Principles, Recent Developments and Perspectives in Boron Neutron Capture Therapy (BNCT)

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ABSTRACT

For decades, BNCT was seen as an attractive concept and an intellectual challenge with no prospect of widespread clinical application. This situation has changed fundamentally in just a few years with the progress in accelerator technology. Low-energy, high-intensity neutron sources can now be integrated into hospitals and are therefore directly available for patient treatment. A pioneer in this field is the development in Japan, where patients are already being treated in three hospitals, using in-house accelerator-based systems. Furthermore, the costs associated with the BNCT treatment of recurrent tumors in the head and neck area are already covered by the healthcare system. It is time to keep up to date with this technology and work to make it available to patients in high-tech medicine in other countries, especially in Europe and North America. This short article summarizes the main principles of BNCT, outlines some aspects of its history and mentions ongoing projects as well as some hurdles that need to be overcome, as well as the scientific questions that need to be addressed for wider availability of the method.

KEYWORDS

Radiation oncology, fast neutron therapy, accelerator-based BNCT (ABNCT), high-linear-energy-transfer (LET), ICRU, IAEA, DGBNCT
INTRODUCTION

The interaction of neutrons with matter depends on their energy. So-called fast neutrons have an energy high enough to knock out the nucleus of a hydrogen atom in biological material and generate recoil protons, which act as direct ionizing particles with high-linear-energy transfer (high LET). In radiation oncology, this effect is used in fast neutron therapy. Neutrons with lower kinetic energy, so-called epithermal or thermal neutrons, cannot generate recoil protons. However, they cannot exist as “free” neutrons, but instead cause nuclear reactions. This is used in medicine for boron neutron capture therapy (BNCT).

SOME BASIC PRINCIPLES OF BNCT

BNCT is based on the ability of the non-radioactive isotope boron-10 to capture thermal neutrons with a very high probability (cross section $\sigma_{th}$, 3,835 b [1]). This nuclear reaction leads immediately to the production of two particles, a helium and a lithium nucleus. They have a high linear-energy transfer but short path lengths in water or tissue in the range of 4.5–10 µm, which corresponds approximately to the diameter of a single cell. In BNCT, the patient receives a drug containing B-10, which is preferentially taken up by cancer cells. When exposed to thermal neutrons, the high LET particles resulting from the neutron capture reaction $^{10}$B(n,\alpha)$^4$Li have the potential to selectively destroy cancer cells with high B-10 uptake. Neighboring normal tissues, even if infiltrated by the tumor, are spared. This offers the possibility of a kind of “cellular surgery”, in which tumor cells are removed from the normal tissue without damaging it. Since BNCT preferentially destroys tumor cells, this provides a modality that can also be used again in pre-irradiated regions, as the pre-irradiated normal cells are only slightly targeted.

WHAT DOES HIGH-LET RADIATION MEAN FOR BIOLOGICAL SYSTEMS?

The linear energy transfer (LET) for charged particles in any medium is defined as the quotient of the average energy that a charged particle with a certain energy transfers locally to the medium when it traverses a given distance [2]. This results in a high density of ionization. In a biological system, high ionization density leads to double-strand breaks that cannot be repaired, as well as single-strand breaks that occur with low LET irradiation. The oxygen enhancement ratio (OER) is reduced [3], which means that this type of irradiation is also effective in hypoxic areas of the tumor. A small difference in radiosensitivity is observed between different cell lines, which implies that radioresistant cells are also damaged. In summary, the relative biological effectiveness (RBE) of high LET irradiation is high [4]. If one considers only the tumor to be treated, these are all considerable advantages. Unfortunately, all these factors also apply to normal tissue, which is also more affected by high-LET radiation than by low-LET radiation. In the worst case, the damage caused to the normal structures is greater than to the tumor, and the desired therapeutic effect does not occur. Radiation with a high LET is particularly useful in medical applications, especially if this radiation quality can be used in a targeted manner and reaches as few or no normal tissues as possible. This is the case with BNCT.

WHAT MAKES BNCT DIFFERENT FROM ALL OTHER CURRENTLY AVAILABLE MODALITIES IN RADIATION ONCOLOGY?

