THE NCT TRIALS IN FINLAND

I. Auterinen[4], H. Joensuu[1], M. Kouri[1,14], L. Kankaanranta[1], T. Seppälä[2,3,14], M. Kallio[2,5], M. Kulvik[2,5], J. Laakso[6], J. Vähätalo[7], M. Kortesniemi[2,3,8,9], P. Kotiluoto[4], T. Seren[4], J. Karila[3], A. Brander[9], E. Järviluoma[10], P. Ryynänen[3], A. Paetau[11], I. Ruokonen[6], H. Minn[13], M. Tenhunen[1], J. Jääskeläinen[12], M. Färkkilä[5], S. Savolainen[8,9,14]

[1]Department of Oncology, Helsinki University Central Hospital; [2]Clinical Research Institute, Helsinki University Central Hospital; [3]Department of Physical Sciences, University of Helsinki; [4]VTT Processes, Technical Research Centre of Finland; [5]Department of Neurology, Helsinki University Central Hospital; [6]Institute of Biomedicine, University of Helsinki; [7]Laboratory of Radiochemistry, University of Helsinki; [8]Department of Laboratory Diagnostics, Helsinki University Central Hospital; [9]Department of Radiology, Helsinki University Central Hospital; [10]Pharmacy, Helsinki University Central Hospital; [11]Department of Pathology, Helsinki University Central Hospital; [12]Department of Neurosurgery, Helsinki University Central Hospital, [13]Turku PET Centre, Turku, Finland, [14]Boneca Corp. (formerly NC-Treatment Ltd), Helsinki, Finland

ABSTRACT

Clinical trials with BPA mediated BNCT have been performed since May 1999 at the Finnish BNCT facility at the FiR 1 research reactor. The licence holder for the clinical irradiations is Boneca Corporation. Glioblastoma (GB) patients have been treated in two protocols, one for newly diagnosed glioblastoma multiforme (protocol P-01) and the other for patients with recurrent or progressing glioblastoma who have received prior cranial conventional external beam radiotherapy (protocol P-03). The number of irradiated patients sofar is 21 in P-01 and 4 in P-03. The BPA-fructose has been given as 2-hour i.v. infusion at BPA-dosages ranging from 290 to 450 mg/kg prior to neutron beam irradiation. Tumour responses have been followed using MRI. BNCT has been generally well tolerated. No treatment-related deaths have taken place. At the Turku PET Centre in Finland ^{18}F-BPA uptake studies have been performed. Magnetic resonance spectroscopic imaging is developed for boron carrier distribution measurements during the infusion prior to irradiation. For mapping the boron distribution during the irradiation prompt-gamma SPECT technology has been studied.

Introduction

A research project to carry out clinical application of boron neutron capture therapy (BNCT) was established in Finland in the early 1990's [1]. As the primary requirement the suitability of the 250 kW FiR 1 nuclear reactor, operated by VTT (Technical Research Centre of Finland), was evaluated [2]. The reactor is located at Otaniemi, Espoo, about 6 kilometres from the largest hospital of Finland, the Helsinki University Central Hospital (see Fig. 1). An epithermal neutron beam (Fig. 2) was constructed in 1996 based on a new neutron moderator material Fluental™ developed at VTT, and the FiR 1 reactor building was renovated to become a dedicated BNCT facility [3]. 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 relative biological efficiency (RBE) of the FiR 1 beam as compared with a conventional Linac 6 MV photon beam was estimated to be about 1.25 in the dog brain [5].

Glioblastoma multiforme was chosen as the first tumour type to be treated, because treatment results with conventional therapies are uniformly poor in this disease, and the pioneering work on BPA-based BNCT performed at other facilities has produced preclinical and clinical data that improves treatment safety [6]. The patients are treated within the context of research protocols approved by an institutional ethical committee. Patients are treated in collaboration with the Helsinki University Central Hospital, VTT, and the Boneca Corporation.

