EORTC TRIALS IN BNCT: THE CURRENT SITUATION

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The development of Boron Neutron Capture Therapy (BNCT) towards a clinical treatment modality for tumors needs the frame of prospective clinical trials. Therefore, the EORTC-BNCT Group developed trial protocols representing different stages of clinical testing which will be introduced in the following paragraphs.

EORTC protocol 11001

^{10}B uptake in different tumors using the boron compounds BSH and BPA

The EORTC protocol 11001 aims at translational research. The purpose of this study is to identify tumor entities that may obtain benefit from Boron Neutron Capture Therapy due to a selective uptake of the compounds sodium mercaptoundecahydro-closo-dodecaborate (BSH) and para-boronophenylalanine (BPA). The study is designed to determine the ^{10}B uptake in a tumor or a metastatic lesion at the time of the planned surgical resection. The concentration of ^{10}B after application of BSH or BPA or BSH and BPA in blood, tumor and normal surrounding tissues is determined.

Until recently, relatively little attention has been paid to explore the uptake of existing boron compounds in different tumors in order to investigate the potential of BNCT in a wider scale of tumor entities. Due to the different mechanisms of accumulation [1] a combined application of BSH and BPA may lead to a higher absolute amount of boron atoms in single tumor cells or lead to a more homogeneous boron distribution in different areas of the tumor e.g. areas with different cellularity, areas that contain metabolically active tumor cells or necrotic cells.

To evaluate a boron compound it is imperative to gain knowledge of both the macroscopic boron concentration in tissues as delivered by this agent as well as the boron microdistribution and concentration within normal and malignant cells. Data on macroscopical boron uptake of different tumors and of surrounding healthy tissues are prerequisites to identify tumors, which may be treated with BNCT due to a selective uptake of a boron compound. These studies can be performed using a number of analytical techniques, such as prompt γ-ray spectroscopy and atomic emission spectroscopy which yield average boron concentrations from gross tissue specimens. Volumes that can be measured with those methods however are much larger than the volume irradiated by the ^{10}B(n,α)^{7}Li reaction. Since the fission fragments of the boron capture reaction have only enough kinetic energy to penetrate ~0.5-1 cell diameter in tissue the clinical efficacy of the therapy has higher probability if the boron is positioned closely to the cell nucleus. Due to the short range of ^{4}He and ^{7}Li particles, the location of the capture reaction on a subcellular level makes the microdistribution of the ^{10}B atoms of critical importance for the success of the method [2, 3].

The ability to image and to quantify the boron concentration in a spatial distribution in tissue sections and inside individual cells would, from a microdosimetry point of view, help in the understanding of the mechanisms of selectivity and lead to the possibility to optimize the boron delivery. Methods to provide data on spatial distribution of ^{10}B concentration are under evaluation. A European research activity supported within Framework Program 5 (QLK3-CT- 1999-01067), which also includes this trial, is developing methods to measure the subcellular boron distribution. The secondary ion mass spectrometry (SIMS)-based technique of ion microscopy is particularly well suited for boron microlocalisation studies. The ion microscope maintains the spatial integrity of an analyte sputtered from the surface of the sample, producing images of isotopic distributions, which can be related to tissue histology with the

resolution comparable to a high quality light microscope. The analysis of boron by the ion microscope is not affected by the elemental spatialisation (free or bound chemical form of boron) within the biological matrix. This is a distinct advantage over many other techniques, because it is possible to analyze any experimental compound developed for BNCT. Furthermore, the ion microscope is capable of monitoring physiologically relevant species such as K, Na, Mg and Ca along with ^{10}B for the evaluation of pathological effects as well as potential artefacts induced during sample preparation [4,Smith, 2001 #179]. Dedicated imaging instruments (laser secondary neutral mass spectrometry (Laser-SNMS) and time of flight secondary ion mass spectrometry (TOFSIMS)) with extremely high sensitivity will be used for quantitatively locating ^{10}B in biological matrices. Electron energy loss spectroscopy (EELS) is especially well suited for the detection of light elements. For the image of elements in biological samples EELS is potentially capable of greater spatial resolution than any other localization method available but ultra thin sections are required [5].

