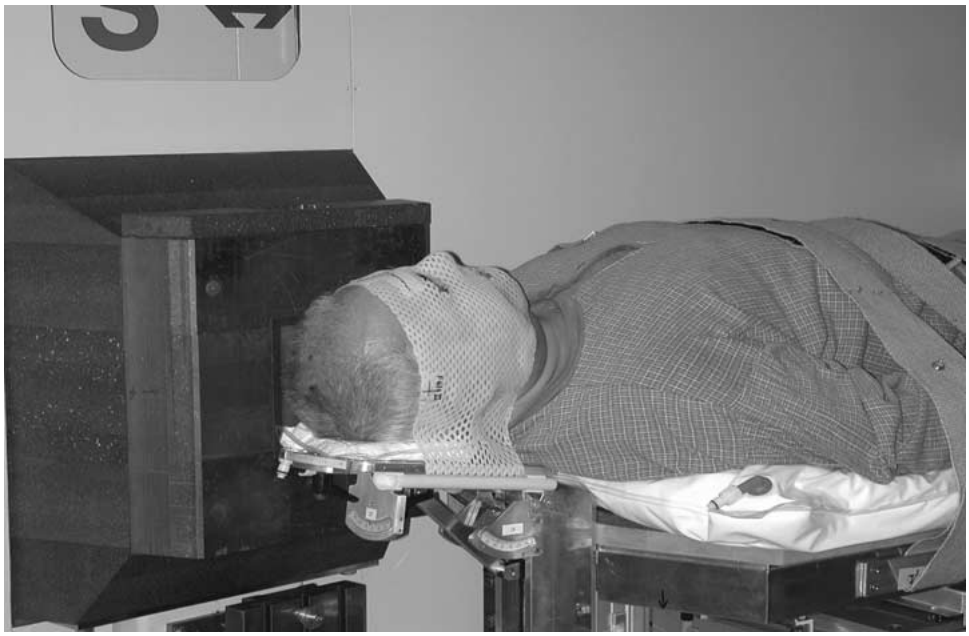

Figure 3. Patient in the treatment position at the epithermal neutron port.

observation. Any adverse effects are recorded in Case Record Form and any significant toxicities are reported to the Swedish Medical Product Agency.

Results

The 6-h infusion of 900 mg BPA/kg body weight was shown to be safe and resulted in the average blood–boron concentration of 24 μg/g (range 15–32 μg/g) at the time of irradiation (approximately 2–3 h post-infusion). Figure 4 summarizes the pharmacokinetics of boron concentration in the blood. The maximum boron concentration in the blood was observed at the end of infusion and ranged from 24 to 50 μg/g. Mean blood–boron concentration at 6 and 18 h post-infusion was 17 μg/g (range 10–24 μg/g) and 7 μg/g (range 3–11 μg/g), respectively. No serious BPA-F related toxicity was observed. However, mild and transient side effects such and tiredness and diarrhaea occurred during the infusion time.

Peak and average weighted radiation doses to the brain were in the ranges of 8.0–15.5 Gy(W) and 3.3–6.1 Gy(W), respectively. Figure 5 shows examples of typical dose distribution resulting from irradiation of tumors at different locations. Table 6 presents a

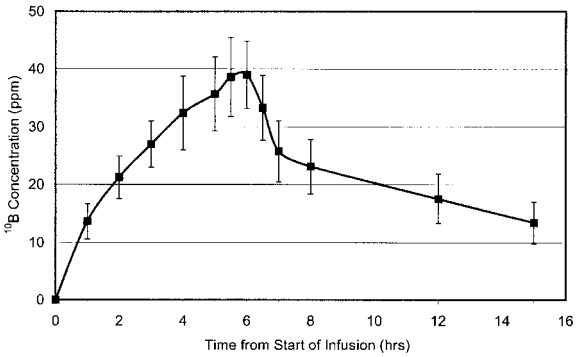

Figure 4. Boron-10 concentration in the blood (average ± standard deviation of 18 patients) as a function of time. Most of the irradiations took place between hours 8 and 9.

summary of observed adverse effects. At the time of writing this preliminary report, no acute adverse side effects have been noticed that would prevent the study from being continued. Postmortem examination of the brain of one patient who died due to pulmonary embolism 3 months post-BNCT did not show any radiation-induced damage to normal brain and, according to a preliminary evaluation, the tumor showed signs of reduced vitality. As of October 14, 2002, five of the remaining 16 patients died due most likely to

