*Journal of Neuro-Oncology* **62:** 1–5, 2003.


# A critical assessment of boron neutron capture therapy: an overview

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*Key words:* boron neutron capture therapy, critical assessment

**Summary**

Boron neutron capture therapy (BNCT) is based on the nuclear reaction that occurs when boron-10 is irradiated with neutrons of the appropriate energy to produce high-energy alpha particles and recoiling lithium-7 nuclei. BNCT has been used clinically to treat patients with high-grade gliomas, and a much smaller number with primary and metastatic melanoma. The purpose of this special issue of the Journal of Neuro-Oncology is to provide a critical and realistic assessment of various aspects of basic and clinical BNCT research in order to better understand its present status and future potential. Topics that are covered include neutron sources, tumor-targeted boron delivery agents, brain tumor models to assess therapeutic efficacy, computational dosimetry and treatment planning, results of clinical trails in the United States, Japan and Europe, pharmacokinetic studies of sodium borocaptate and boronophenylalanine (BPA), positron emission tomography imaging of BPA for treatment planning, and finally an overview of the challenges and problems that must be faced if BNCT is to become a useful treatment modality for brain tumors. Clinical studies have demonstrated the safety of BNCT. The next challenge is an unequivocal demonstration of therapeutic efficacy in one or more of the clinical trails that either are in progress or are planned over the next few years.

The treatment of glioblastomas and anaplastic astrocytomas by surgery, chemotherapy and conventional radiation therapy has had only limited success and the survival of patients today is not significantly different from that of 30 years ago. These tumors almost invariably recur, usually within 2 cm of the original margins of resection, but not infrequently at greater distances. Effective therapy, therefore, must encompass a much larger volume than that which has been radiographically defined, even by the most sensitive imaging techniques. The challenge facing physicians and surgeons treating patients with high-grade gliomas is to achieve total eradication of the tumor without damaging or destroying tumor-infiltrated normal brain.

Boron neutron capture therapy (BNCT), which is the subject of this special issue of the Journal of Neuro-Oncology, is based on the nuclear reaction that occurs when boron-10, a stable isotope, is irradiated with neutrons of the appropriate energy to produce boron-11 in an unstable form, which then undergoes instantaneous nuclear fission to produce high-energy alpha particles and recoiling lithium-7 nuclei ($^{10}B + n_{th} \rightarrow [^{11}B] \rightarrow$ alpha particles $+^{7}$ Li). These heavy charged particles have pathlengths of approximately one cell diameter and deposit most of their energy within the boron-containing cells. If enough low-energy thermal neutrons ($n_{th}$) reach the treatment volume, and the $^{10}B$ is selectively delivered to tumor cells in amounts higher than in the surrounding normal tissues, then they can be destroyed as a result of the $^{10}B(n, \alpha)\ ^{7}Li$ capture reaction. In theory, BNCT provides a means for the specific molecular and cellular targeting of high linear energy transfer radiation to tumor cells with the concomitant sparing of normal cells.

Clinical trials of BNCT in the United States in the 1950s and early 1960s were unsuccessful due to a lack of tumor-selective boron-containing drugs and low-energy thermal neutron beams that were attenuated exponentially as a function of depth in tissue. Since then, considerable effort has been directed towards the design and synthesis of boron-containing delivery agents that have more desirable biochemical and biological properties. In parallel with this, higher-energy

epithermal neutron beams, which have greater tissue penetrating properties, have been developed. Two boron-containing drugs, one a polyhedral borane, referred to as sodium borocaptate ($Na_2B_{12}H_{11}SH$ or 'BSH'), and the other, a dihydroxyboryl derivative of phenylalanine, referred to as boronophenylalanine (BPA), have been used clinically. Interested readers are referred to several recent reviews [1–3] and monographs [4,5] that provide more detailed information relating to all aspects of BNCT.

The purpose of this special issue of the Journal is to provide a critical and realistic assessment of various aspects of basic and clinical BNCT research in order to better understand its present status and future potential. Topics that are covered include neutron sources, tumor-targeting boron delivery agents, brain tumor models to assess therapeutic efficacy, computational dosimetry and treatment planning, results of clinical trials in the United States, Japan and Europe, pharmacokinetic studies of BSH and BPA, positron emission tomography (PET) imaging of BPA for treatment planning, and finally an overview of the challenges and problems that must be faced if BNCT is to become a useful treatment modality for brain tumors.

