A STUDY OF THE PRODUCTION OF NEUTRONS FOR BORON NEUTRON CAPTURE THERAPY USING A PROTON ACCELERATOR*

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Abstract

Boron Neutron Capture Therapy (BNCT) is a binary cancer therapy particularly well-suited to treating aggressive tumours that exhibit a high degree of infiltration of the surrounding healthy tissue. Such tumours, for example of the brain and lung, provide some of the most challenging problems in oncology. The first element of the therapy is boron-10 which is preferentially introduced into the cancerous cells using a carrier compound. Boron-10 has a very high capture cross-section with the other element of the therapy, thermal neutrons, resulting in the production of a lithium nucleus and an alpha particle which destroy the cell they are created in. However, a large flux of neutrons is required and until recently the only source used was a nuclear reactor. In Birmingham, studies of an existing BNCT facility using a 2.8 MeV proton beam and a solid lithium target have found a way to increase the beam power to a sufficient level to allow clinical trials, while maintaining the target solid. In this paper, we will introduce BNCT, describe the work in Birmingham and compare with other accelerator-driven BNCT projects around the World.

BNCT

BNCT is a form of radiotherapy in which a stable isotope of boron (boron-10) is bound to a non-toxic carrier molecule (such as 1-p-borono-phenyl alanine (BPA)) which is preferentially absorbed by tumour. When the tissues are exposed to low energy neutrons, the following reaction occurs:

$$^{1}n + ^{10}B \rightarrow ^{4}He + ^{7}Li + 2.8MeV$$

The alpha particle and lithium nucleus produced have mean free paths which are the same as the cell sizes. Thus, they deposit most of their energy in the cancerous cell in which they are created, thereby destroying it. Provided a sufficient boron concentration exists in the tumour cells, the high neutron capture cross-section of ^{10}B ensures that most of the energy from the neutron beam is deposited where it is needed and the damage to healthy tissue surrounding the tumour is minimised compared to other therapies (see figure 1). In addition, it means BNCT does not rely heavily on imaging to define the target volume to be treated so it is particularly well suited for tumours where the disease is infiltrating into the healthy tissue belonging to vital organs. Such tumours are some of the most aggressive and difficult to treat with standard techniques.

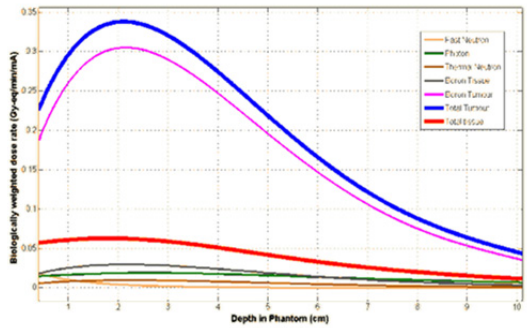

Figure 1: Comparison between the dose delivered to tumour and healthy cells using BNCT for realistic uptakes on the carrier compound BPA.

A number of trials of BNCT have been carried out, focussing on a highly aggressive type of brain tumour called a glioblastoma multiforme (GBM). This is the most common type of primary, malignant brain tumour, with about 13000 people being diagnosed in Europe each year. Data on progression free survival of glioma patients treated in Japan with an approach which combines BNCT with x-ray radiotherapy can be compared with results from the highly regarded randomised trial performed by Stupp et al [1] (the current state-of-the-art). This study employed a drug called temozolomide and the most striking outcome was an approximate doubling of the number of patients surviving 2 years from around 12% to 25%. The data from Tsukuba [2] on BNCT shows a further factor of 2 improvement in 2 year survival, to 45.7%. It should be noted, however, that the number of patients is extremely small (12 in the study of Yamamoto et al) and these results will need to be reproduced in a larger population before any conclusions can be drawn.

It is important to note that the improved success shown in studies which combine BNCT with x-ray therapy is entirely to be expected from the data recently published in Birmingham [3]. This shows that BPA uptake is dominated by a common transporter system, the L-amino acid transporter-1 (LAT-1). Further (see figure 2):

a) LAT-1 expression is shown in 30-90 % of tumour cells (i.e. a high proportion but < 100%)
b) Indices of proliferation are lower (i.e. in a real tumour not all cells are actively dividing).

At present the research on LAT-1 is aimed at developing a better understanding of BPA-based BNCT, but in time it could develop into a selection methodology for patients who will benefit most from this new treatment. It is, however, already clear that since not all tumour cells express LAT-1, and BPA uptake is mediated by LAT-1,

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any treatment strategy based on a single delivery of BPA-based BNCT alone will not succeed. An approach which combines BNCT with a powerful treatment that targets all cells (eg x-ray radiotherapy) then looks optimal.