In this trial the boron uptake in three dedicated solid tumors is intended to be analyzed.

1. Thyroid cancer: model for a peptide secreting tumor with high amino acid metabolism
2. Head and Neck cancer: model for a squamous cell tumor and
3. Liver metastases of colorectal adenocarcinoma: model for metastases of adenocarcinoma of the aero-digestive tract.

As this study is aiming at basic and translational research rather than the direct translation of a therapeutic strategy into a clinical modality the character of those tumors as models has to be stressed.

The trial has 3 main objectives:

1. To find solid tumor entities apart from melanoma and glioblastoma multiforme, that may obtain benefit from BNCT due to a selective uptake of the investigated compounds (BSH or BPA or both).
2. To investigate the feasibility and the potential of applying subsequently BSH and BPA in patients to obtain a favorable absolute ^{10}B-concentration in the tumor and optimized tumor to blood and tumor to healthy tissue ^{10}B-rates. If feasible, this therapeutic option will be used in further clinical trials.
3. To collect human data on tissue uptake of BSH and BPA and on the sub-cellular spatial distribution of ^{10}B as delivered by BSH and BPA with the intention to use the results to optimize the application of boron compounds for BNCT.

Prior to the planned removal of the solid tumor, a boron compound will be administered i.v. at a low, non-toxic dose. A single application of either BSH or BPA or a subsequent application of BSH and BPA will be tested in all of the three tumor entities. During the planned surgical intervention, tissue samples from tumor and surrounding tissues will be collected. No interference of the planned surgery, with respect to additional intervention and effort, will be caused by this trial. Blood samples will be collected at defined time points to measure the blood boron concentration. The collected tissues and the blood samples will be investigated for boron concentration by ICP-AES and/or PGRS. Additional samples will be prepared for analysis with new methods: TOF-SIMS, Laser SNMS and/or EELS. Either BSH or BPA or a combination of BSH and BPA will be administered in 3 patients per tumor type. The course of the study will be as follows:

1. Three patients per tumor type will be treated with BSH.
2. Three patients per tumor type will be treated with BPA.

The samples of these six patients will be analyzed. If either BSH or BPA are not taken up by this special tumor type, the combination of BSH and BPA will not be investigated in this tumor type. If a boron uptake is detected, this tumor type will be further investigated:

3. Three patients with the same tumor type will be treated with the combination of BSH and BPA.

So far, 8 patients have been included in the trial, results are pending.

EORTC protocol 11961

Postoperative Treatment of Glioblastoma with BNCT at the Petten Irradiation Facility, Phase I Clinical Trial

EORTC study protocol 11961 is designed as a phase I trial evaluating the healthy tissue tolerance of brain after BNCT. The study will determine the maximal tolerated radiation dose and the dose limiting toxicity of BNCT of brain tumors using the epithermal neutron source for BNCT of the research reactor High Flux Reactor (HFR) in Petten (NL). Furthermore, the trial aims to investigate the systemic toxicity of the boron compound $Na_2B_{12}H_{11}SH$ (BSH) at one given real-time pharmacokinetically guided boron blood concentration.

The trial is designed as dose escalation trial, which escalates the irradiation dose by increasing irradiation time. Cohorts of patients suffering from glioblastoma are irradiated with four fractions of BNCT after complete resection of the tumor. After an observation period of 6 months, the dose is increased by 10% for the next cohort. 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 are calculated and reported in defined points and volumes. The data are compared to the detected and scored radiation toxicity. The findings on systemic toxicity due to BSH alone are 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. Pharmacokinetic data are collected for BSH administered on 4 subsequent days according to 4 fractions of irradiation. The trial as well included a tissue uptake study during the planned surgery for patients entered in the first cohort. As secondary end-point patient survival and tumor response are evaluated [6, 7].

So far, 30 patients have been entered into the study, 21 males and 9 females. Mean age of the patients at on study registration was 60 years (50-74). The performance status at inclusion was very good with a median Karnofski index of 90 (70-100). Central pathology review at the German Brain Tumor Reference Centre in Bonn revealed Glioblastoma Multiforme (WHO grade IV) in all patients.