The lead article by Harling and Riley [6] critically reviews the current status of fission reactor-based neutron beams for BNCT. Since 1994, a transition has been made from low-energy thermal neutron beams, used in the earlier clinical studies, to higher-energy epithermal beams, which have a greater depth of penetration and are now used routinely for BNCT of brain tumors. Reactor-based epithermal beams are available in Japan, several European countries, the United States and Argentina and their use is described in five of the articles that report on clinical trials. Harling and Riley's article concludes with a discussion of the design and construction of new low-power reactors, specifically designed for NCT, which could meet future needs.

The next article by Blue and Yanch [7] focuses on the development of low-energy, light-ion, accelerator-based neutron sources (ABNSs) for NCT. A major advantage of accelerators is that they can be sited within a hospital complex, and indeed one such accelerator, located at the Queen Elizabeth Hospital/University of Birmingham in the United Kingdom, will be used for a clinical trial that will be initiated in the near future. The components of ABNSs have been designed and tested and their feasibility for clinical use has been established. A detailed discussion of the technical requirements for ABNSs is presented and a comparison with nuclear reactor beams suggests that ABNSs can deliver high-quality beams that actually might be superior to those produced by reactors. Since accelerators can be fabricated by more standardized procedures than those used to construct nuclear reactors, this could eliminate the complicated beam characterizations that currently are required for each reactor and would permit easier comparison of clinical results.

Turning to chemical studies, Hawthorne and Lee [8] provide a critical assessment of tumor-targeting boron compounds and limitations that have impeded progress in this field of research. The past history and current efforts in boron compound development together with possible new boron delivery agents are discussed. The authors conclude with a discussion of future directions in the development of boron delivery agents for BNCT. Carlsson et al. [9] review tumor receptor-targeting liposomes as potential boron delivery agents. Molecular targeting of receptors that are over-expressed on tumor cells is an attractive approach and currently is a very active area of research. However, only a few investigators, among whom Carlsson and his group were the first, have directed their efforts to the delivery of $^{10}B$-containing epidermal growth factor (EGF) bioconjugates for Neutron Capture Therapy. Possible molecular targets include EGFR, EGFRvIII and the platelet derived growth factor receptor (PDGF), the expression of which may be amplified in high-grade gliomas. The biologic and chemical requirements for receptor-targeting liposomes are discussed and their future potential is assessed.

Shifting to biological studies, Barth et al. [10] summarize their studies on the use of rat brain tumor models to assess the efficacy of BNCT. Although no animal brain tumor model can exactly simulate human high-grade gliomas, studies with two rat tumors, the F98 glioma and 9L gliosarcoma, have provided important information that has influenced the design of clinical BNCT protocols. The use of BPA as a brain tumor-targeting agent was first demonstrated with these tumor models. The importance of optimizing the delivery of BPA and BSH has been convincingly demonstrated in the F98 glioma model, as well as with the MRA 27 melanoma, which has been developed as a model for metastatic brain tumors. Finally, studies on molecular targeting of EGFR have provided proof-of-principle for the use of high molecular weight, receptor-targeting boron delivery agents.

The complex questions of computational dosimetry and treatment planning are addressed by Nigg [11]. Treatment planning algorithms for BNCT have relied

on a mathematical technique based on random sampling (Monte Carlo) stochastic simulation to adjust for the complex geometry of the human brain. Boron quantitation is a key issue for NCT treatment planning and although there may be real-time methods to approximate gross tumor boron concentrations at some point in time in the future, it is highly unlikely that real-time boron concentrations can be measured in small clusters of cells or individual tumor cells and biological effectiveness may be the ultimate dosimeter.

