APPROACH TO BORON NEUTRON CAPTURE THERAPY IN EUROPE: GOALS OF A EUROPEAN COLLABORATION ON BORON NEUTRON CAPTURE THERAPY

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Abstract: A European Collaboration on Boron Neutron Capture Therapy has been founded in 1989. This Collaboration wants to create all necessary conditions to establish neutron capture therapy as a clinical therapy in Europe. For this, two main goals are being pursued:
1. To initiate, at the High Flux Reactor in Petten (The Netherlands) clinical trials of glioma and melanoma
2. To create conditions that other tumors can be treated at this and at other sites.

In this paper, the approach towards clinical trials of gliomas with boron neutron capture therapy is detailed. The necessary development of an epithermal neutron beam, and the necessary healthy tissue tolerance studies are discussed in view of the particularities of the radiobiology of boron neutron capture therapy.

Introduction to Boron Neutron Capture Therapy

Boron neutron capture therapy (BNCT) is based on the high cross section of the boron-10 nuclide for thermal neutrons. Upon capture, the boron nucleus disintegrates into highly energetic alpha- and lithium-7 particles. One event liberates enough energy to, in principle, kill a cell. The nuclides that are present in the body (hydrogen, nitrogen, carbon, oxygen) posess such low cross sections for thermal neutrons that already modest amounts of boron (in the order of several tens of microgram boron per gram tissue) suffice to deliver a substantially increased dose to that tissue.

BNCT was tried clinically in the United States in the late 1950's and early 1960's. These trials resulted in a failure, and were consequently abandoned. In Japan, clinical trials for glioma (Hatanaka, since 1968) [1] and melanoma (Mishima, since 1987) [2] are being pursued. World-wide, a greatly increased interest in BNCT can be observed. This interest is based on the fact that we now know which factors led to the failure of BNCT in the past. Problems were encountered with the poor penetration of the thermal neutron beam into tissue, a poor differential between tumorous and healthy tissue of the boron compounds used, and an excessive radiation dose especially to the skin.

Better boronated tumor seekers are now available. More is known about the radiation biology of the dose components that are encountered in BNCT. Finally, epithermal neutron beams are accessible that permit to treat tumors at depth.

For the above-mentioned Goal 2, namely the treatment of tumors other than gliomas and melanomas, it will be necessary to develop new and improved tumor seekers. This requires advances in boron chemistry, and an intense collaboration of boron chemists with, e.g., biochemists and biologists. The development of other neutron sources, also part of Goal 2, aims at existing research reactors and their conversion or modification to extract sufficiently intense epithermal neutron beams. Of great potential usefulness are accelerator-based neutron beams. The physical and technical feasibility is presently under experimental evaluation.

Here, emphasis will be placed on the approach to Goal 1. It is the aim of the European Collaboration to initiate clinical trials of glioma by the end of 1991.

Epithermal Neutron Beams for BNCT

As mentioned above, a thermal neutron beam was used in the past, and is being used currently, for BNCT. Thermal neutrons (i.e. neutrons having a kinetic energy corresponding to room temperature, around 0.025 eV) are capable of being captured immediately by all elements in the body, and therefore have only a limited depth to which they can penetrate before reacting. Epithermal neutrons, i.e. neutrons in the energy range of 1 eV to 10 keV, cannot as such be captured efficiently by the atoms of the body. They will, however, lose energy through collisions, and thus will eventually reduce their energy to thermal values. In biological material, the maximum thermal neutron flux occurs at around 2 cm depth, with many neutrons penetrating much further.

Beams of epithermal neutrons can be produced by filtration from fission spectrum neutrons obtained from a reactor, or spallation neutrons obtained from an accelerator. These beams, because of incomplete filtration, will contain a number of fast neutrons (i.e. neutrons with energies far above 10 keV), and gamma photons emerging from the reactor and produced in filter and structural materials.

Determination of the Biological Effects of Neutron Beams

In order for such beams to be useful, their biological effect on the tissue present in the beam must be known. The biological effect of the beam will determine which dose can be administered to the target volume (containing the tumor and healthy tissue) without inducing unacceptably high damage. This must be known before clinical trials can be embarked upon.

