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The EORTC Boron Neutron Capture Therapy (BNCT) Group: achievements and future projects

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Abstract

Boron Neutron Capture Therapy (BNCT) is an experimental treatment modality that takes place in a nuclear research reactor. To progress from preclinical studies to patient treatment is a challenge requiring strict quality management and special solutions to licensing, liability, insurance, responsibility and logistics. The European Organisation for the Research and Treatment of Cancer (EORTC) BNCT group has started the first European clinical trial of BNCT for glioblastoma patients at the European High Flux Reactor (HFR) in Petten, The Netherlands, conducted by the Department of Radiotherapy of the University of Essen, Germany. A very strict quality management had to be installed following the European rules on safety and quality assurance for nuclear research reactors, for radioprotection, for radiotherapy and for clinical trials. The EORTC BNCT Group has created a virtual European-wide hospital to handle the complex management of patients treated with BNCT. New clinical trials are currently under development.

Keywords: Boron Neutron Capture Therapy; Neutrons; High LET radiation; Clinical trials; Glioblastoma

1. Introduction

Boron Neutron Capture Therapy (BNCT) was first attempted some 40–50 years ago in the USA. Due to well-documented reasons [1], the trials were effectively a failure. Despite this, Prof. Hatanaka in Japan in the 1960s treated many patients with a varying degree of success [2]. This alone stimulated a revival of BNCT research in USA and Europe, leading to a re-start of clinical trials at Brookhaven [3], Boston [4] and Petten [5]. Even more recently, as reported at the 9th International Symposium on NCT in Osaka, clinical trials on BNCT have started in Finland (May 1999), the Czech Republic (2000) and Sweden (2001).

BNCT is a binary form of an experimental treatment modality 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 a He-nucleus, two densely ionising particles with high biological effectiveness and short range in tissues. A selective targeting of this reaction to tumour cells would lead to a highly effective treatment while sparing healthy tissues, resulting in a 'targeted and timed cell surgery'. BNCT takes place in a nuclear research reactor and requires a multidisciplinary effort, involving radiotherapists, neuro-surgeons, medical physicists, reactor physicists and engineers, as well as pharmacists, pharmacologists, radiobiologists and chemists. To progress from preclinical studies to patient treatment is a tremendous step, and the co-ordination of such an effort requires an overall, multitasking approach. A very strict quality management of safety and quality assurance for nuclear research reactors, for radioprotection, for radiotherapy and for clinical trials is also mandatory [6]. A major step which allowed the co-ordination of all of these activities and the staff involved to be improved was the creation of a dedicated EORTC BNCT Group in 1997, able to start the first BNCT European clinical trial already in the first year of its existence.

2. EORTC BNCT Group clinical trials

EORTC protocol 11961 is a phase I trial aiming to establish under well defined conditions a safe radiation dose of BNCT using the boron compound, sodium borocaptate ($Na_2B_{12}H_{10}SH$ or BSH). 25 patients suffering

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from glioblastoma multiform older than 50 years of age have so far been entered into the study, being referred from five neuro-surgical centres in four European countries. After complete resection of the tumour, BNCT is performed in four fractions on 4 consecutive days at the European High Flux Reactor (HFR) in Petten (NL). 21 patients eventually received BNCT; 4 were excluded after surgery.

The patients were irradiated in four cohorts at increasing radiation dose levels. In the first cohort, a BSH dose of 100 mg/kg was administered 13–14 h prior to surgery. Blood, tumour, skin, brain, muscle, cerebrospinal fluid and dura samples were taken during brain surgery. Blood samples were taken regularly during 48 h after surgery. The boron content was measured by Inductively Coupled Plasma-Optical Emission Spectroscopy (ICP-OES) by the Nuclear Research and Consultancy Group NRG, Petten. On the basis of the measured boron concentration in blood during the radiation, which was taken on an average of 30 parts per million (ppm) ^{10}B over four fractions, the absorbed doses from the different physical dose components and the biologically weighted doses are calculated and reported in defined points and volumes. The dosimetry data are compared with the detected and scored radiation toxicity.

