Introducing BNCT treatment in new treatment facilities

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Abstract. The physical and radiobiological studies that should be performed before the initiation of BNCT are discussed. The need for dose-escalation versus response studies in large animal models is questioned. These studies are time consuming, expensive and legally difficult in some countries and may be dispensable.

Considerable effort is being made, in different countries, to construct new neutron sources for boron neutron capture therapy (BNCT) with epithermal neutrons. Due to the particular properties of the production of neutrons, which differs between each of the facilities, it is very pertinent to ask when such a facility can be used for treating patients. This question is of fundamental importance for giving a positive answer to the question whether the treatment of a patient is ethically permissible. The potential harm inflicted to the patient must be seen in relation to the severity of the disease and the potential impact of the treatment on the course of the disease.

New treatment modalities need to be tested for their potential damage to healthy tissue. In clinical trials, this is usually done by dose escalation schemes. This is usually carried out in a Phase I clinical trial. The dose (of, e.g., a chemotherapeutic agent) is increased stepwise from a level known to induce only minor damage in animals, until dose-limiting toxicity signs are found in patients. The maximum tolerated dose in animals is usually backed off from considerably when entering a new chemotherapeutic agent in clinical Phase I trials.

In radiotherapy, the same principle pertains. Here, radiation dose is increased step-wise. Due to the fact, however, that prior radiotherapy of the healthy tissue exposed might result in a reduced tolerance to additional exposure, BNCT can in most cases only be applied when no prior treatment with radiotherapy has been done. This is different from most Phase I trials with chemotherapeutic agents. In order to ethically justify the exchange of a proven radiotherapeutic treatment with an experimental treatment, the dose level prescribed must be close to the limit of exposure for the tissues to be exposed.

In many of the tissues exposed to damaging conditions, the effect of the damage is often only seen after long observation periods, and sometimes without early warning signs. Especially in the tissue of the CNS, damage occurs with lag times of many months. It was therefore considered essential that realistic models for damage to healthy CNS tissue were tested prior to the initial treatment of patients. These studies comprised of a great number of large animals which were observed for over a year, or until they developed significant life-deteriorating damage. For the facility at the High Flux Reactor of the Joint Research Centre in Petten, The Netherlands, 42 dogs were entered into this study[1]. The study took around two years to be completed. The study resulted in a safe radiation dose for the treatment of the first group of patients in protocol EORTC 11961. At the same time, the starting radiation dose for the trial was high enough to expect some effect on the treated disease.

Clearly, a program in which large animals are treated prior to the treatment of patients, is extremely costly, and difficult to implement. Furthermore, it would require that a clinical study in patients is started only several years after the completion of a facility. It would therefore be of great value if ways could be found how to avoid the performance of such a

study. Its ethical justification is poor unless all information concerning past experiences from all sources has been collected and analysed.

It is therefore suggested here that all available information on the physical properties and radiobiological effects of the neutron sources should be collected.

Specifically, information about the following radiobiological aspects of BNCT in epithermal neutron beams should be brought together and exchanged:

(a) physical dosimetry and geometry of the beams free in air

(b) dosimetry in the different experimental set-ups c. through f.

(c) dose-response functions from cell culture experimental models

(d) dose-response functions from experiments in small animal models

(e) dose-response functions from experiments in large animal models

(f) dose-related effects of patient treatment

The items a. through e. are the steps achieved so far in all epithermal neutron beams used for patient treatment.

Inter-comparison between the physical properties and the radiobiological effects of fully tested neutron sources might serve as a predictive tool for new, or not yet fully tested neutron sources.

A predictive tool will require a few assumptions, which ideally should be tested experimentally. Until such experiments are carried out and resulted in appropriate conclusions, the data already available should be tested for the following hypotheses:

(1) Are doses in BNCT additive when multiplied by uniform RBE/CF values?

(2) In larger organs, are doses best represented by point values or by volume-integrated values?

With a predictive tool, the investigation of the radiobiological effect of new neutron sources, which is expensive, time-consuming, and legally as well as ethically problematic, might be considerably reduced. The time lag between finalising a neutron source and making use of it for the benefit of patients might thereby be shortened.

In addition, information will be gained how the increase of the boron concentration in healthy tissue might effect the total radiation dose which can be delivered safely.

It should therefore be the aim of future exchange and discussions to evaluate whether the above steps a. through d. might be sufficient to allow the initiation of patient treatment with all reasonable safety for the patient. If this is the case, step e. could be avoided. This would have great beneficial impact for the initiation of the treatment of patients, as step e. is very time-consuming, very expensive, legally difficult in some countries, and ethically problematic.

REFERENCE

[1] GABEL, D.; PHILIPP, K. I. H.; WHEELER, F. J., AND HUISKAMP, R. The compound factor of the $^{10}B(n,\alpha)^{7}Li$ reaction from Borocaptate Sodium and the relative biological effectiveness of recoil protons for induction of brain damage in boron neutron capture therapy. Radiation Research; 1998;149:378–386.