# First clinical results from the EORTC Phase I Trial "postoperative treatment of glioblastoma with BNCT at the Petten irradiation facility"

**W. Sauerwein, K. Hideghéty, J. Rassow**
Department of Radiotherapy, University of Essen, Germany


**M.J. Devries**
NDDO Oncology, Amsterdam, Netherlands

**C. Götz**
Neurochirurgische Klinik, Klinikum Großhadern München, Munich, Germany

**P. Paquis**
Dept. de Neurochirurgie, Hôpital Pasteur, Nice, France

**F. Grochulla**
Kllinik für Neurochirurgie, Zentralkrankenhaus Bremen, Germany,

**J.G. Wolbers**
Department of Neurosurgery, University Hospital "Vrije Universiteit",
Amsterdam, Netherlands

**K. Haselsberger**
Klinik für Neurochirurgie, Karl-Franzens-Universität, Graz, Austria

**B. Turowski**
Institut für Neuroradiologie, Johann-Wolfgang–von-Goethe-Universität,
Frankfurt, Germany

**R.L. Moss**
HFR Unit, Joint Research Centre, European Commission, Petten, Netherlands

**F. Stecher-Rasmussen**
Nuclear Research and Consultancy Group NRG, Petten, Netherlands

**D. Touw**
Pharmacy,University/Academic Hospital "Vrije Universiteit", Amsterdam, Netherlands

**O.D. Wiestler**
Department of Neuropathology, German Brain Tumour Reference Centre,
Universitätsklinikum Bonn, Germany

**H. Fankhauser**
Service de Neurochirurgie CHUV, Lausanne, Switzerland

**D. Gabel**
Chemistry Department, University of Bremen, Germany

**the EORTC BNCT Study Group**

**Abstract.** Based on the pre-clinical work of the European Collaboration on Boron Neutron Capture Therapy a study protocol was prepared in 1995 to initiate Boron Neutron Capture Therapy (BNCT) in patients at the High Flux Reactor (HFR) in Petten. Bio-distribution and pharmacokinetics data of the boron drug $Na_2B_{12}H_{11}SH$ (BSH) as well as the radiobiological effects of BNCT with BSH in healthy brain tissue of dogs were considered in designing the strategy for this clinical Phase I trial. The primary goal of the radiation dose escalation study is the investigation of possible adverse events due to BNCT; i.e. to establish the dose limiting toxicity and the maximal tolerated dose. The treatment is delivered in 4 fractions at a defined average boron concentration in blood. Cohorts of 10 patients are treated per dose group. The starting dose was set at 80% of the dose at which neurological symptoms occurred in preclinical dog experiments following a single fraction. After an observation period of at least 6 months, the dose is increased by 10% for the next cohort if less then three severe side effects related to the treatment occurred. The results of the first cohort are presented here. The evaluated dose level can be considered safe.

## 1. INTRODUCTION

Boron Neutron Capture Therapy (BNCT) is based on the reaction occurring between the non-radioactive isotope $^{10}B$ and thermal neutrons. A low energy neutron is captured by the $^{10}B$-nucleus, which disintegrates into a Li- and He-nucleus, two densely ionising particles with high biological effectiveness and short range in tissue. A selective targeting of this reaction to tumour cells would lead to a highly effective treatment while sparing healthy tissue, resulting in a "targeted and timed cell surgery" [1]. This innovative idea had been published already by Locher in 1936 [2]. It was not until the 50's and 60's that the first clinical trials of BNCT were performed, namely at the Brookhaven National Laboratories and MIT. The results were disappointing due to inadequate boron-compounds and sub-optimal neutron sources but further pioneering clinical applications were performed in Japan in the late 60's [3]. These applications, which reported some outstanding results, were not in the frame of controlled prospective clinical trials. However, the specific efforts of H. Hatanaka and his co-workers [4,5] led to a reconsideration of clinical applications with BNCT in the United States as well as in Europe. This article reports the initial results of the first European clinical trial, which was started as a multinational effort in 1997, after almost 10 years of preparation [6–11].

The demonstration project, which is financed by the European BIOMED II Program had the objective to investigate the feasibility of BNCT at the High Flux Reactor (HFR) in Petten (NL) following the EORTC protocol 11961 [12,13]. The aim of the study is to investigate the systemic toxicity due to the boron carrier $Na_2B_{12}H_{11}SH$ (BSH) at one given real time pharmacokinetic guided boron blood concentration. Furthermore, the study will detemine the maximal tolerated radiation dose and the dose limiting toxicity of BNCT to healthy tissues in cranial location using the epithermal beam at the BNCT irradiation facility of the HFR [14]. The demonstration project is intended to establish and evaluate the structure of a trans-national co-operation for patient treatment in Europe using a unique facility [15,16].