Two different approaches to this (and any similar) problem can be envisaged. One approach would be to arrive at the exact conditions of the clinical trial from known basic facts (the deductive approach). The alternative approach would be empirical (the inductive approach).

In principle, it would be of great reassurance if treatment of BNCT could rely on deduction from known principles. It would then be necessary to identify and quantify the different components to the biologically effective dose in the target, to quantify the biological response to these different dose components, and to tailor, with these data, the incident beam such that the tumor receives a maximum dose, while healthy tissue is not inflicted an unpermissibly high dose.

As will be detailed below, this approach is presently not feasible in BNCT, and perhaps might never be possible.

In BNCT, there are a variety of dose components that contribute to the total dose. For an epithermal neutron beam, which would allow to treat tumors at depth und thus overcome some of the problems encountered in the initial clinical trials, these dose components come from the incident beam (mainly fast neutrons and gamma photons), and from neutron capture reactions of the thermal neutrons generated with hydrogen (giving rise to a 2.2 MeV gamma photon) and nitrogen (generating a carbon-14 ion and a proton of an energy of 0.56 MeV available for ionization).

In addition to the doses associated with the epithermal beam impinging on the target, there is a dose component generated by the $^{10}B(n,\alpha)^{7}Li$ capture reaction wherever boron is present in the irradiation volume.

Depth-dose profiles for the different dose components will have shapes like those shown in Fig. 1 for the epithermal neutron beam of the Medical Research Reactor of the Brookhaven National Laboratory [3].

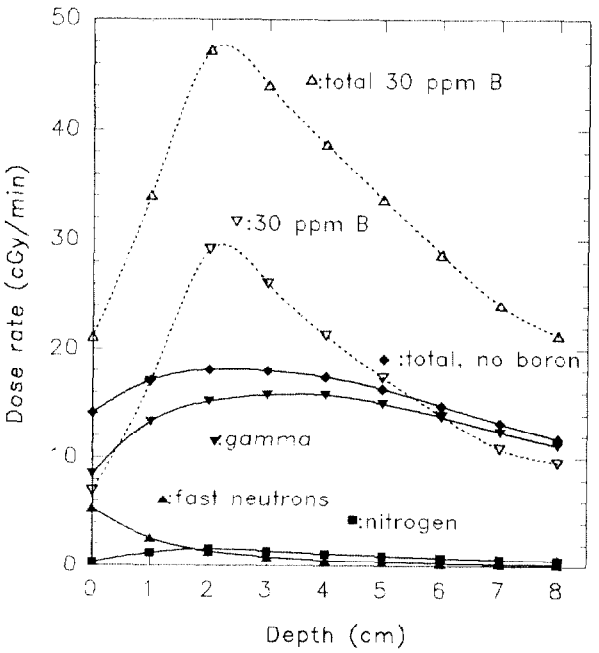

Fig. 1. Depth-dose profiles in a cylindrical phantom of the epithermal beam of the Brookhaven Medical Research Reactor. (Data adapted from [3])

The necessary information about these different dose components would have to come from adequate physical dosimetry of the different beam components in the different volume elements in the target. In conventional radiotherapy, a sum of all dose components, multiplied when indicated with their appropriate RBE values, would give a good estimate of the actual expected dose in each of the volume elements of the target.

There are considerable problems to estimate the biologically effective dose associated with the boron capture reaction. These problems cannot be solved easily, and might perhaps elude estimation altogether. This arises from the fact that the alpha and the lithium particles generated in the boron capture event have, in biological tissue, ranges that are commensurate with the dimensions of a cell. Thus, the energy deposited in the nucleus of a cell will depend considerably on the location of the boron capture event in relation to the cell nucleus [4]. (The energy deposited in the nuclei of single cells has been termed "hit size" by Bond [5], in order to differentiate it from dose, which is an average quantity. Subsequently, "hit size" will be used to indicate the energy deposited in a cell nucleus.) Calculations by Gabel for typical cells [4] have indicated that the hit sizes from this reaction might vary by almost a factor of 10, depending on whether the same amount of boron is distributed uniformly throughout the tissue or whether present only on the surface of the cells. (The latter case might arise when antibodies are used to carry boron.) Furthermore, because of the energy and the high LET values of the two particles, Poisson statistics will result in a large variation of hit sizes. Analysis of cell biological experiments [4], taking into account the statistical variations of hit sizes, infers the existence of a Hit Size Effectiveness Function [5]. This implies that not every cell whose nucleus receives a hit size from the $^{10}B(n,\alpha)^{7}Li$ reaction, will die as a consequence. The probability of reproductive death will increase with increasing hit size.