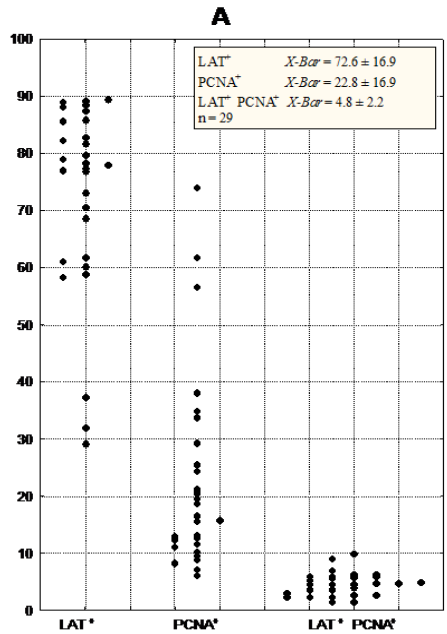

Figure 2: LAT-1 expression and proliferation index of the highest rages (Grade IV) human gliomas.

In addition to GBM, BNCT has found clinical utility in the treatment of recurrent head and neck cancer (mainly Squamous Cell Carcinoma (SCC)) where published data from Helsinki shows that this treatment is well tolerated and capable of providing good life extension [4]. BNCT has also been shown to have potential in the treatment of metastatic colon cancer in the liver, primary and metastatic melanoma and lung cancer.

NEUTRON PRODUCTION

Producing a sufficient flux of neutrons with the correct energy is a particular problem with BNCT. The requirement is a flux of around 10^9 epithermal neutrons/cm^2/s for a session of less than 30 minutes. In addition, as well as being mainly at epithermal energies, the beam should not also have neutrons above 1 MeV, as these add to the dose to healthy tissue in an uncontrollable manner. Currently, the only source used is a (usually research) nuclear reactor. Reactors in Japan, the US, the Netherlands, Finland and Argentina have or are being used for BNCT studies [5].

Nuclear reactors are clearly not ideal locations for treating patients, some of whom may be very unwell. This is part of reason why so few patients have so far been treated with the therapy. It is possible to make the neutrons with particle accelerators, but here the beam requirements create significant technical problems. In particular, the requirement for a large flux of epithermal neutrons, after moderation, with no or a very limited flux of neutrons above 1 MeV, requires a low energy proton beam (< 10 MeV). This means that the best neutron production reactions to use are beams of either protons or deuterons on lithium or beryllium targets (see figure 3). Producing a sufficient neutron flux then requires a beam power of at least 12 kW and probably more like 20 kW. This then makes heat removal and avoiding/handling blistering of the target the most difficult aspects of accelerator production, particularly with a lithium target. Each of the options, with examples, is discussed below.

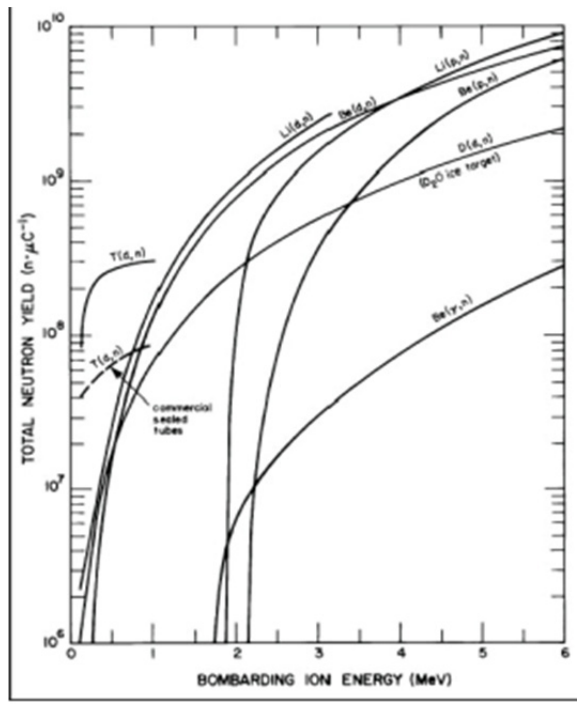

Figure 3: Reactions for the production of neutrons at low beam energy

Solid Lithium Target

Protons at 3 MeV penetrate only 400 μm in to lithium, so the power from the beam is deposited in a very thin layer. Further, the melting point of lithium is only 181 °C, so preventing it melting is the most difficult aspect of this target. In almost all cases, the lithium is bonded to a copper or aluminium backing and the backing is cooled using light or heavy water. As ^{7}Li(p,n)^{7}Be reaction has a threshold at 1.88 MeV, ideally what is required is a very thin layer of lithium, so that the remaining and unuseful beam power is deposited directly in the copper. However, tests of such targets have shown that the lithium tends to blister and separate from the backing at the required beam powers [6].