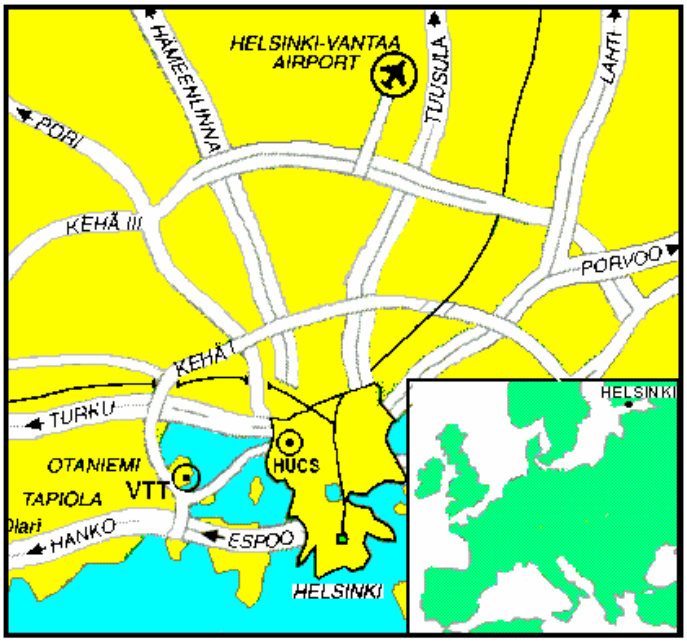

Fig.1. The BNCT facility at VTT is located only a 6 km drive from the premises of the University Hospital (HUCH/HUCS) in the heart of the Helsinki metropolitan area.

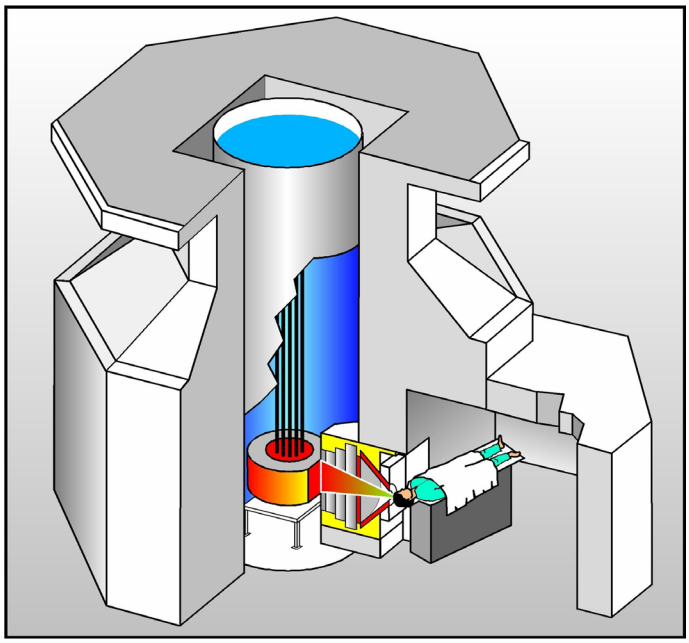

Fig.2. The BNCT facility at FiR 1 nuclear research reactor. The epithermal (0.5 eV-10 keV) neutron fluence rate is 1.1×10^9 n/cm^2/sec at the exit plane using a 14 cm diameter collimator at 250 kW power. The undesired fast neutron dose per epithermal fluence is 2 Gy/10^{13}cm^{-2} and the corresponding gamma contamination 0.5 Gy/10^{13}cm^{-2}.

Licensing

The Radiation and Nuclear Safety Authority (STUK) gave in May 1999 to the BNCT facility at FiR 1 the licence to perform BNCT radiotherapy complying with experimental protocols accepted by the ethical committees. The licence required also an inspection and approval by the municipal health care authorities as well as an approval by the regional governmental medical authority.

The operating license of the reactor is by the Technical Research Centre of Finland (VTT), an independent government research organisation under the ministry for trade and industry. The license was renewed beginning of 2000 for 12 years. The reactor is now explicitly licensed as part of a BNCT treatment facility. The radiotherapy license holder is Boneca Corporation. Boneca Corporation is a firm owned by the Clinical Research Institute of the Helsinki University Central Hospital, VTT and Sitra, the Finnish National Fund for Research and Development. The management organisation for the radiotherapy license is shown in Fig. 3.