For these reasons, the concepts of "dose" and "RBE" can be misleading in BNCT.

As a consequence, only an empirical, i.e. inductive, approach towards BNCT can be followed in a given therapy situation with a given compound. This will be reflected in treatment planning.

Treatment Planning in BNCT

In conventional radiotherapy, considerable effort is devoted to maximize the dose to the tumor and at the same time spare healthy tissue. This is achieved by tailoring the beam shape for each of several irradiation ports.

In BNCT, the approach must be different. This is due to the fact that the incident beam is not as such of therapeutic efficacy. Upon collision with a sufficient number of atoms, the epithermal neutrons have reduced their energy such as to be captured by boron (and hydrogen and nitrogen). During the process, the initial direction of the neutrons will gradually be lost, and consequently the edges of the beam will become diffuse in comparison with conventional therapy beams. A broad range of penetration depths will exist for these neutrons (in marked contrast to the Bragg peak observed for accelerated heavy particles). Therefore, not only will the beam be diffuse laterally, but also vary considerably in its dose to tissue along the beam axis. The hydrogen capture reaction gives rise to long-reaching gamma photons, which in the absence of boron are responsible for the major fraction of the dose deposited in tissue, and will add to the broadending of the beam.

In BNCT, the hit size to a tumor cell is due mostly to the hit size from boron, and thus cannot be influenced by the shape and properties of the external beam. Treatment planning is indeed achieved by the choice of compound. Therefore, the properties of the beam are of greatly reduced importance, as far as its lateral and depth profiles are concerned. This is illustrated in Fig. 2. In conventional radiotherapy, the hit size to one cell is very close, if not identical, to the hit size to its immediate neighbors. In BNCT, each cell will receive a hit size which is due to a very great extent only to the amount of boron this very cell has accumulated.

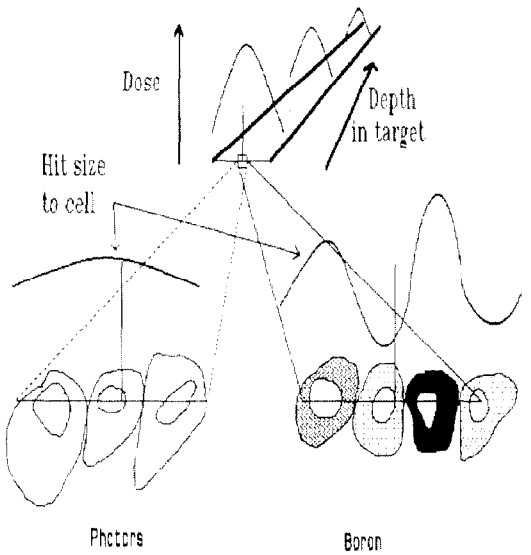

Fig. 2. Schematic presentation of hit sizes to cells in a target from photons, compared to hit sizes from the $^{10}B(n,\alpha)^{7}Li$ reaction. The target will attenuate the beam and, in the case of a neutron beam, broaden it. In the case of photons, hit sizes to adjacent cells will be similar, if not identical. Hit sizes to cells in BNCT will be dependent mostly on the boron accumulation in each of the cells, and will therefore vary greatly between one cell and its immediate neighbors.

In healthy tissue, one will have to expect that boron will be present in different cells in different amounts. The determina-

tion of boron concentrations averaged over as little as several cells, not to mention weighable amounts of tissue, will not allow to draw conclusions for the hit size to each of the cells present. In order for this to be predicted, the distribution of boron in each of these cells and their immediate neighbors needs to be known. There are presently no techniques to measure this. In the tissues of an individual patient, this distribution will remain unknown even if such techniques were available.