An alternative approach has been taken in the University of Birmingham in the UK. This employs a 0.7 mm thick disk of lithium of diameter 4 cm firmly bonded to a copper backing. A Dynamitron accelerator, run at 2.8 MeV, is mounted vertically and accelerates the proton beam downwards. The copper is cooled from below using a submerged heavy water jet [7]. The beam is steered in an annulus around the target using two steering magnets. With this system, the temperature in the lithium from the

4.2 kW beam is kept below the melting point. Further, no blistering of the target is seen.

A 40 cm thick moderator and reflector system has been designed to deliver an epithermal neutron beam to a patient at right angles to the beam direction. With this arrangement, no neutrons above 1 MeV are produced in the direction of the patient. However, with the current beam power, the treatment time is too long and an increase by a factor of 2.5 to 3 is required to make this tolerable for clinical trials.

A number of studies have been done to determine how to make this increase. These include optimisation studies of the moderator and the target cooling. This work is on-going, but has produced encouraging results. The ultimate test will need an upgrade to the Dynamitron to deliver the required beam current. This has also been studied and looks feasible. A proposal has been submitted to implement the changes and undertake clinical trials of the therapy.

Liquid Lithium Target

The alternative to a solid lithium target is a liquid one. A number of studies of flowing liquid lithium targets for BNCT are taking place. The advantages of this over a solid target are clear: the heat deposited is carried away by the lithium, which can be cooled outside of the target and the effective volume of lithium exposed to the beam is much larger, so the damage resulting from it is spread over this larger volume. However, such a target is more complex than a simple solid target and requires the infrastructure to prepare, circulate and cool the lithium. In addition, there is a significant health and safety risk in a hospital environment. Further, the flow rate must be sufficient to maintain the temperature below the boiling point at the pressure in the target region, typically about 340°C.

As an example, a target made from a flowing film of liquid lithium has been studied in Osaka University in Japan [8]. The plan is for a 0.5 mm thick film of 50 mm width and 50 mm length for use with a beam of 3 MeV and a current of up to 20 mA. Tests have demonstrated that a stable flow should be possible at a flow rate of 30 m/s, which will be sufficient to keep the lithium temperature below the required level. It is now planned to build a demonstration project using this target.

Beryllium Target

Beryllium has the advantage of higher melting point, higher thermal conductivity and the ability to be directly cooled with water. However, as shown by Figure 3, higher proton beam energies are required for the same neutron yield. This increases both the cost and complexity of the accelerator. In addition, the mean neutron energy is higher, leading to the need for more moderation. This places the patient further from the source and hence increases the total neutron yield required. In addition, there is a significant contribution of high energy neutrons.

A BNCT facility has recently started trials at the Kyoto University Research Reaction Institute (KURRI) using a beryllium target [9]. They employ a 30 MeV cyclotron which can accelerate a 2 mA H- ion beam, though typically 1 mA is used. The beam spot is increased to 80 mm diameter and steered around the 160 mm diameter target using scanning magnets. The thickness of the beryllium is set to be slightly less than the range of 30 MeV protons. It is cooled from behind using water. The neutron energy peaks at around 1 MeV so the target is followed by a moderator system to reduce this to the required energy of around 10 keV. The measured flux of thermal neutrons in a phantom is 1.8×10^9 $cm^{-2}s^{-1}$. As expected, however, the flux of high energy neutrons exceeds the target value.

To reduce the flux of high energy neutrons, an alternative approach is being taken in Argentina [10]. The plan there is a use a low energy deuteron beam of 1.4 MeV and a very thin beryllium target, around 8 μm thick, which has the effect of supressing the production of high energy neutrons. A facility to test this concept and to start producing neutrons is under construction.

CONCLUSIONS

Boron Neutron Capture Therapy has shown great potential for the treatment of certain types of aggressive tumours that are otherwise difficult to treat, in particular those that infiltrate the surrounding healthy tissue. The main difficulty in the therapy is producing a sufficient flux of epithermal neutrons to keep the treatment session time to a tolerable level with an accelerator, while also controlling the rate of high energy neutrons. A number of projects around the world are pursuing three basic options to achieve these goals. One has started treatment.

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