There are some inherent problems with all current therapy techniques in radiation oncology. Dose is always delivered to a volume of tissue. Normal tissue inside the target volume receives the full dose and will be destroyed. There is a buildup/fallout region outside the target volume, and a significant dose will be delivered to normal tissues in this region. Image guidance techniques are not perfect, and the target will vary with imaging modalities that are available. Finally, a physician will define the volume to be treated, which will vary depending on the physician. Advanced conventional external beam radiotherapy with photons or particles, or alternative approaches, such as brachytherapy or intraoperative RT, are means for mitigating these facts, but they cannot eliminate them. Some kind of “disease targeted therapy” is needed, where the treated volume is determined at the biological level and the treatment can be designed to damage only the cancer cells wherever they are, but not the normal tissues. BNCT has all the prerequisites to meet these requirements and has the potential to make a significant contribution to optimizing radiation oncology.

SOME MAJOR CHALLENGES

After all that has been said so far, BNCT should experience a home run in oncology. Unfortunately, beautiful principles are not always easy to turn into advantages on closer inspection. The boron carrier, which selectively delivers boron-10 into the tumor cells at a high concentration, obviously poses a particular challenge [5–8]. However, this aspect of BNCT will not be investigated further here. If we concentrate exclusively on the dose distribution achieved in the patient under optimal conditions, a complex picture also emerges [9]. Although our previous explanations have correctly described the most significant dose component resulting from the capture of thermal neutrons in B-10, two essential aspects have been neglected. Firstly, there is no radiation source that exclusively produces neutrons of the quality suitable for BNCT. There are always fast neutrons involved, which, with the production of recoil protons, deliver an additional dose component with a high RBE, especially to distal tissues. The neutron beam also contains photons of different origin and energy. Of greater importance, however, is the production of gamma radiation in the patient him/herself, which results from the capture of neutrons in hydrogen. A further component are protons resulting from the capture of neutrons in nitrogen. The spectrum of these different dose components with different RBE that also change at depth make prescribing and reporting difficult. Several
approaches have been published. However, up to now, there is no standardized and widely accepted procedure [10, 11].

SOME ASPECTS ON HISTORY

Shortly after the discovery of the neutron by Chadwick in 1932 [12] and the description of the $^10B(n,\alpha)^7Li$ reaction by Taylor and Goldhaber 1935 [13], the basic idea to use neutron capture reactions in cancer treatment was published by Locher in 1936 [14]. Early clinical applications started in the United States in 1951. The clinical results were disappointing and led to a discontinuation of research in this field in the United States. In 1968 in Japan, Hiroshi Hatanaka started the renewal of BNCT, introducing into clinical application the boron compound disodium mercaptoundecahydro-closo-dodecaborate Na$^2_2B_{12}H_{12}SH$ (BSH), which had been synthesized by Soloway et al. [15, 16]. Hatanaka reported exciting results, with a five-year survival rate of 58% in a small group of highly selected patients with grade 3 and 4 malignant gliomas [17], thereby stimulating a restart of clinical research on BNCT in both Europe and the United States.

However, the development of BNCT has been hampered by the fact that, until recently, the quality and intensity of the neutron field required for BNCT could only be achieved using a nuclear research reactor. These facilities were usually far away from hospitals, and their availability for patient treatment was limited in time. As a result, no large clinical studies with statistically relevant results could be carried out, even when early clinical trials could show a benefit for patients suffering from a recurrent cancer in the head and neck area [18–20]. In recent years, however, the appearance of accelerator-based neutron sources that can be placed in hospitals is currently leading to a change in paradigm. Progress in BNCT, which has been slow to materialize over many decades, is now suddenly gaining surprising momentum [21]. Multiple hospitals, especially in Japan and other Asian countries, e.g. China, Taiwan and South Korea, are preparing BNCT or are already treating patients (cf. Tab. I.). Most importantly, in Japan the costs of BNCT for the indication “recurrent head and neck cancer” are already covered by the public health system. In Europe, two BNCT centers will soon be treating patients, the Helsinki University Hospital [22] and the Italian Centro Nazionale di Adroterapia Oncologica CNAO, in Pavia [23].