The Safety of BNCT Treatment

In order to initiate clinical trials with BNCT, as with any other new therapy modality, it must be made plausible that the treatment does not carry an undue risk to the patient; indeed, it must be made sure, in the case of BNCT and in conjunction with its earlier failure, that the risk to the patient is minimal. To ensure safety is of primary concern for the initial treatment planning; efficacy of treatment is consequently not as important in the first steps. Therefore, the effect of the therapy on healthy tissue must be estimated. A thorough study of the tolerance to the therapy of healthy tissue exposed to the beam must thus be conducted.

Healthy tissue tolerance will be studied in dogs. The dogs will be given $Na_2B_{12}H_{11}SH$ (BSH) in different amounts, and they will then be exposed to different neutron levels. BSH is used by Hatanaka [1] for treating gliomas, and will be used in the initial study in Europe. From the initial studies on healthy tissue tolerance in dogs carried out in the United States, as well as from the dose-depth profiles of such beams in phantoms, the likely tissue at risk is not the skin, but tissue at a few centimeters depth (i.e. brain tissue) (see also Fig. 1). White matter necrosis would occur with such treatment, and this will take several months to develop. (In previous experience of the late 50's and early 60's, skin was the most radiosensitive organ. This was due to both the high boron concentration in the skin and the simultaneous use of a thermal neutron beam. With beams of moderate mean energy, and using the presently available boron compounds, skin is no longer the dose limiting healthy tissue.)

From a knowledge of the dose components at different depths, operational factors can be derived when this study includes different levels of boron concentration and neutron exposure. These factors then allow the neccessary exposure planning.

Due to the importance of localization of boron, the maximally tolerated dose will be compound dependent. Thus, studies with one compound (e.g. BSH) will not yield much information for the treatment using a different boron compound (e.g. p-dihydroxyboryl phenylalanine). Equally, studies for one target organ (e.g. brain tissue) cannot, even for the same compound, be transferred easily to other treatment areas.

In order to transfer results from this animal study to patients, the pharmacokinetics of the boron compound needs to be known in both. The European Collaboration therefore has placed great emphasis on a thorough pharmacokinetic study of BSH in brain tumor patients.

Requirements on the Epithermal Neutron Beam

The quality of the incident neutron beam is, of course, of great importance for the success of the treatment. As detailed above, there are not only epithermal neutrons present in the beam, but also unwanted components. These include fast neutrons and gamma photons. The number of fast neutrons relative to those of epithermal neutrons, expressed as the mean energy of the beam, should be as low as possible. This can be achieved by filtering away neutrons of unwanted energy by means of suitable filter materials. Filter materials of potential use are: aluminum, sulfur, deuterium, oxygen, titanium. There is a price to be paid for heavy filtration, in terms of loss of intensity of the beam.

Gamma photons have to be absorbed by the use of appropriate shielding material. Shielding materials include bismuth and argon (liquid).

Extensive calculations of these different filter and shielding materials have been carried out for the High Flux Reactor (HFR) in Petten (The Netherlands). The first goal was to explore which range of mean energies, beam intensities, and gamma contaminations can be achieved. With these data at hand, and based on the projected healthy tissue tolerance, beam design goals were defined. These are:

Neutron fluence	$\geq 10^9$ n cm^{-2} s^{-1}
Mean neutron energy	$\leq$ 8.1 keV
Incident gamma dose	$\leq$ 0.5 Gy / $3 \cdot 10^{12}$ n cm^{-2}

The neutron fluence of this beam would be enough to deliver a theraupeutic dose, in a single session, in a period of around one hour. Most probably, a fractionated treatment will be aimed for. This is based on the general practice and experience in conventional radiotherapy, the unavoidable and considerable gamma component to the total dose, and the limit to which radiation can be delivered to the skull whithout inducing unwanted side effects.

A beam with the above characteristics will be achieved by combinations of aluminum, sulfur, titanium, cadmium, and liquid argon as filter materials. All other materials were found to be less useful for the beam construction.

The filter will be installed in the HB11 beam hole of the HFR, during the summer break of 1990.

The Next Steps

Following the installation of the beam, its physical parameters will be carefully measured and compared with the calculated values. Extensive dosimetry in phantoms will be carried out and complemented by cell survival assays. Thereafter, the above-mentioned study of healthy tissue tolerance will begin. It is anticipated that clinical trials can start towards the end of 1991.

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