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Boron neutron capture therapy of brain tumors: clinical trials at the Finnish facility using boronophenylalanine

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Summary

Two clinical trials are currently running at the Finnish dedicated boron neutron capture therapy (BNCT) facility. Between May 1999 and December 2001, 18 patients with supratentorial glioblastoma were treated with boronophenylalanine (BPA)-based BNCT within a context of a prospective clinical trial (protocol P-01). All patients underwent prior surgery, but none had received conventional radiotherapy or cancer chemotherapy before BNCT. BPA-fructose was given as 2-h infusion at BPA-dosages ranging from 290 to 400 mg/kg prior to neutron beam irradiation, which was given as a single fraction from two fields. The average planning target volume dose ranged from 30 to 61 Gy (W), and the average normal brain dose from 3 to 6 Gy (W). The treatment was generally well tolerated, and none of the patients have died during the first months following BNCT. The estimated 1-year overall survival is 61%. In another trial (protocol P-03), three patients with recurring or progressing glioblastoma following surgery and conventional cranial radiotherapy to 50–60 Gy, were treated with BPA-based BNCT using the BPA dosage of 290 mg/kg. The average planning target dose in these patients was 25–29 Gy (W), and the average whole brain dose 2–3 Gy (W). All three patients tolerated brain reirradiation with BNCT, and none died during the first three months following BNCT. We conclude that BPA-based BNCT has been relatively well tolerated both in previously irradiated and unirradiated glioblastoma patients. Efficacy comparisons with conventional photon radiation are difficult due to patient selection and confounding factors such as other treatments given, but the results support continuation of clinical research on BPA-based BNCT.

Introduction

The first patient was treated with boron neutron capture therapy (BNCT) at the Finnish Research Reactor (FiR 1) in May 1999. The reactor is located within the Helsinki metropolitan area (about one million inhabitants) at Otaniemi, Espoo, about 6 km from the largest hospital of Finland, the Helsinki University Central Hospital. The FiR 1 reactor, a light-water moderated 250 kW Triga Mark II nuclear research reactor, was taken in use in 1962. It functioned as a training and research reactor for neutron activation analysis, isotope production, and neutron physics until the mid-1990s. In 1996, an epithermal neutron beam was