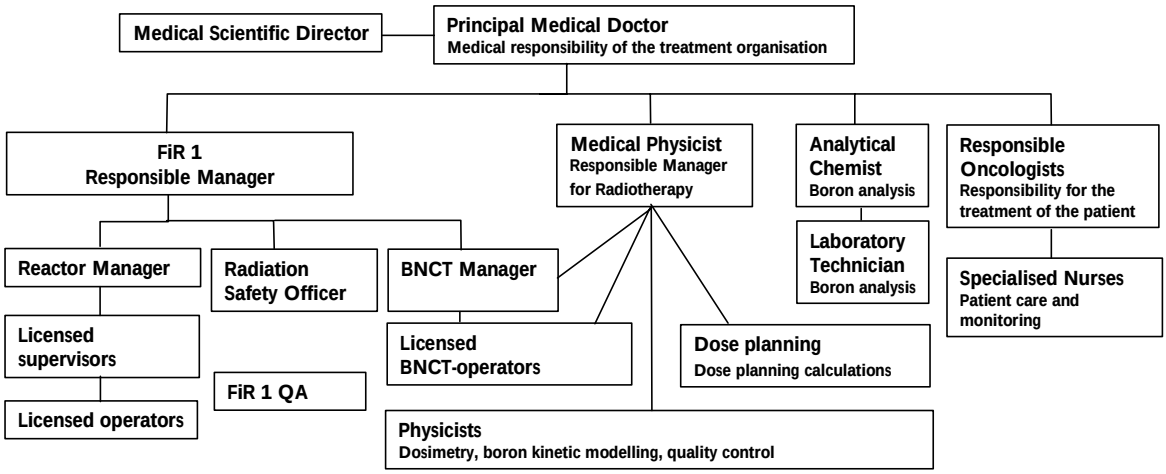

Fig. 3. The management organisation for the radiotherapy license.

Boronophenylalanine (BPA)

For the clinical protocols until now the boron carrier compound L-boronophenylalanine (L-BPA) has been purchased from Katchem Ltd (Praque, Czech Republic) [7]. Resently BPA produced with current good manufacturing practice (cGMP), as required now by the national authorities in Finland, has been purchased. At the pharmacy of the Helsinki University Central Hospital L-BPA is complexed with fructose to form L-BPA-F. The L-BPA-F-solution is infused intravenously prior to neutron irradiation.

Whole blood boron concentration is monitored from samples taken before, during, and following L-BPA-F infusion at about 20 min intervals using inductively coupled plasma-atomic emission spectrometry (ICP-AES) [8]. This year a rapid method for the direct analysis of boron in whole blood by ICP-AES [9] has been implemented.

Estimation of the average whole blood boron concentration during irradiation is based on kinetic models [10]. These models estimate the clearance of boron from the blood after BPA-F infusion with accuracy of about 1 ppm or less during the first and second radiation fields. Recently, a more capable kinetic model was developed [11].

Imaging for dose calculation and diagnostics

MRI

Conventional cranial imaging for BNCT dose planning is done one to three weeks before BNCT delivery with a 1.5T MRI imager. Gadolinium-DTPA is used as a contrast agent. MRI detectable markers are placed on the skin to mark the reference points for head positioning, and their locations are tattooed on the skin. MRIs taken before craniotomy and one to two days after craniotomy are used in dose planning as additional information regarding tumour localization, tumour volume, and presence of oedema. MRI is used also to follow tumour responses after treatment.

PET and MRS

One of the ongoing research projects in Finland is to assess directly the macroscopic spatial and temporal distribution of ^{10}B within the brain and the tumour using PET (Fig. 4) and magnetic resonance spectroscopy (MRS) technologies. Techniques such as ^{18}F-BPA PET [12,13] and MRS [14,15] may turn out to be valuable in identifying tumours of different histological types that accumulate BPA more than the surrounding tissue, may aid in optimizing boron compound administration, dose planning and boron dose estimation, and may help in understanding the treatment results.