## 1. PATIENTS AND METHODS

So far, 14 patients have been entered into the study, 12 males and 2 females coming from five neurosurgical centres in 4 European countries. Mean age of the patients at on study registration was 62 years (51–74). The performance status at inclusion was very good with a median Karnofski index of 90 (70–100). The initial tumour localisation was temporal in 4 cases, frontal in 4 cases, parietal in 1 case, occipital in 1 case, temporo-occipital in 2 cases, temporo-frontal in 1 case and parieto-occipital in 1 case. The average target volume was 135,7 $cm^3$ (range 29–213 $cm^3$). Central pathology review at the German Brain Tumour Reference Centre in Bonn revealed Glioblastoma Multiforme (WHO grade IV) in 11 patients and Gliosarcoma (WHO grade IV) in 3 patients.

BSH was administered 13–14 hours prior to surgery at a dose of 1 mg/kg/min. Blood, tumour, skin, brain, muscle, cerebro-spinal fluid and dura samples were taken during the operation. Blood samples continued to be taken regularly during 48 hours after surgery. The boron content was measured by ICP-OE-spectroscopy at Nuclear Research and Consultancy Group NRG Petten [17].

Of the 14 patients 3 had partial, 4 subtotal and 7 complete tumour resection. The three patients with a remaining tumour volume larger than 30 % of the initial tumour size had to be excluded. One patient could not undergo BNCT because of an intercurrent infection and prolonged recovery after the surgery.

The first patient cohort (10 patients) was treated by BNCT with the epithermal beam at the HFR in Petten [18–21] which is owned by the European Commission. The starting radiation dose level, which was derived from previous animal experiments, was set at 8.6 Gy boron neutron capture absorbed dose $D_B$ [22] prescribed at the Dose Group Identification Point (DGIP) [12]. For the other dose components limiting maxima were defined, which were never reached. The DGIP was set at a point that is physically well defined and can be clearly identified in each patient: namely, the maximum of the thermal neutron fluence in the patient. The size of the circular beam was fixed at 12 cm diameter; the distance from the beam exit in the wall to the beam entrance in the patient was 30 cm.

The only variable parameter, the orientation of the patient's head relative to the beam, was selected on the basis of the planning target volume localisation. A single field was used for the treatment of the first 5 patients. The last 5 patients were irradiated with two oblique beams which resulted in two separate thermal neutron fluence peaks, one in the planning target volume in the operated area and one outside. Consequently a larger volume was irradiated in the second five patients but the boron neutron capture absorbed dose, which is defined for a cohort of patients, was the same for the whole group of the 10 patients, namely 8.6 Gy.

The patients travelled to Amsterdam by public transport, where they were admitted to the Department of Neurosurgery of the Academic Hospital of the Vrije Universieit Amsterdam for 1 week. During this period BNCT was performed in 4 fractions on 4 consecutive days, except one case, in whom the third and fourth fractions of irradiation were delivered subsequently on the same day.

The day prior to the first irradiation, 100 mg/kg BSH was administered i.v. at a dose rate of 1mg/kg/min. On the following days both the amount (range 9.5–70.4 mg/kg) and the time point of BSH administration (range 10–25 hours prior to the radiation) were modified in order to achieve an average boron concentration of 30 ppm $^{10}B$ in blood over the four fractions. The amount, start of the infusion and duration were adapted each day after obtaining the actual pharmacokinetic data (from the regularly taken blood samples) by prompt gamma spectroscopy. In the 10 patients treated mean blood boron concentration over the four fractions of BNCT was 30.3 ppm (range 27.3–32.3 ppm).

On the basis of the measured real boron concentration in blood during the radiation and of the actual delivered monitor units, the absorbed doses from the different physical dose components and the weighted dose were calculated and reported in defined points and volumes. The data were compared to the detected and scored radiation toxicity. The findings on systemic toxicity due to BSH alone have been reported and evaluated separately The

radiation toxicity is recorded and reported as early radiation toxicity if it occurs within 90 days after the end of BNCT, and as late radiation toxicity if it occurs later than 90 days. Four different toxicity scales were used for grading the events. These scales address acute systemic (drug) toxicity, early radiation toxicity, and -- using two scales -- late radiation toxicity. The latter two comprise the EORTC/RTOG (European Organization for Research and Treatment of Cancer / [U.S] Radiation Therapy Oncology Group) scale, which is an established, validated but not very precise method; and the SOMA scale, an improved but not yet validated approach [23]. It allows a more detailed determination of observed effects, for example neurological deficits.