Follow-up includes Magnetic Resonance Imaging (MRI) and evaluation of systemic toxicity due to BSH, as well as early and late radiation toxicity. Four different toxicity scales were used for grading the events. After careful evaluation of the data from the first three cohorts of patients, no limiting toxicity has been detected. Early and late radiation toxicity for the applied dose levels were slightly lower compared with conventional radiotherapy for glioblastoma with photons at a dose of 60 Gy in 6 weeks.

The feasibility of performing BNCT in a multinational approach using the epithermal beam of the Petten HFR, that has been demonstrated by EORTC 11961, will be the basis for the future clinical trials of the EORTC BNCT group. The 5th Framework Program of the European Commission now supports the project 'Therapeutic Strategies for Boron Neutron Capture Therapy: Boron Imaging' performed by a large consortium including the EORTC BNCT Group, the Universities of Essen, Munster and Reims, the Nuclear Research and Consultancy Group NRG and the Joint Research Center of the European Commission in Petten. Under this project, the EORTC BNCT Group will conduct three clinical trials, to be opened to patient accrual within the next few months.

In protocol 11001, low doses of either BSH or 4-dihydroxyboryl-phenylalanine (BPA) or both agents will be administered to patients with various types of solid tumours in order to identify further tumour entities with selective boron uptake that may gain potential benefit from BNCT. Another main objective of this trial is to investigate the feasibility of the combined application of BSH and BPA in humans.

Protocol 11011 will be an early phase II study of BNCT using the compound BPA in patients with metastatic melanoma. The primary objective is the detection of antitumour activity of BNCT as palliative radiotherapy in metastatic skin melanoma. A secondary endpoint is the characterisation of the spectrum and frequency of toxicity of BPA, in particular the cumulative toxicity due to repeated administration of BPA during fractionated BNCT. A boron uptake study will be optionally performed administering BPA prior to surgery.

A third protocol is intended to be a phase I pharmacokinetically-guided escalation of BSH dose in patients with glioblastoma. In the first part of the study, escalated doses of BSH will be administered approximately 14 h prior to surgery. Toxicity of the drug and boron uptake in the tumour and in healthy tissues will be investigated. In the second part of the study, patients will receive fractionated BNCT after surgery using the technique which was established in trial 11961. The ^{10}B concentration in blood is escalated for cohorts of 3 patients, while the applied radiation dose will be kept constant at a level established to be safe. The systemic toxicity of the drug will be evaluated, as well as early and late radiation toxicity and survival. There will be no cross-over between the first and second parts of the trial.

In all of these studies, special attention will be paid to the detection of the boron concentration and its spatial distribution inside individual cells. Blood, tumour and surrounding healthy tissue samples will be collected during surgery, after application of boron compounds. In addition to established methods, new techniques will be developed based on Secondary Ion Mass Spectrometry (SIMS), Secondary Neutral Mass Spectrometry (SNMS) and Electron Energy Loss Spectroscopy (EELS). These trials will give unprecedented insight into the BNCT mechanism of action and will allow a better understanding of the potential of BNCT in targeting tumour cells by boron compounds and in the selective elimination of cancer cells whilst sparing adjacent normal tissues by the short range high LET irradiation.

Following suggestions from the Department of Energy (DOE) and the National Cancer Institute (NCI), a close co-operation has been established between the BNCT programme at the University of Harvard/Massachusetts Institute of Technology (MIT) and the EORTC BNCT Group.

3. Organisation

The initial drive to perform BNCT came primarily from neuro-surgeons, physicists, chemists and radiobiologists [1]. However, BNCT is essentially radiotherapy. A clinical trial must therefore be led by a

radiotherapist and has to follow all the quality requirements foreseen for clinical trials in radiotherapy. Furthermore, BNCT uses new non-registered drugs; hence, the requirements for early clinical trials for drug development have also to be applied.

To perform a clinical trial at a nuclear research reactor is strictly beyond the standard procedures associated with the licensing authorities in medical practice. Conventional radiotherapy takes place in a well-established hospital environment under the complete responsibility of medically qualified personnel, and under the licence and permissions of the appropriate authorities. BNCT involves non-medically qualified staff and takes place in a non-hospital environment, in particular a nuclear research reactor. It thus requires special solutions to licensing, liability, insurance, responsibility and logistics and can only be performed if strict quality management procedures are installed [6].