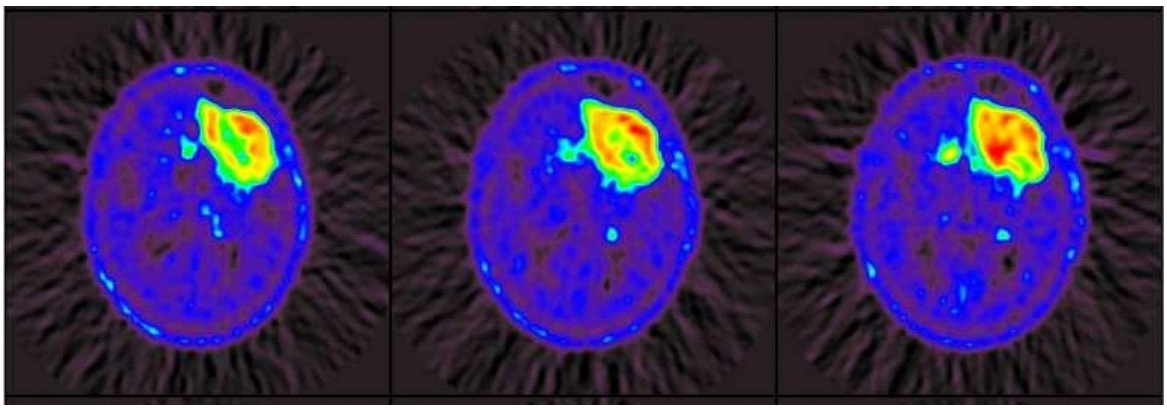

Fig. 4. ^{18}F-BPA PET image of a patient with recurrent anaplastic astrosytoma in the left frontal lobe showing clear uptake of ^{18}F-BPA by this tumour. (Imaging done at the Turku PET Centre; principal investigator Heikki Minn).

Prompt gamma imaging

For mapping the boron distribution during the irradation prompt-gamma SPECT technology has been studied [16]. The feasibility of using CdZnTe and Si detectors for measuring distributions of the boron and hydrogen neutron capture events on-line in a patient during a BNCT irradiation has been evaluated. Both the boron capture and hydrogen capture gammas could be observed with these detectors in the test measurements (Fig. 5).

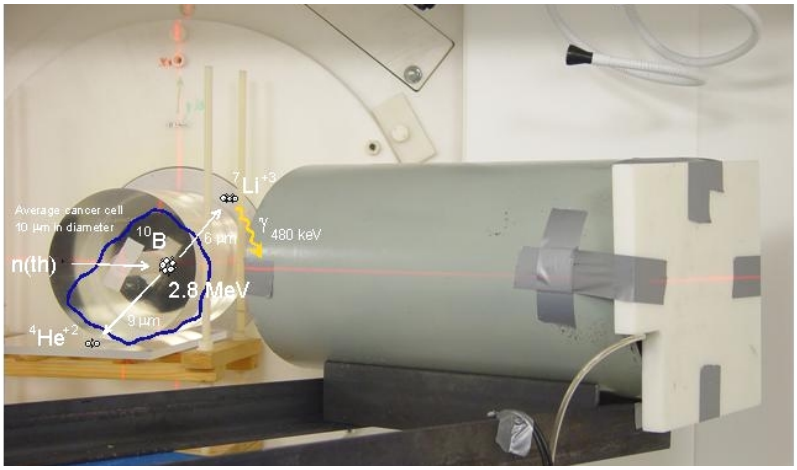

Fig. 5. Set up for testing detectors, detector shielding and collimation for prompt gamma imaging.

Dose planning

The 3D Monte Carlo software packages BNCT_Rtpe and SERA (INEEL/MSU, Idaho Falls/Bozeman, USA) are used in the BNCT dose planning. The tissue compositions for transport computations are according to the ICRU Report 46. The weighted total dose (D_W) is defined as the sum of physical dose components (D_i) multiplied by weighting factors (w_i)

$$D_W = w_g D_g + w_B D_B + w_N D_N + w_{fast\_n} D_{fast\_n}, \qquad (1)$$

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 [17]. The weighting factor for boron dose w_B is taken as 3.8 in the target and the tumour, and 1.3 in the normal brain. Weighting factors w_N and w_{fast_n} are taken as 3.2, and w_g is considered to be 1.0 [18,19]. The fluence-to-kerma conversions of the weighted nitrogen and the weighted fast neutron doses are calculated using a nitrogen concentration of 1.84 w-% and a hydrogen concentration of 10.57 w-%, assuming the brain tissue to be composed of equal proportions of the white and gray matter [20].