## 2. RESULTS

### 2.1. Tissue uptake study

Samplings during surgery resulted in a tumour/blood boron concentration ratio normalised at 100 mg/kg BSH 13 hours after the end of BSH infusion of 0.63 (range 0.26 – 1.3). The results of this tissue uptake study were not used to perform the patient treatment in Petten.

### 2.2. Toxicity evaluation

With respect to the study drug BSH the following observations were made: One event of serious toxicity was reported and described as possibly related to BSH concerning one patient who developed a grade IV agranulocytosis during the week of BNCT. The agranulocytosis was treated by GSF and resolved within 36 hours. Grade 1 toxicity, regarding haematological changes in 3 cases, erythema and urticaria in 1case, erythema in another 1 case, flash like sensation in 2 cases, nausea and vomiting in 1, hypokaliaemia and hyponatraemia in 1 case were detected and interpreted as possibly related to BSH. Grade 1, 2 and 3 fever possibly related to the study medication occurred in three patients.

Acute radiation toxicity was slightly less than observed in conventional radiotherapy: Mild erythema in 3 cases, focal alopecia in 9 cases, taste change (4 cases), headache, decreased lacrimation, behavioural changes, mild pruritus of an ear, tinnitus (each in one case) and mild dry mouth (2 cases) were reported in the first 3 months after the end of BNCT.

Compared to other treatment modalities in oncology, the acute toxicity of BNCT under the defined circumstances was acceptable.

Late radiation toxicity outside the brain was mild and consisted of: ongoing alopecia (in 5 cases), slight atrophy of the skin (2 patients), skin pigmentation changes, lens opacity, low grade blurred vision, low grade hearing loss, atrophy of oral mucosa, hormonal changes each in 1 patient.

The interpretation of the relationship of neurological events to BNCT proved to be very difficult especially in cases of progressive tumour recurrence. Minor neurological symptoms such as slight incoordination, paresthesia of the right hand and mild dysphasia possibly due to BNCT were completely resolved. A minor intellectual deficit, one grade 1 personality change and in two cases grade 1 headache was considered as possibly related to BNCT. The two neurotoxic events (both grade 3) with headache and psychosis with aggressive behaviour developed probably due to tumour progression and were unlikely to be caused by BNCT.

One serious adverse event was interpreted as probably BNCT related toxicity. In this specific case BNCT was given in November 1997 in four fractions with no evidence of any adverse event. After surgery the patient had discrete motor speech disturbance, which became slowly progressive from March 1998 onwards caused by a recurrent tumour, which was confirmed by MRI. An acute right facial nerve palsy associated with distal paresis of the right arm developed in May 1998. These symptoms were related to a progressive infarction in the perfusion territory of the thalamostriate arteries originating from the middle cerebral artery. At that time the tumour was progressing. Further MRI' s demonstrated tumour progression and an increase of the infarction size. Following a period of worsening neurological symptoms the patient died in December 1998 due to tumour progression. A clear attribution of the symptoms mentioned above either due to the tumour or infarction could not be made. Furthermore the infarction itself may be due to the progressive tumour or due to radiation induced vascular damage to the wall of the thalamostriate arteries.

### 2.3. Survival

The mean survival of the first patient group at the time of monitoring was 9.5 months after the first surgery for glioblastoma and 8.4 months after the last day of BNCT. Two of the 10 treated patients were alive. All patients with a fatal course died from recurrent disease. The patients who are alive are suffering from tumour recurrence. The outcome is as expected, taking into consideration the criteria for patient selection. The mean survival of the 4 patients not eligible for treatment with BNCT was 6.5 months after the initial surgery. All 4 patients died due to local progression of the glioblastoma.

## 3. CONCLUSIONS

After careful evaluation of the data, we can conclude that the starting BNCT dose level was safe, but probably high enough to reach the dose limiting toxicity within the frame of this radiation dose escalating trial. The observed toxicity due to BSH i.e. the effects on the haematological system needs further investigations, i.e. a defined dose escalation study investigating the toxic effects of the drug. Early and late radiation toxicity is slightly lower compared to conventional radiotherapy for glioblastoma with photons at a dose of 60 Gy in 6 weeks. The results concerning survival are similar, as expected.

The feasibility of performing BNCT using the epithermal beam at HFR Petten in a multinational approach could be demonstrated. However the therapeutic potential of BNCT cannot yet be evaluated at this point. Glioblastoma multiforme constitutes a good model for a phase I trial giving the opportunity to offer patients with a very poor prognosis and without expected benefit from all currently available treatments a therapeutic modality which at least shortens the treatment time. Glioblastoma multiforme however may not be the disease to judge the utility of BNCT and the therapeutic benefit deriving from BNCT. Future attempts will, therefore, focus on other tumour entities in addition to refining the protocol for glioblastoma patients.

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