POTENTIAL INDICATIONS FOR BNCT

In this early stage of clinical validation, it is necessary to concentrate on situations that are not successfully treated by existing conventional methods. The main candidates are locally recurrent head and neck tumors that have received all local treatment options (evidence level 2B already established/reimbursed by the Japanese health care system). The authors also see great potential for BNCT in locally recurrent breast cancer after several unsuccessful local therapies (breast-conserving procedure, followed by mastectomy and possibly multiple radiotherapies), but especially in “cancer en cuirasse”. Further promising candidates are melanoma of the mucosa, skin melanoma not responding on checkpoint inhibitors, as well as radio- and chemotherapy resistant tumors (such as adenoidcystic carcinoma of the salivary glands, soft tissue sarcoma) and tumors with poor outcome (such as high-grade glioma and malignant meningioma).

FUTURE PERSPECTIVES

There is still much work to be done to develop BNCT into a reimbursable modality of radiotherapy that complements conventional techniques. One prerequisite is, of course, more BNCT centers, especially in Europe and the United States. This requires major investment, which – at least in Europe – can only be made in conjunction with academic institutions and the public sector. Irrespective of the financial aspects, BNCT also poses a particular challenge for regulatory authorities. There is, on the one hand, a complex irradiation device without real medical history but dedicated radiation protection issues, and on the other hand, a drug without any effect in the absence of neutrons. There will need to be a discussion as to whether this chemical compound and its formulation have to be considered as a drug or as a medical device, or should rules developed for radiopharmaceuticals be applied? Such discussions are just beginning.

However, in this article if we focus on the research efforts still required we also find a large number of open questions and challenges that urgently need to be addressed. The following list highlights the most important areas but is by no means exhaustive. If, as a first step, we focus on clinical research to provide evidence that BNCT benefits patients and is even better compared to existing (less expensive) treatments, two important issues need to be clarified. First of all, it is necessary to develop standards for prescribing, but especially for reporting as quickly as possible, so that procedures and results can be compared [11]. The community will have to join efforts to prepare an ICRU Report on “Prescribing, Recording and Reporting BNCT”.

When prescribing, assumptions have to be made and models must be used, as not all factors that are necessary for determining the irradiation time and radiation dose can be measured (for example, the boron concentration in the tumor). Currently, different centers are using different models for their calculations. Methods need to be developed that allow clear communication between the different centers without misunderstandings. Another general concern is the development of clinical trial strategies for BNCT as a binary treatment modality with two different agents, namely neutrons and a boron drug, neither of which by itself has any effect on the tumor [24]. The study design must be adapted to the objective, e.g. certification of the neutron source as a medical device or a Phase I toxicity study, etc.

Irrespective of clinical research, there are open questions that arise in the context of basic or preclinical research that require the collaboration of many disciplines. This starts with the cross-section of low-Z biological materials for thermal neutrons that
Tab. I. Ongoing BNCT projects with accelerators worldwide, as far as the authors are informed. Due to the dynamic nature of the projects, the authors cannot guarantee their accuracy. A regularly updated version of this list is available at https://dgbnct.com/index.php/bnct-centers-worldwide.