The doses are computed as a function of the average boron concentration in the whole blood during each irradiation field. For the boron concentration, tumour-to-whole blood ratio of 3.5:1 and the normal brain-to-whole blood ratio of 1:1 are assumed. The computational head model consists of the skin, the skull, the brain, the target volume, and the tumour regions in protocol P-01. In addition to these structures, also the sinuses are outlined in protocol P-03. When computing the average brain dose, the entire brain and the tumour site are included in the computation volume. The target volume is defined to consist of the enhancing tumour present in MRI, the surrounding oedema, plus a 1 to 2 cm margin in the brain tissue in 3 dimensions. Two fields are irradiated in all cases, and an attempt is made to exclude the contralateral hemisphere from the radiation field whenever possible.

The treatment planning system is capable of calculating the activation reaction rates of the *in vivo* $^{55}Mn(n,\gamma)$ activation foils/wires placed on the beam entry points, in the ipsilateral ear canal, and at the base of the nose for measuring the thermal neutron fluences.

Patient positioning

Patient positioning simulation for irradiation is carried out one day preceding irradiation. The patient positioning system includes a custom made treatment coach equipped with electrical controls for the couch table position in 3 dimensions, a beam aperture simulator, and a total of 9 crosshair lasers. The beam entry and exit coordinates given by the dose planning program are transformed to the positioning coordinate system with help of 3 detectable reference markers, which are placed on the patient's skin before carrying out the dose planning MRI. Patient positioning is performed in the treatment simulation room located at the BNCT facility. The computed beam exit and entry points are first localized and marked on the skin. After finding the optimal head and body position relative to the beam aperture, head and body vacuum immobilizers are shaped to secure head position during neutron beam irradiation (Fig. 6). This year niches on both sides of the beam aperture have been machined for spacious positioning of the patient (Fig. 7)

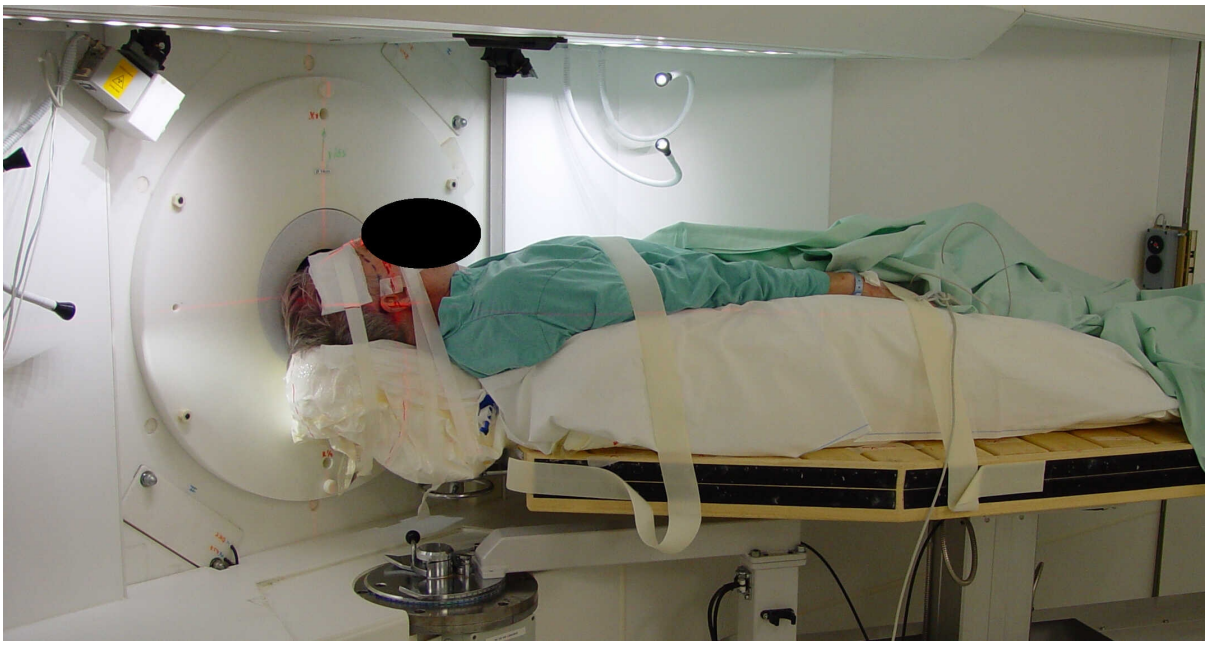

Fig. 6. Patient in the irradiation room immobilized on the treatment coach by head and body vacuum immobilizers.