Three patients with a remaining tumor volume larger than 30 % of the initial tumor size had to be excluded from the procedure of BNCT. One patient could not undergo BNCT because of an intercurrent infection and prolonged recovery after the surgery. All of the 16 patients entered for treatment in the cohorts 2-4 where treated with BNCT.

Up to today four cohorts of patients (26 patients) were treated with BNCT with the epithermal beam at the HFR in Petten. The starting radiation dose level, was set at 8.6 Gy boron neutron capture

absorbed dose D_B prescribed at the Dose Group Identification Point (DGIP). The DGIP is set at the maximum of the thermal neutron fluence in the patient. For the other dose components limiting maxima are defined, which were never reached [8].

The orientation of the patient's head relative to the beam, was selected on the basis of the planning target volume localization. A single field was used for the treatment of the first 5 patients. All other patients were irradiated with two beams which resulted in two separate thermal neutron fluence peaks, one in the planning target volume in the operated area and one outside this area. Consequently a larger volume was irradiated than in the first 5 patients of cohort 1 but the boron neutron capture absorbed dose, which is defined for a cohort of patients, was the same for all patients treated within one cohort.

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.

On 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 - 107.1 mg/kg) and the time point of BSH administration (range 8 - 14 hours prior to the radiation) were modified 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 ray spectroscopy. In the 26 patients treated the mean blood boron concentration over the four fractions of BNCT was 30.2 ppm (range 27.3-32.3 ppm).

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 hematological changes, erythema and urticaria, erythema, flash like sensation during infusion, nausea and vomiting, hypokaliaemia and hyponatraemia 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, focal alopecia in all patients, taste change, headache, decreased lacrimation, behavioral change, mild pruritus of an ear, tinnitus and mild dry mouth were reported of possibly related to BNCT.

Late radiation toxicity outside the brain was mild and consisted of: ongoing alopecia which resolved in all cases after 3-6 month in all patients, slight atrophy of the skin, skin pigmentation changes, lens opacity, low grade blurred vision, low grade hearing loss, atrophy of oral mucosa, hormonal changes. The interpretation of the relationship of neurological events to BNCT proved to be very difficult especially in cases of progressive tumor recurrence [9].

One patient who was treated in the first dose group with one irradiation field developed a recurrent tumor 4 month after BNCT which was confirmed by MRI. 6 month after BNCT a progressive infarction in the perfusion territory of the thalamostriate arteries originating from the middle cerebral artery. Further MRI' s demonstrated tumor progression and an increase of the infarction size. Following a period of worsening neurological symptoms the patient died in December 1998 due to tumor progression. Because of location of the recurrent tumor relative to the infarction the external advisory board of the study judged upon the infarction as not BNCT related but caused by the recurrent tumor.

In one other patient who was treated in the 4th dose group brain infarction has been observed. The patient was suffering from adipositas per magna and hypertonia which could not be sufficiently treated despite a combination of 3 antihypertensive drugs. Ultrasonography of the carotid arteries prior to surgery showed mild to moderate arteriosclerotic plaques. The patient developed in addition to a recurrent tumor multiple bilateral infarctions in the stem ganglia and considerable brain atrophia. The first infarction was present 5 month after BNCT, 8 month after the treatment an MRI revealed multiple lesions. The patient had progressive neurological symptoms and died from pneumonia after receiving corticosteroids to treat edema surrounding the recurrent tumor for several month. An autopsy with histological examination of the brain did not show lesions in the vasculature which are typical for radiation damage. Reference radiology discussed hypoxia as one possible reason for the observed lesions which might have been occurred during seizure, or a sudden hypotension caused by the comorbidity. However, such sudden event was never reported. A multifactorial reason of the observed lesions can also be discussed. Final judgement of this case by the external advisory board is pending.

All patients but one with a fatal course died from recurrent disease. One patient died from pneumonia A number of patients underwent additional therapy such as chemotherapy or re-operation for the recurrent tumor after BNCT. 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.

BSH proved to be safe for clinical application at a dose of 100 mg BSH/kg infused and at a dose rate of 1 mg/kg/min. The observed toxicity due to BSH needs further investigations, i.e. a defined dose escalation study investigating the toxic effects of the drug.