The treatment is performed at the European High Flux Reactor HFR in Petten and patients are enrolled from five different countries [7]. The patients travel from their home countries to the Medical Centre of the Vrije Universiteit Amsterdam, where they stay for 1 week, to be treated with BNCT on 4 consecutive days at the HFR in Petten by the Department of Radiotherapy of Essen University supported by the Joint Research Centre of the European Commission and the NRG [8]. A virtual Europeanwide hospital has been created by the EORTC BNCT Group with operating theatres in Graz (A), Munich (D), Bremen (D) Essen (D), Nice (F), Lausanne (CH) and Amsterdam (NL), a radiotherapy department in Frankfurt (D), a reference pathologist in Bonn (D), a radiotherapy department in Essen (D) with treatment planning and a treatment facility in Petten (NL), a patient care unit and a pharmacy in Amsterdam.

BNCT treatment is planned using custom-built treatment planning codes, written essentially by mathematicians and physicists with a nuclear background. The codes, not being commercial products, have peculiarities that require special solutions, e.g. image data transfer and conversion, a complicated output scheme which must indicate four different radiation dose components, unusual RBE or weighting factors and values for boron concentration in blood.

BNCT being performed at a nuclear reactor site and involving personnel with no medical background, it has to be ensured that all staff members are thoroughly trained in cases of emergency and that their behaviour and demeanour are the same as expected of the staff in a medical department.

4. Quality control of the study medication

In study 11961, the compound BSH (^{10}B-enriched) is used, which is formulated in vials each containing 1000 mg of the substance. Supplying companies must produce the compound according to a drug master file and have a written procedure for preparation and quality control of the final product and its intermediates. The material is imported into The Netherlands by the Pharmacist of the Medical Centre of the Vrije Universiteit Amsterdam (VUMC). Quality control checks are performed at VUMC with each batch that is imported. The new studies of the EORTC BNCT will also employ the compound BPA and the same procedures will be applied.

5. The absorbed dose in BNCT

Transfer and evaluation of radio-oncological experiences demand the correct definition of relevant treatment parameters, comparable prescription of the planned dose and its spatial and temporal distribution in the target volume and in the organs at risk, complete recording of treatment plan, treatment technique and treatment optimisation and clear reporting of specified parameters. These general conditions are valid in BNCT as well. Moreover, the standards and definitions of conventional radiotherapy defined and published in the ICRU reports [9,10] or other international accepted standards (i.e. ASTM [11], DIN 25 401 [12]) have to be taken into account performing Neutron Capture Therapy. Nevertheless, it has to be stressed that the ICRU recommendations cannot be applied directly and completely in BNCT.

A common language had to be found and used for the special purposes of BNCT. This language must be understandable for everybody practising radiotherapy. The joint efforts made by the EORTC BNCT Group and the International Society for Neutron Capture Therapy to overcome this problem led to a recently published document of the International Atomic Energy Agency recommending the reporting of the absorbed dose in BNCT similar to the ongoing EORTC protocol 11961 [13].

BNCT is a highly complex radiotherapy modality using different dose components which have different LET and therefore different biological effects. At any point in the irradiated volume, four major dose components have to be taken into consideration. The major dose component is the boron neutron capture absorbed dose D_B delivered by high LET alpha particles and lithium ions from neutron capture of boron-10 by the $^{10}B(n,\alpha)\ ^{7}Li$ reaction. The dose component D_B depends on the concentration and the subcellular spatial distribution of ^{10}B which cannot be measured. The other components are the neutron absorbed dose D_n which is delivered by the thermal, epithermal, fast neutrons and their secondary generated particles (protons, alpha particles, heavy ions), the gamma ray absorbed dose D_g

delivered by the gamma radiation present in the primary beam or generated by the $^{1}H(n,\gamma)$ ^{2}H neutron capture reaction and the high-LET proton dose D_N delivered by the secondary protons generated by the neutron capture reaction in nitrogen $^{14}N(n,p)^{14}C$.