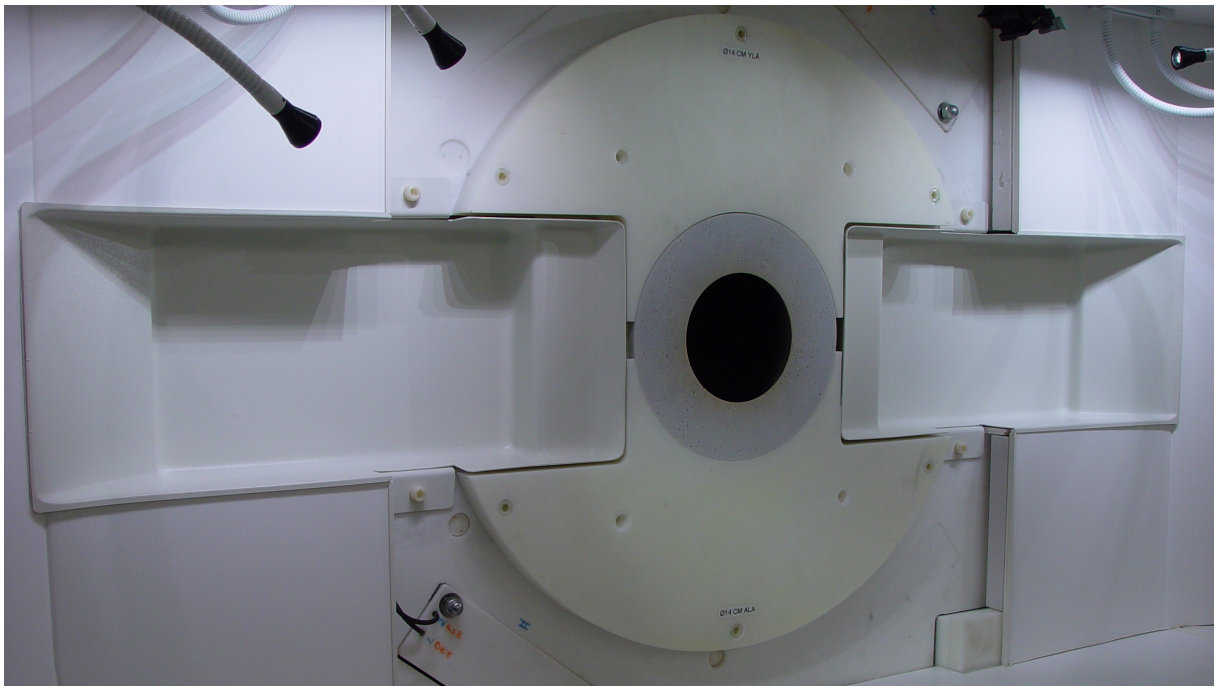

Fig. 7. Niches on both sides of the beam aperture for easier positioning of the patient.

Clinical protocols

Two prospective, nonrandomised, phase I studies focusing on feasibility of BNCT have been initiated (protocols P-01 and P-03) [21]. Both protocols continue recruiting patients. The principal investigator is professor Heikki Joensuu.

Protocol P-01

P-01 is a prospective, nonrandomised, phase I to II study focusing on feasibility of giving BNCT as primary radiotherapy to patients with newly diagnosed glioblastoma multiforme. 21 glioblastoma patients have been enrolled between May 1999 and March 2003. Prior conventional radiotherapy or cancer chemotherapy is not allowed. BPA-F is given intravenously over 2 hours. The BPA-F dosage given was in the beginning 290 BPA/kg body weight and has been stepwise increased to 450 mg BPA/kg body weight. The average weighted brain doses have ranged from 3 to 6 Gy (W), and the brain weighted peak doses have been 8 to 14 Gy (W) [21].

The BPA-F infusion has been well tolerated, and BNCT-related acute toxicity has been acceptable. The only serious adverse event possibly related to BNCT consists of acute abdominal pain leading to laparotomy in one case. Transient dysphasia lasting for a few days has been observed, as well as transient amnesia. Some patients have had an epileptic fit within the first week following BNCT. All patients have received further cancer treatments following recurrence.