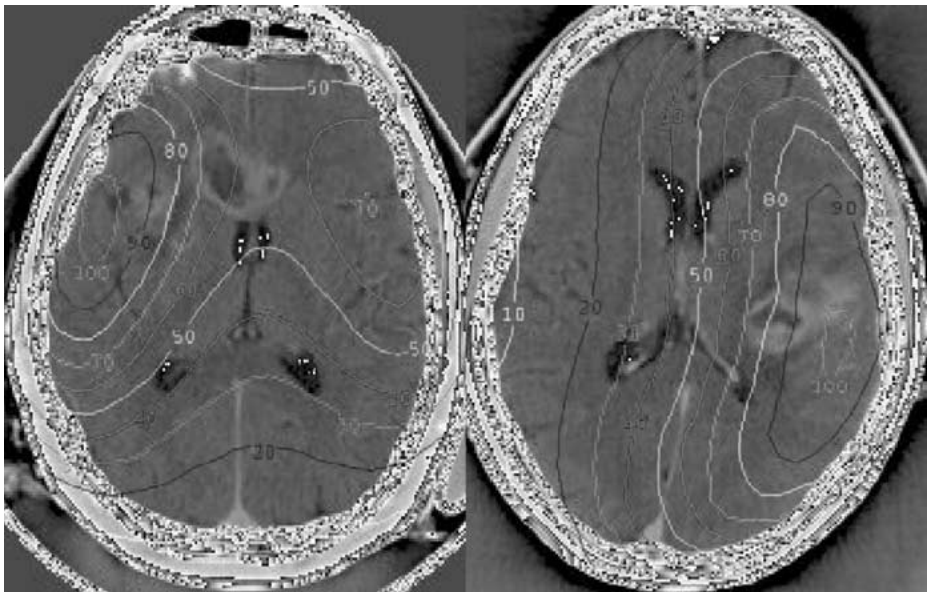

Figure 5. Examples of isodoses resulting from irradiation of tumors at different locations. Left panel: Two lateral-opposite fields were used to treat deep tumor invading corpus calosum. Sixty percent of the irradiation was applied to the ipsilateral hemisphere from where the tumor had originated. Right panel: Two equal unilateral fields were used to treat unifocal tumor limited to ipsilateral hemisphere. Hundred percent corresponds to the prescribed peak normal-brain dose.

Table 6. Adverse effects

Type of adverse effect	Number of events	Number of patients
Alopecia	17	17
Epilepsy	9	5
Depression	5	5
Abdominal pain	4	3
Thrombosis	3	3
Aphasia	2	2

tumor progression (unfortunately, no autopsy was performed) 5.1, 6.9, 7.1, 13.1 and 17.1 months post-BNCT (Table 4). However, due to the short follow-up time of this group of patients ranging from 6.9 to 18.9 months (median 12.4 months) post-BNCT and to the fact that the study is still in progress, it is too early to analyze the outcome. Detailed evaluation of the time to progression, survival time, side effects, and quality of life will be done according to the protocol only after the completion of the current study.

Discussion

The idea of clinical BNCT at Studsvik crystallized in May 1996 when the Studsvik management set up a team of scientist and physicians to evaluate the feasibility of a BNCT facility. In October 1998 the Studsvik Board made the decision to finance the project and the first GBM patient was treated in March 2001. The fact that 10 months later 17 patients have been treated in clinical BNCT trials sets new standards. This relatively fast recruitment of patients was possible thanks to the critical involvement of the medical community from the very beginning of the BNCT project in Sweden. The project is also an example of successful collaboration between academia, industry and the local government, as indicated by the affiliations of the authors of this paper.

The current Phase II trials in Sweden are to a great extent based on the results of the Phase I/II clinical BNCT trials carried out at Brookhaven National Laboratory between 1994 and 1999 as reported by Chanana et al. [3], Aziz et al. [4] and Diaz et al. [5]. The safety (Phase I) part of the Brookhaven trials provided data on the tolerance limits of the normal brain to irradiation with epithermal neutron beam in the presence of BPA. The fact that no severe toxicity was observed in patients treated to the peak and average normal brain dose of, respectively, 15 Gy(W) and 6 Gy(W), set the upper radiation dose limits. Furthermore, the Phase II part of the Brookhaven studies, showed lack of correlation between the nominal radiation doses delivered to

target volume and time to progression or the total survival time. 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 or 290 mg BPA/kg body weight was not effective in delivery of boron to at least a subpopulation of tumor cells. This conclusion was supported by recently published results of secondary ion mass spectrometry measurements of boron concentration in tumor cells dispersed in the normal brain [14] showing that, after a 2-h infusion of BPA, the boron concentration in invading tumor cells was only 37% of that in the bulk of the tumor, while the ratio increased to 71% and 100% when the infusion time was increased to 6 h and 24 h, respectively. The advantage of longer infusion times was also supported by results of preclinical studies by Joel et al. [15] indicating that the tumor to blood–boron concentration ratio remains 3.7 even during longer infusion time and that the increase of the boron concentration in the blood from about 12 to 21 μg/g resulted in the corresponding increase of boron concentration in the tumor from 45 to 78 μg/g after 2- and 6-h infusion, respectively. Furthermore, the boron concentration in tumor cells exposed to BPA in *in vitro* studies by Wittig et al. [16] increased with time up to 6 h. It is possible that the time needed for BPA to cross the blood–brain barrier, reach tumor cells and be transported to cytoplasm should be longer than 2 or 3 h offered by the Brookhaven protocols. Also other benefits of higher boron concentration are clear: shorter irradiation time and lower neutron fluence are needed to deliver the prescribed doses, which, in turn, reduce background dose from the proton recoil and the secondary radiation produced by neutron capture in hydrogen and in nitrogen. These facts lead us to increase the infusion time to 6 h. As the neutron irradiation is carried out at about 2.5 h post-infusion, BPA is present in the blood for a period of time about threefold longer as compared to other clinical BNCT protocols using BPA as the boron delivery agent [3,17,18]. As presented in the Results section, the applied infusion protocol was safe and resulted in a significant increase of boron concentration in the blood at the time of neutron irradiation.

Due to the short time of follow-up the effect of the increased infusion time and the total boron concentration on the efficacy of BNCT is not clear yet. It is also difficult, if not impossible, to discuss the effect of the increased total boron concentration and of the radiation doses to tumor (GTV) or target (CTV) due to essentially unknown concentration of boron in the individual tumor cells present in each of these regions of interest. The hypothesis that the increased infusion time and the higher total BPA doses result in higher radiation doses to tumor cells may be tested by comparison of the results obtained by BNCT protocols using shorter infusion times. To make such an analysis possible it is crucial that common standards regarding BNCT dosimetry and post-BNCT reporting are agreed upon and implemented. Furthermore, in order to facilitate communication with broad medical community, standards used in BNCT should as much as possible adhere to those of conventional radiation therapy.

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