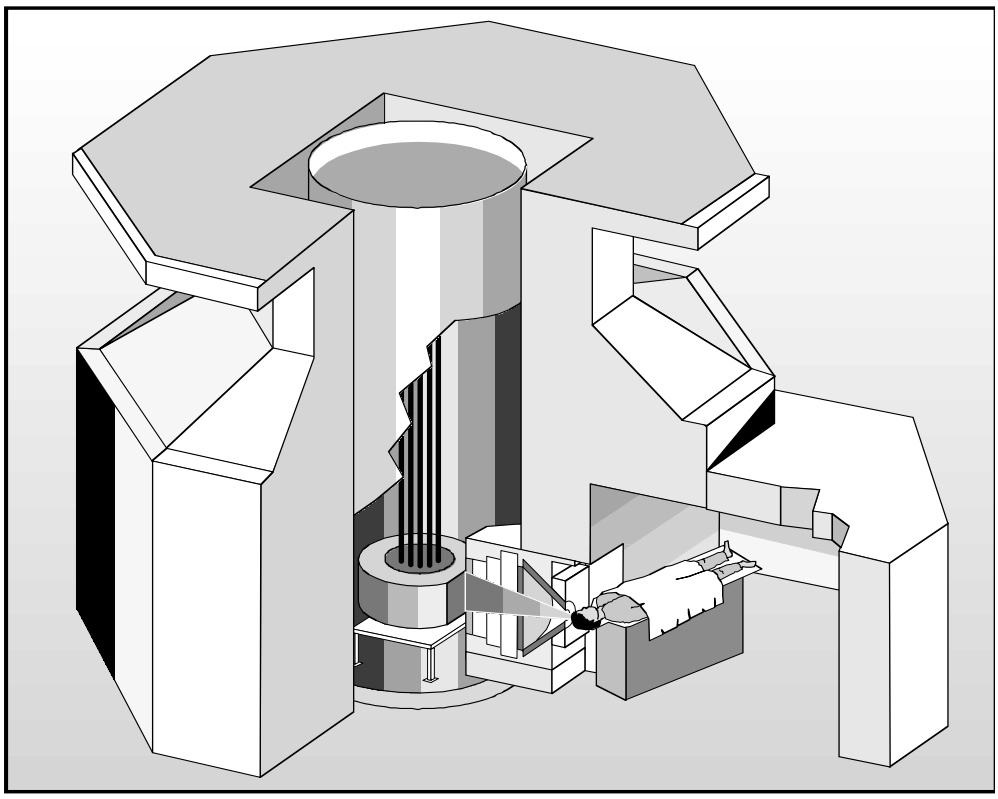

Figure 1. Schematic drawing of the BNCT facility at Fir 1.

constructed based on a new neutron moderator material Fluental™ developed at VTT (Technical Research Centre of Finland) [1,2]. After successful demonstration of a high purity epithermal beam, the patient irradiation room was constructed by cutting partly into the concrete shielding of the reactor (Figure 1). The Fluental™ moderator was shortened to create at that time the highest intensity and best purity epithermal neutron beam for BNCT. The whole reactor building was renovated including construction of irradiation simulation and monitoring rooms, and a laboratory for boron analysis, creating a dedicated clinical BNCT facility at the reactor site [3].

Patients are treated in a collaboration with the Helsinki University Central Hospital, VTT, and the NC-Treatment Ltd. The Finnish BNCT multispeciality team consists of radiation therapists and clinical oncologists, neurologists, neurosurgeons, radiologists, pathologists, radiation physicists, chemists, pharmacists, nurses, and the nuclear reactor facility personnel. The BNCT facility has been licensed for clinical use and is being surveyed by Finnish Nuclear and Radiation Safety Authority (STUK). The FiR 1 neutron beam is particularly well suited for BNCT because of its low hydrogen-recoil and incident gamma doses, and its high intensity and penetrating neutron spectrum characteristics [4].

To improve patient safety and to further characterize the properties of the FiR 1 neutron beam, beagle dogs were irradiated with the FiR 1 beam before starting the current clinical trials. The beagles were irradiated using escalating neutron doses without the ^{10}B carrier compound L-boronophenylalanine-fructose (L-BPA-F), but one dose group was infused with 700 mg L-BPA/kg body weight. In these experiments the relative biological efficiency (RBE) of the FiR 1 beam as compared with a conventional Linac 6 MV photon beam turned out to be about 1.25 in the dog brain [5]. Glioblastoma multiforme was chosen as the first tumor type to be treated, because treatment results achieved with conventional therapies are uniformly poor in this disease. Moreover, the pioneering work on

BPA-based BNCT performed at other BNCT facilities, notably at the Brookhaven National Laboratory, had already produced preclinical and clinical data that further improves safety of irradiations and formed a basis for further development of clinical BNCT [6,7]. In this paper we describe the methodology used by the Finnish BNCT consortium in clinical BNCT trials, and describe shortly the first clinical results obtained at the Finnish BNCT facility. Since BNCT is considered as an experimental form of radiation therapy, all our patients have been treated within the context of clinical research protocols approved by an institutional ethical committee, and a written informed consent was obtained from all patients.