Protocol P-03

The main purpose of P-03 is to find out whether BPA-based BNCT is feasible in adult patients with recurrent or progressing supratentorial GB or anaplastic astrocytoma who have received 50 to 60 Gy conventionally fractionated (1.8-2.0 Gy/day, 5 days per week) external beam radiotherapy to the PTV. This protocol was opened in February 2001, and four patients have been treated since. A BPA-F dosage of 290 mg/kg is given over 2 hours. The brain peak dose is limited to 8 Gy (W), the average normal brain dose to 6 Gy (W), and the minimum planned tumour dose must be $\geq$17 Gy (W) (requires a favorable tumour location). In the first 3 to 6 patients the normal brain peak dose will be limited to a maximum of 7 Gy (W). The protocol will accrue a maximum of 22 patients.

The therapy has been well tolerated, and no serious short-term toxicity has been encountered. The small number of patients treated precludes making firm conclusions, but taking into account the very poor outcome of patients with recurring/progressing glioblastoma after full-dose conventional radiotherapy and the relatively good tolerability of BNCT in the first patients, the protocol will remain open and continues to accrue more patients.

Conclusions and acknowledgements

BPA-based BNCT is relatively well tolerated. The small patient numbers treated, the extent of primary and secondary surgery, patient selection, and concomitant and other therapies confound efficacy comparisons with conventional radiation therapy. The relatively favourable 1-year survival and absence of serious adverse effects warrant further study on BPA-based BNCT. In the Finnish clinical BNCT research and development program the two open protocols for glioma will continue and new protocols will be opened in the future.

The BNCT research and development in Finland is financed by the Boneca Corporation, the Technology Development Centre of Finland and the Academy of Finland.

References

1. Savolainen S, Auterinen I, Kallio M, Kärkkäinen M, Kosunen, A, Aschan C, Benczik J, Färkkilä M., Hiismäki P, Kaita K, Kulvik M, Ryynänen P, Seppälä T, Seren T, Tanner V, Toivonen M, Vähätalo J, Ylä-Mella H: *The Finnish boron neutron capture therapy program - an overview on scientific projects* In: Advances in Neutron Capture Therapy, International Congress Series 1132, Volume I, Medicine and Physics. Larsson B, Crawford J, Weinreich R(Eds). Elsevier Science B, Amsterdam, pp. 342-347, 1997.
2. Auterinen I., Hiismäki P, Epithermal BNCT neutron beam design for a Triga II reactor, Advances in Neutron Capture Therapy. Proceedings of the 5th International Symposium on Neutron Capture Therapy. Columbus, OH, September 14 - 17, 1992. (SOLOWAY, A.H. & BARTH, R. F., Eds.). Plenum Press (1993), p. 81 - 84.
3. Auterinen I, Hiismäki P, Kotiluoto P, Rosenberg RJ, Salmenhaara S, Seppälä T, Serén T, Tanner V, Aschan C, Kortesniemi M, K.osunen A, Lampinen J, Savolainen S, Toivonen M, Välimäki P: Metamorphosis of a 35 years old Triga reactor into a modern BNCT facility. In: *Frontiers in Neutron Capture Therapy*. Hawthorne MF, Shelly K, Wiersema RJ (Eds). Plenum Press, New York, 1: 267-275, 2001.
4. Wheeler FJ, Nigg DW, Capala J, *et al*. Boron neutron capture therapy (BNCT): implications of neutron beam and boron compound characteristics. *Med Phys* 26: 1237-1244, 1999.
5. Benczik J. Relative biological effectiveness of reactor produced epithermal neutrons for the canine brain. Thesis, University of Helsinki, 2000.
6. Chanana AD, Capala J, Chadha M, *et al*. Boron neutron capture therapy for glioblastoma multiforme: interim results from the phase I/II dose-escalation studies. *Neurosurgery* 44: 1182-1192, 1999.
7. Kulvik M, Vähätalo J, Buchar E, Färkkilä M, Järviluoma E, Jääskeläinen J, Ki O, Laakso J, Rasilainen M, Ruokonen I and Kallio M, Clinical implementation of 4-dihydroxyborylphenylalanine synthesised by an asymmetric pathway, European Journal of Pharmaceutical Sciences, Volume 18, Issue 2, February 2003, Pages 155-163.
8. Laakso J, Kulvik M, Ruokonen I, Vähätalo J, Zilliacus R, Färkkilä M, Kallio M: Atomic emission method for total boron in blood during neutron-capture therapy. Clin Chem 47: 1796–1803, 2001
9. Bauer WF, Micca PL and White BM, A rapid method for the direct analysis of boron in whole blood by atomic emission spectroscopy. In 'Advances in Neutron Capture Therapy' Soloway AH, Barth RF and Carpenter DE (Editors), Plenum Press, New York, 1993, pp 403-407.