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>CENTER / LOCATION</th>
<th>VENDORS</th>
<th>ACCELERATOR (ENERGY)</th>
<th>TARGET</th>
<th>STATUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAPAN</td>
<td>Kyoto University</td>
<td>Sumitomo HI</td>
<td>Cyclotron (30 MeV)</td>
<td>Be</td>
<td>Prototype no longer in clinical operation</td>
</tr>
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<td>Clinical trials / reimbursed treatments</td>
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<td>Be</td>
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<tr>
<td>JAPAN</td>
<td>University of Tsukuba</td>
<td>Own development</td>
<td>RFQ+DTL (8 MeV)</td>
<td>Be</td>
<td>Commissioning</td>
</tr>
<tr>
<td>JAPAN</td>
<td>National Cancer Center Hospital</td>
<td>CICS</td>
<td>RFQ (2.5 MeV)</td>
<td>Li</td>
<td>Clinical trials</td>
</tr>
<tr>
<td>JAPAN</td>
<td>Edogawa Hospital BNCT Center</td>
<td>CICS</td>
<td>RFQ (2.5 MeV)</td>
<td>Li</td>
<td>Construction</td>
</tr>
<tr>
<td>JAPAN</td>
<td>Nagoya University</td>
<td>Own development based on IBA Dynamitron</td>
<td>Electrostatic (2.5 MeV)</td>
<td>Encapsulated liquid Li</td>
<td>In operation (Research facility, no patient treatments intended)</td>
</tr>
<tr>
<td>JAPAN</td>
<td>Shonan Kamakura General Hospital</td>
<td>Neutron Therapeutics, nuBeam</td>
<td>Electrostatic (2.8 MeV)</td>
<td>Rotating Li</td>
<td>Commissioning</td>
</tr>
<tr>
<td>FINLAND</td>
<td>Helsinki University Hospital</td>
<td>Neutron Therapeutics, nuBeam</td>
<td>Electrostatic (2.8 MeV)</td>
<td>Rotating Li</td>
<td>Commissioning</td>
</tr>
<tr>
<td>ARGENTINA</td>
<td>Comision Nacional Energia Atomica (CNEA)</td>
<td>CNEA own development</td>
<td>Electrostatic Quadrupole (1.45 MeV)</td>
<td>Be and $^{10}$C</td>
<td>Construction</td>
</tr>
<tr>
<td>RUSSIAN FEDERATION</td>
<td>Budker Institute of Nuclear Physics + RONC (N.N. Blokhin Russian Cancer Research Center)</td>
<td>Budker institute (own development)</td>
<td>Electrostatic Tandem (2.3 MeV)</td>
<td>Solid Li</td>
<td>In operation at Budker. No patient treatment. Developing at Cancer Center</td>
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<tr>
<td>ISRAEL</td>
<td>Soreq Applied Research Accelerator Facility</td>
<td>Research Instruments GmbH</td>
<td>RFQ+Superconducting LINAC (4 MeV)</td>
<td>Liquid Li</td>
<td>In operation</td>
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<td>CHINA</td>
<td>Humanity Hospital Xiamen</td>
<td>Neuboron NeuPex (TAE LS accelerator)</td>
<td>Electrostatic Tandem (2.3 MeV)</td>
<td>Solid Li</td>
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<tr>
<td>CHINA</td>
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<td>Linear</td>
<td>?</td>
<td>Developing</td>
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<tr>
<td>CHINA</td>
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<td>?</td>
<td>Developing</td>
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<tr>
<td>CHINA</td>
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<td>Linear</td>
<td>?</td>
<td>Developing</td>
</tr>
<tr>
<td>CHINA</td>
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<td>Sumitomo HI</td>
<td>Cyclotron</td>
<td>?</td>
<td>Construction</td>
</tr>
<tr>
<td>CHINA</td>
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<td>own development</td>
<td>Cyclotron</td>
<td>?</td>
<td>Construction (Research facility, no patient treatments intended)</td>
</tr>
<tr>
<td>TAIWAN</td>
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<td>Unknown</td>
<td>Cyclotron</td>
<td>?</td>
<td>Construction</td>
</tr>
<tr>
<td>UNITED KINGDOM</td>
<td>University of Birmingham (research system)</td>
<td>Neutron Therapeutics, nuBeam</td>
<td>Electrostatic Tandem (2.3 MeV)</td>
<td>Rotating Li</td>
<td>Commissioning (Research facility, no patient treatments intended)</td>
</tr>
<tr>
<td>UNITED KINGDOM</td>
<td>Queen Elisabeth Hospital</td>
<td>TAE Lifesciences</td>
<td>Linear</td>
<td>Solid Li</td>
<td>Developing</td>
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<td>ITALY</td>
<td>Legnaro National Laboratory, Italian Institute of Nuclear Physics (INFN)</td>
<td>own development</td>
<td>Linear</td>
<td>?</td>
<td>Developing (Research facility, no patient treatments intended)</td>
</tr>
<tr>
<td>ITALY</td>
<td>CNAO (Centro Nazionale di Adroterapia Oncologica)</td>
<td>TAE Lifesciences</td>
<td>Linear</td>
<td>Solid Li</td>
<td>Developing</td>
</tr>
<tr>
<td>SPAIN</td>
<td>Granada University Hospital</td>
<td>unknown</td>
<td>Linear</td>
<td>?</td>
<td>Developing</td>
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</table>
CONCLUSIONS

After seven decades of more or less successful clinical research and treatment of some patients, BNCT is in a translational phase and on the verge of becoming a real treatment method for patients. This has mainly been made possible by the development of accelerator-based technology. Patients no longer have to be taken to a research reactor for irradiation; the neutron source is now available in the hospital. This is not only a paradigm shift but also a challenge for clinicians and scientists to focus on the research activities necessary to utilize this newly available treatment for the benefit of our patients.

REFERENCES