After careful evaluation of the data, we can conclude that the starting BNCT dose level was safe. As a dose limiting toxicity has not been reached within four dose groups further escalation of the radiation dose might be possible. 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 tumor entities in addition to refining the protocol for glioblastoma patients.

EORTC protocol 11011

Early Phase II study on BNCT in metastatic melanoma using the boron carrier BPA

The aim of this study is to examine the clinical response of metastatic melanoma following BNCT as a palliative treatment. The trial will be conducted in close collaboration with the BNCT-group at Harvard University/Massachusetts Institute of Technology, who performs patient treatments under the same circumstances within the protocols “A phase II trial for neutron capture therapy in melanoma”, (National Institutes of Health 1 R01 CA90713-01A1) and “A phase I/II trial for

Neutron Capture Therapy in glioblastoma multiforme and intracranial melanoma" (National Institutes of Health, 1 R21 CA94617-01 with principal clinical investigator Dr. Paul Busse). Therefore, this trial aims to be first multi-center trial in BNCT.

Currently brain metastases of melanoma are incurable and are usually treated palliatively with a combination of surgery, conventional radiation therapy and chemotherapy. For inoperable brain metastases in particular, none of the existing treatments e.g. immuno-therapy, chemotherapy and/or conventional radiotherapy, is very effective [10]. The median survival of patients with metastatic disease in the central nervous system is less than 8 months.

The principal objective of the trial is to assess the therapeutic activity and efficacy of BNCT using the boron carrier BPA in patients with metastases of malignant melanoma. BPA will be administered as the fructose complex (BPA-f). The principal end-point is the objective local response to treatment, as defined by the "RECIST" criteria [11]. The overall survival, the duration of local response and time to local progression will be assessed as secondary activity endpoints. Patients treated within this protocol may have several lesions inside the irradiated area. An exploratory analysis will attempt to assess the dose-response relationship at the per-lesion level. The secondary objective is to evaluate the safety of boron neutron capture therapy with the boron carrier BPA-f at the High Flux Reactor-Petten (HFR). The toxicity will be assessed with special attention to the systemic toxicity of the drug in particular the cumulative toxicity due to repeated administration of BPA-f for fractionated BNCT and early and late radiation toxicity, to determine the spectrum and frequency of toxic events. Acute adverse reactions will be graded according to the International "Common Toxicity Criteria". Adverse events that occur 90 days or later after the end of BNCT will be graded according to the EORTC/RTOG late toxicity scale. For the evaluation of the MRI changes in the healthy brain the categories of the SOMA LENT scale
will be used.

For all patients the boron concentration in the blood will be measured before, during and after the BNCT procedure. Furthermore, the trial includes a mandatory biodistribution study of the drug BPA-f before BNCT irradiation. The objective is to further the level of understanding of the pharmacokinetics of BPA-f, through measurement of blood concentrations of ^{10}B especially after repeated administration. In close collaboration with the BNCT-study group at Harvard University/MIT the data will be used to refine the predictive accuracy of a two compartmental pharmacokinetic model developed for a single application by this group from human clinical data [12].

Translational research is part of this study. Besides the biodistribution study, samples of tumor and surrounding healthy tissues will be collected during a planned surgical intervention which takes place several days or weeks prior to the boron neutron capture irradiation. Tissue and blood samples will be used to build up a bank of boronated tissues. The boron concentration in tissues and the subcellular spatial distribution of ^{10}B will be measured to describe the macroscopic and microscopic ^{10}B-distribution. The macroscopic boron concentration will be measured with either Inductively Coupled Plasma Atomic Emission Spectroscopy (ICP-AES) or Prompt Gamma Ray Spectroscopy (PGRS), the subcellular boron concentration and localisation will be detected using one or several of the following methods: Laser Secondary Neutral Mass Spectroscopy (Laser-SNMS), Time of Flight Secondary Ion Mass Spectroscopy (TOF-SIMS) and Electron Energy Loss Spectroscopy (EELS). The data will be used to evaluate the dose distribution and the dose-response relationship more precisely than has been possible to now and to optimize BNCT for different localizations of melanoma.

The trial protocol is accepted by all relevant authorities and the trial will be opened in the very near future.

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