PhD értekezés tézisei

PHASE I CLINICAL STUDY ON BORON NEUTRON CAPTURE THERAPY

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Introduction

Boron neutron capture therapy (BNCT) is a binary treatment modality, based on the high cross section of ^{10}B to capture thermal neutrons producing two densely ionising particles with high biological effectiveness. As binary treatment, BNCT allows to optimise the treatment by manipulation of two independent parameters. One parameter is the boron concentration in tumour and healthy tissues in its vicinity. The other parameter is the thermal neutron fluence rate in the tumour and in the surrounding tissue. Damage to tumour tissue and to healthy tissue will be influenced by both of these parameters.

In 1995 I was asked to participate in the first clinical trial on BNCT in Europe. I took part in the preparation and performance of this trans-national, multi-disciplinary study from 1995 till 2001 as study radiotherapist, responsible physician at the irradiation facility and task leader of the study centre Essen. I have played a major role in defining the trial design, writing the study protocol, creating the study structure, defining the standard operating procedures furthermore in conducting the study and evaluating the results.

The EORTC BNCT Group conducts the first phase I study on BNCT. It is a radiation dose escalation trial on GBM patients with a constant blood boron level in order to study the feasibility of $Na_2B_{12}H_{11}SH$ (BSH) as boron carrier and to define maximal tolerated dose (MTD) and dose limiting toxicity (DLT) of BNCT in cranial localisation. The tissue uptake and pharmacokinetics of BSH have been studied in the first patient group. The trial is currently in progress at the European High Flux Reactor in Petten (NL). The study is performed according to the “Boron Neutron Capture Therapy with Glioblastoma Patients at the Petten Irradiation Facility” EORTC 11 961 phase I clinical “ protocol.

Purposes of the PhD study

It is demonstrated in the present work what kind of challenges and difficulties should have been overcome in order to investigate whether BNCT a new, complex radiotherapy modality, using epithermal neutrons and BSH as boron compound can be applied in a safe manner for patients in a trans-European set-up.

I. The preparation of the first clinical study in Europe will be presented. In addition to the difficulties defining a phase I trial design in the lack of established rules in the radiation oncology, the special features of BNCT had to be taken into consideration as well.

I/1. Clear definition on the aim of the clinical trial, strategy, end points and evaluation criteria were established as a part of my work.

I/2. I provide an inter-comparison on the currently ongoing clinical studies on BNCT. The achieved solutions, furthermore the general conclusions, which could be drawn for clinical research on highly selective new radiation therapy modalities are described in the present thesis.

I/3. As a part of the clinical trial on BNCT BSH pharmacokinetics and tissue uptake investigation has been performed. In this PhD work, the results of the borocaptate uptake in glioblastoma multiforme and surrounding healthy tissues, its potential contribution on localisation of the energy deposition due to boron neutron capture reactions and its radiotherapeutical relevance is described.

I/4. In this work the particular dose concept is analysed which was defined specially for BNCT using epithermal neutron source in order to establish reproducible and comparable dose specification and reporting system as close to the standard recommendations in radiotherapy as it was possible. The limitations and achievements in the complex dose(s) handling are pointed out.

II. Interim results in term of dose-effect relationship of the ongoing EORTC 11 961 phase I study is presented.

III. The conclusion of the interim analysis of the ongoing trial and the direction of further investigations and future perspectives of BNCT are highlighted.

New scientific results, conclusions and suggestions

The approach on the trial design, patient selection, definition on end point, dose escalation strategy and toxicity detection corresponds to criterion of careful introduction of a complex radiation modality into the clinic.

Establishment of a medical infrastructure and appropriate working conditions for an outpatient clinic at the nuclear reactor site applying the European standards and the accepted international rules of radiotherapy provides the basis of the safe patient treatment.

The feasibility of performing BNCT using the epithermal beam at High Flux Reactor (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 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.

The quality management system proved to be essential to assure the high quality of the study, correct interpretation of the collected data and of patient treatment performance.

After careful evaluation of the data, we can conclude that the starting BNCT dose level was safe but probably not high enough to reach the dose limiting toxicity within the frame of this radiation dose escalating trial. Early and late radiation toxicities are clearly 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 using BSH for BNCT has been proved. Further reliable data should be collected on boron bio-distribution on macroscopic and sub-cellular scale. As well as the cellular uptake mechanism and the influence of the macro- and micro-environment on it, should be investigated. However, on the basis of the present knowledge, further optimisation on boron delivery can be introduced in clinical research. As a next step, the maximal tolerated dose of BSH and the combined administration of BSH-BPA could be established in humans.

At the same time the optimisation of thermal neutron delivery can improve the results of the empirical clinical investigation on BNCT. In order to increase the accuracy of neutron transport calculation the tissue inhomogeneity should be taken into account. On that basis the boron dose should be calculated with realistic values of boron concentration of at least macroscopic volumes. To that aim in vivo boron imaging with acceptable resolution should be developed.

The phase I study was an important step toward the development of early trial methodology for radiation oncology and served paramount information on BNCT which defines the direction of further investigations on neutron capture therapies.