Patients and methods

The neutron beam

The neutron beam obtained from FiR 1 is moderated using Fluental™, which is composed of 69% aluminumfluoride, 30% aluminum, and 1% lithium fluoride. Circular collimator apertures of 8, 11, 14, 17, and 20 cm in diameter are available for clinical use. The measured thermal (<0.5 eV), epithermal (0.5 eV–10 keV), and fast neutron (>10 keV) fluence rates are 8.1×10^7, 1.1×10^9, and 3.4×10^7 neutrons/cm^2/s, respectively, at the exit plane using a 14 cm diameter collimator at 250 kW power [8]. The undesired fast neutron dose per epithermal fluence is 2 Gy/10^{13} cm^{-2} and the corresponding gamma contamination 0.5 Gy/10^{13} cm^{-2} [2]. The in-depth dose characteristics of the epithermal neutron beam are shown in Figure 2. The beam monitoring instrumentation includes three neutron sensitive fission counters and one gamma-sensitive ionization chamber positioned in the neutron beam second to the moderator substance [9]. The instrument readings are monitored with a computer program and back-up hardware counters to ensure the beam stability during irradiation. The main purpose of the monitoring system is to provide a dosimetric link with the patient dose during the treatment. The fission chamber count rates have been calibrated to the induced thermal neutron fluence rate and to the absorbed dose rate at reference conditions in a tissue substitute phantom. A computational model for the neutron beam has been constructed, and the model has been verified by several measurement campaigns [10]. The model accurately produces neutron and gamma fields both in free beams and in phantoms. Based on this model, a source description for the treatment planning code has been created.

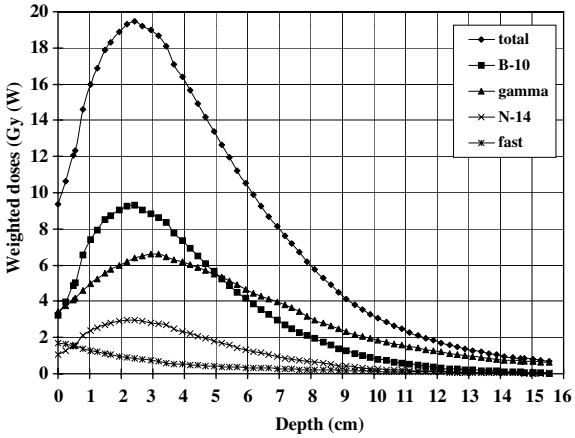

Figure 2. Modeled weighted dose rates to the normal brain in the central axis of a circular 14 cm diameter beam in a patient head. Boron concentration is 13 ppm.

Boronophenylalanine-fructose

Prior to clinical studies, different synthetic batches of L-BPA were investigated [11]. For clinical studies L-BPA was purchased from Katchem Ltd. (Prague, Czech Republic). L-BPA was complexed under aseptic conditions with fructose to form L-BPA-F at the pharmacy of the Helsinki University Central Hospital. The L-BPA-F solution was prepared at a concentration of 30 g L-BPA/L by combining L-BPA with 10% molar excess of fructose in water. The final pH of the L-BPA-F solution was adjusted to 7.6 and tested for pyrogens before use. The infused amount of L-BPA varied between 290 and 400 mg/kg given at a constant rate over 2 h intravenously before irradiation (Table 2). L-BPA-F solution was infused at the BNCT facility, and irradiation with the neutron beam started about 45 min after completion of infusion.

Blood samples for monitoring whole blood boron concentration were taken immediately before starting L-BPA-F infusion, and thereafter at about 20 min intervals during L-BPA-F infusion, following infusion, after treating the first portal with epithermal neutron irradiation, and the last one or two samples were taken after completion of irradiation. The blood samples were analyzed for blood boron concentration using inductively coupled plasma-atomic emission spectrometry (ICP-AES) as described elsewhere [12]. Estimation of

the average whole blood boron concentration during irradiation was based on kinetic models [13].

Radiation dose planning

Conventional cranial imaging for BNCT dose planning was done 1–3 weeks before BNCT delivery with a 1.5T Magnetom Vision MRI imager. Gadolinium-DTPA was used as a contrast agent. MRI detectable markers were placed on the skin before MRI to mark the reference points for head positioning, and their locations were tattooed on the skin. The MRIs taken before craniotomy and 1–2 days after craniotomy were not used for dose planning, but were examined for additional information regarding tumor localization, tumor volume, and presence of edema.