In the EORTC trial 11961, for the definition of D_B, a homogeneous boron distribution in tissue has been assumed. The ^{10}B-concentration c_B (ppm) in the irradiated volume depends directly on the ^{10}B-concentration in blood that can be measured. Regarding the presence of ^{10}B in the irradiated volume, two aspects have to be taken into account. At very high concentrations of ^{10}B (>100 ppm), the neutron transport is affected and the neutron distribution is altered. For realistic values of ^{10}B concentration in patients, the neutron distribution is perturbed insignificantly. For the calculations of the absorbed dose D_B, the ^{10}B-concentration in the target volume is assumed equal to the ^{10}B-concentration measured in blood.

For such a complex beam, the measured or calculated dose values will not lead to the effects commonly observed for the same dose in conventional radiotherapy. This is especially due to the microscopic distribution of the high LET particles resulting from neutron capture in ^{10}B, having a range of only 10 μm. The same measured boron concentration in tissue may lead to completely different biological effects if the boron is bound to the cell membrane or distributed in the cytoplasm. Therefore, it became necessary to perform a phase I dose finding study under well-defined conditions to relate dose values to reproducible effects.

6. Concluding remarks

Only with the support of the EORTC has it become possible to realise a first BNCT trial in Europe, establishing a multidisciplinary, multicultural collaboration on a European level with appropriate quality management structures.

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References

1. Sauerwein W. Principles and history of neutron capture therapy. *Strahlenther Onkol* 1993, **169**, 1–6.
2. Hatanaka H. Clinical experience of boron-neutron capture therapy for gliomas—a comparison with conventional chemo-immuno-radiotherapy. In Hatanaka H, ed. *Boron-Neutron Capture Therapy for Tumours*. Niigata, Japan, Nishimura, 1986, 349–380.
3. Chadha M, Capala J, Coderre JA, *et al*. 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* 1998, **40**, 829–834.
4. Madoc-Jones H, Zamenhof R, Solares G, *et al*. Aphase-I dose-escalation trial of BNCT for subjects with metastatic subcutaneous melanoma of the extremities. In Mishima Y, ed. *Cancer Neutron Capture Therapy*. New York, Plenum Press, 1995.
5. Hideghéty K, Sauerwein W, Haselsberger K, *et al*. Post-operative treatment of glioblastoma with BNCT at the Petten Irradiation Facility (EORTC Protocol 11961). *Strahlenther Onkol* 1999, **175**(Suppl. II), 111–114.
6. Rassow J, Stecher-Rasmussen F, Voorbraak W, Moss R, Vroegindeweij C, Hideghéty K, Sauerwein W. Comparison of quality assurance for performance and safety characteristics of the facility for Boron Neutron Capture therapy in Petten/NL with medical accelerators. *J Radiother Oncol* 2001, **59**, 99–108.
7. Moss R. *The BNCT Facility at the HFR Petten: Quality Assurance for Reactor Facilities in Clinical Trials*. IAEA Joint Technical Committee Meeting on 'Current Issues Relating to Neutron Capture Therapy (F1-TCM-1095)'. IAEA Headquarters, Vienna, 14–18 June 1999.
8. Sauerwein W, Moss RL, Rassow J, *et al*. and the EORTC BNCT Study Group. Organisation and management of the first clinical trial of BNCT in Europe (EORTC Protocol 11961). *Strahlenther Onkol* 1999, **175**(Suppl. II), 108–111.
9. ICRU-50. *Prescribing, Recording and Reporting Photon Beam Therapy*. International Commission on Radiation Units and Measurements. Bethesda, MD, 1993.
10. ICRU-45. *Clinical Neutron Dosimetry Part I: Determination of Absorbed Dose in a Patient Treated by External Beams of Fast Neutrons*. International Commission on Radiation Units and Measurements. Bethesda, MD, 1989.
11. ASTM-Standard E170, vol. 12.02. 1993. *Standard terminology relating to radiation measurements and dosimetry*. American Society for Testing and Materials, 1993.
12. DIN 25 401-1. *Begriffe der Kerntechnik–Physikalische und chemische Grundlagen*. Deutsches Institut für Normung. Beuth Verlag, Berlin, 1986.
13. International Atomic Energy Agency (IAEA). *Current Status of Neutron Capture Therapy (IAEA-TECDOC-1223)*. IAEA, Vienna, 2001.