10. Ryynänen PM, Kortesniemi M, Coderre JA, Diaz AZ, Hiismäki P, Savolainen SE: Models for estimation of the (10)B concentration after BPA-fructose complex infusion in patients during epithermal neutron irradiation in BNCT. Int J Radiat Oncol Biol Phys 48: 1145-1154, 2000
11. Ryynänen P, Kangasmaki A, Hiismäki P, Coderre J, Diaz AZ, et al. Non-linear model for the kinetics of ^{10}B in blood after BPA-fructose complex infusion. Phys Med Biol 2002; 47: 737-45..
12. Kabalka GW, Smith GT, Dyke JP, Reid WS, Longford CPD, Roberts TG, Reddy NK, Buonocore E, Hübner KF: Evaluation of fluorine-18-BPA-fructose for boron neutron capture therapy treatment planning. J Nucl Med 38: 1762-1767, 1997
13. Imahori Y, Ueda S, Ohmori Y, Kusuki T, Ono K, Fujii R, Ido T: Fluorine-18-labeled fluoroboronophenylalanine PET in patients with glioma. J Nucl Med 39: 325-333, 1998
14. Zuo CS, Prasad PV, Busse P, Tang L, Zamenhof RG: Proton nuclear magnetic resonance measurement of p-boronophenylalanine (BPA): a therapeutic agent for boron neutron capture therapy. Med Phys 26, 1230-1236, 1999
15. Heikkinen S, Kangasmaki A, Timonen M, Kankaanranta L, Häkkinen A-M, Lundbom N, Vähätalo J and Savolainen S, ^{1}H MRS of a boron neutron capture therapy ^{10}B-carrier, L-p-boronophenylalanine–fructose complex, BPA–F: phantom studies at 1.5 and 3.0 T, Phys. Med. Biol. 48 1027-1039, 2003.
16. Auterinen I; Kotiluoto P; Anttila K; Seren T; Kekki T; Renvall T; Tiitta A; Kaschuck Yu; Trykov L. Evaluations for prompt-gamma imaging of boron and hydrogen neutron capture reactions in boron neutron capture therapy (BNCT), Research and Development in Neutron Capture Therapy. Proceedings of the 10th International Congress on Neutron Capture Therapy. Essen, DE, 8-13 Sept. 2002.Sauerwein W, Moss R & Wittig A. Monduzzi Editore (2002), p.887-890.
17. Seppälä T, Kotiluoto P, Savolainen S, Auterinen I, Hiismäki P, Seren T, Kosunen A, Aschan C, Kortesniemi M, Toivonen M: Determining and reporting the doses in the treatment of glioma patients in the epithermal neutron beam at the Finnish BNCT facility (FiR 1), IAEA-TECDOC-1223. Current status of neutron capture therapy. IAEA, pp. 275 – 288, 2001
18. Chadha M, Capala J, Coderre JA, Elowitz EH, Iwai J, Joel DD, Liu HB, Wielopolski L and Chanana AD: Boron Neutron-Capture Therapy (BNCT) for Glioblastoma Multiforme (GBM) Using the Epithermal Neutron Beam at the Brookhaven National Laboratory. Int J Radiat Oncol Biol Phys 40: 829-834, 1998
19. Coderre JA, Morris GM: Review: The radiation biology of boron neutron capture therapy, Rad Res 151: 1-18, 1999
20. Brooks RA, DiChiro G, Keller MR: Explanation of cerebral white-gray contrast in computed tomography. J Comp Assist Tomog 4, 489-491, 1980
21. Joensuu, Heikki; Kankaanranta, Leena; Seppälä, Tiina et al.. Boron neutron capture therapy of brain tumors: clinical trials at the Finnish facility using boronophenylalanine. Journal of Neuro-Oncology, vol. 62 (2003), p. 123 - 134.