The 3D Monte Carlo software packages BNCT_Rtpe and/or SERA (INEEL/MSU, Idaho Falls/Bozeman, USA) were used in the BNCT dose planning. Contrast enhanced T1-weighted MR images were used to construct a computed 3D model of the patient's head. The tissue compositions for transport computations were defined according to the ICRU Report 46 [14]. The weighted total dose (D_W) was defined as the sum of physical dose components (D_i) multiplied by weighting factors (w_i) of each dose component in a tissue

$$D_W = w_g D_g + w_B D_B + w_N D_N + w_{fast\_n} D_{fast\_n},$$

where D_g is the gamma dose, D_B the boron dose, D_N the nitrogen dose, and D_{fast_n} the fast neutron dose [15]. The weighting factor for boron dose w_B was taken as 3.8 in the target and the tumor, and 1.3 in the normal brain. Weighting factors w_N and w_{fast_n} were taken as 3.2, and w_g was considered to be 1.0 in the target, the tumor, and the normal brain [16,17]. The fluence-to-kerma conversions of the weighted nitrogen and the weighted fast neutron doses were calculated using a nitrogen concentration of 1.84 wt % and a hydrogen concentration of 10.57 wt %, assuming the brain tissue to be composed of equal proportions of the white and gray matter [18]. The unit for the physical dose components is Gy and for the weighted dose Gy (W).

The doses in the tumor, the target volume, and in the sensitive tissues were computed individually as a function of the average boron concentration in the whole blood during irradiation. For the boron concentration, tumor-to-whole blood ratio of 3.5 : 1 and the normal brain-to-whole blood ratio of 1 : 1 were assumed. The computational head model consisted of the skin, the skull, the brain, the target volume, and the tumor regions in protocol P-01. In addition to these structures, the sinuses were also outlined in protocol P-03. When computing the average brain dose, the entire brain and the tumor site were included in the computation volume. The target volume was defined to consist of the enhancing tumor present in MRI, the surrounding edema, plus a 1–2 cm margin in the brain tissue in three dimensions. Two fields were irradiated in all cases, and an attempt was made to exclude the contralateral hemisphere from the target volume whenever possible. Maximum doses allowed in dose planning were determined for different anatomical structures.

Patient positioning

Patient positioning simulation for irradiation was carried out one day preceding irradiation. The beam entry and exit coordinates were provided by the dose planning program. The entry and exit coordinates given by the dose planning program were transformed in a Microsoft Excel program to a positioning coordinate system with the help of three detectable reference markers, which were placed on the patient's skin before carrying out the dose planning MRI. Patient positioning was performed in the treatment simulation room located next to the nuclear reactor. The computed beam exit and entry points were first localized and marked on the skin. After finding the optimal head position relative to the beam aperture, head and body vacuum immobilizers were shaped to secure maintained head and body position during neutron beam irradiation. The patient positioning system included a custom-made treatment coach equipped with electrical controls for the couch table position in three dimensions (Te-Pa Medical Oy, Lappeenranta, Finland), a beam aperture simulator, and a total of nine crosshair lasers. The crosshair laser system was fixed to the center of the beam aperture, and provided an identical coordinate system for head positioning both in the simulation room and in the irradiation room.

Irradiation and monitoring of the irradiation dose

Following BPA-F infusion, the patient was placed in the preshaped vacuum immobilizers on the treatment couch. The correctness of the head position for treatment was verified using positioning lasers first in the simulator and then at the irradiation site immediately before irradiation. All treatments were given as one single fraction. The irradiation time of the first field ranged

from 15.2 to 40.2 min (median, 29.6 min), patient repositioning between the fields took about 20 min, and irradiation of the second field lasted from 14.5 to 37.2 min (median, 21.5 min). Hence, the irradiation procedure typically lasted for about 1 h. Apertures of 11 or 14 cm in diameter were used in all irradiations. During neutron beam irradiation, the patient position was monitored with two television cameras. Pulse and blood oxygen level were monitored during irradiation. Vital signs were recorded before irradiation, and at 2-h intervals following irradiation for 8 h.

The nominal irradiation time computed with a dose planning program was adjusted based on the whole blood boron concentrations measured at the reactor site with ICP-AES. The blood boron analysis results were available about 10 min after sampling. The average blood boron concentration during each neutron irradiation was estimated based on kinetic models and preirradiation blood boron concentration data. Two kinetic models, an open two-compartment model and a biexponential fit are currently in use in the Finnish BNCT-trials (Figure 3). These models estimate the clearance of boron from the blood after BPA-F infusion of 290 mg BPA/kg body weight with accuracy of about 1 ppm or less during the first and second radiation fields [13]. Recently, a more capable kinetic model was developed [19]. The target beam monitor counts were set based on the corrected irradiation times. The irradiation was terminated by a reactor scram when the set beam monitor counts were reached.

Absorbed gamma doses were measured using *in vivo* thermoluminescence dosimeters (TLD) placed in the ipsilateral ear canal, at the fixation point ventral to the contralateral ear, at the base of the nose, and on the skin over the 7th cervical vertebra, the thyroid, the sternum, and on the umbilicus. Thermal neutron fluences were measured with Mn(n, γ) activation foils/wires placed on the beam entry points, in the ipsilateral ear canal, and at the base of the nose.

Patient follow-up

After neutron beam irradiation, the patients were followed up at the Department of Oncology, Helsinki University Central Hospital for about 2–3 days for possible acute radiation-related adverse effects. Dexamethasone was routinely prescribed to prevent radiation-related edema, and all patients also received antiepileptic medication. Neurological status and adverse effects were recorded using structured forms. Brain MRI examinations were scheduled to be performed 1, 3, 6, 9, 12, 18, and 24 months after irradiation using gadolinium-DTPA as a contrast agent, and clinical follow-up visits were performed at 1–3 month intervals during the first post-irradiation year.

Protocols

Protocol P-01

P-01 is a prospective, nonrandomized, phase I to II study focusing on feasibility of giving BNCT as primary radiotherapy to patients with newly diagnosed glioblastoma multiforme. Eighteen glioblastoma patients have been enrolled between May 1999 and December 2001. Eleven patients were male and the median age was 55.5 (ranging 31–67). The median time interval from surgery to BNCT was 31.5 days (ranging from 15 to 43 days). The inclusion and exclusion criteria are presented in Table 1. BPA is given intravenously complexed with fructose as 30 g BPA/L aqueous solution over 2 h, and the BPA-F dosage given

Table 1. P-01 protocol inclusion and exclusion criteria (BNCT as primary treatment for glioblastoma following surgery)

Inclusion criteria
Histologically confirmed glioblastoma multiforme
Supratentorial location
Age 18–75
Karnofsky's performance status 70% or higher
Adequate antiepileptic medication
Written informed consent is obtained and the patient is able to understand the nature of the trial
Exclusion criteria
Radiation tolerance of the optic chiasma or the basal ganglia is estimated to be exceeded in dose planning, or an adequate dose is not considered to be achieved in the deep-seated parts of the target
Less than 30% of the tumor has been removed at surgery based on comparison of the preoperative MRI and a postoperative MRI taken no longer than 72 h after craniotomy
Over 6 week time interval from craniotomy to BNCT
Prior cranial radiation therapy, cancer immunotherapy, chemotherapy or gene therapy
Serious cardiac insufficiency, liver or renal disease, or infection
Presence of a cardiac pacemaker, or metallic prostheses or implants in the head and neck area that prohibit MRI
Pregnancy or breast feeding
Phenylketonuria
Dexamethason is contraindicated

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