The next group of five papers describes clinical studies that have been carried out on BNCT. Nakagawa and his co-authors [12] review the Japanese experience with BNCT, which began with the studies of Hatanaka in the late 1960s and extend to the present time. Survival data and radiation side effects of BNCT, using BSH as the capture agent, have been analyzed and a new protocol for treating patients is presented. This prescribes a minimum tumor physical dose of 15 Gy and a target volume dose of 18 Gy from the $^{10}B(n, \alpha)\,^{7}Li$ capture reaction dose component and a gamma dose of 10 Gy. Clinical results obtained in 10 patients treated with this protocol are described. Diaz [13] has summarized the results obtained in the Phase I/II clinical trial that was carried out at the Brookhaven National Laboratory in Upton, New York, between 1994 and 2000. The primary objective of this trial was to evaluate the safety of BNCT using BPA as the capture agent in patients with GBM. A total of 53 patients were treated and it was concluded that the upper limit for a safe dose to the brain was ~6 photon-equivalent Gy (Gy-Eq), using 1, 2 or 3 irradiation fields. All patients who received an average brain dose of 6.7 Gy-Eq or higher had some evidence of toxicity (usually somnolence) and several had grade 2 or 3 toxicity based on EORTC/RTOG common toxicity criteria. Median time to progression decreased from 34.5 weeks for one field to 18 weeks for the three-field group. When survival was used as an endpoint, this was dependent upon the aggressiveness of the post-recurrence treatment rather than on the actual radiation dose given at the time of BNCT. Busse and his colleagues [14] have provided a critical assessment of the results from the Harvard-Massachusetts Institute of Technology Phase I clinical trial for intracranial tumors (both GBM and melanoma). A total of 24 patients were treated using BPA as the boron delivery agent. Acute toxicity primarily was associated with increased intracranial pressure. Two melanoma patients showed a complete radiographic response and 13 of 17 evaluable patients had a measurable reduction in tumor volume following BNCT. Joensuu and his co-workers [15] at the University of Helsinki and VTT Processes in Finland, report on a series of 18 patients with supratentorial GBMs, who received BPA followed by BNCT, which was given as a single fraction with two fields. The target volume doses ranged from 30 to 61 Gy-Eq and the average normal brain doses were 3–6 Gy-Eq. The estimated overall one year survival was 61%. In addition, three patients with recurrent or progressing tumors were treated. Treatment was relatively well tolerated by all patients and it was concluded that further clinical trials were warranted. Finally, Capala et al. [16] present a preliminary report of 17 patients who have been treated in Sweden using the Studsvik medical reactor beginning in March 2001 and continuing to the present time. Again, BPA has been used as the capture agent, infused over 6 h at a dose of 900 mg/kg b.w., which is approximately three times that which has been used in other studies. No severe BNCT-related toxicity has been observed, but due to the short follow-up time, no survival data have been presented.

Turning to pharmacokinetic and biodistribution studies, Hideghety et al. [17] report on the tissue uptake of BSH in a series of 13 patients who received the drug at a dose of 100 mg/kg body weight. Tumor boron concentrations showed considerable intra-tumoral and patient-to-patient variability and were consistently greater than those of normal brain, but always less than the concurrent blood boron concentrations. This is in agreement with data previously reported by The Ohio State University group (Neurosurgery 47: 608–622, 2000). In this issue of the Journal of Neuro-Oncology, the OSU group presents a detailed pharmacokinetic analysis of BSH in patients with high-grade gliomas [18]. The plasma disposition of the drug was consistent with a three-compartment open model with zero-order input and first-order elimination from the central compartment. A pharmacokinetic model was developed to select the optimum dosing paradigm and it was concluded that although multiple infusions of BSH might increase absolute tumor boron concentrations, they would not improve tumor to plasma boron concentration ratios over those attainable by a single i.v. infusion. In the next paper, Kiger et al. [19] report on pharmacokinetic modeling for BPA using an open two-compartment model for predicting blood boron concentrations following i.v. infusion. The prediction error and its potential effect on the simulated dose delivered for each radiation field was calculated using three different strategies. It was concluded that the error in dose, which was based on the blood boron

concentration, was <10%. Turning to the topic of real-time tumor localization of BPA, Kabalka and his co-workers [20] report on the use of PET to develop BNCT treatment plans for melanoma metastatic to the brain. PET imaging clearly identified intracerebral metastases following administration of $^{18}$F-BPA. Lung and salivary gland uptake also was intense, indicating high concentrations of BPA at these sites. Nevertheless, the data could be used to generate a treatment plan and PET potentially can be used to identify other histopathologic types of metastatic brain tumors that might be candidates for treatment by BNCT. Finally, the concluding paper by Gupta and his colleagues [21] provides an analysis of all of the problems and challenges that must be faced if BNCT is to become a clinically useful treatment modality. Their paper integrates much of what was discussed in more detail in each of the preceding papers included in this special issue of the Journal.

The major question is 'How to move BNCT forward clinically'? Despite considerable effort, no new boron-containing drugs other than a polyhedral borane dianion [*closo* $B_{10}H_{10}]^{2-}$ or 'GB-10', which was synthesized and evaluated over 45 years ago, has Food and Drug Administration (FDA) approval for use for clinical BNCT at this time. In the face of this, clinicians are faced with the problem of how to improve clinical results with the two drugs currently in use, BSH and BPA. Optimizing their delivery is one such approach, and animal studies, summarized by Barth et al. [10] convincingly show that improved delivery can significantly enhance therapeutic efficacy. This clearly is one line of investigation that can be pursued clinically. The development of new and better tumor localizing low and high molecular weight boron delivery agents could have a significant impact on efficacy. As is evident from the papers reported in this special issue of the Journal, BNCT represents an extraordinary joining together of technology and biology to treat a malignancy, high-grade gliomas, which have been and remain incurable. Sadly, the lack of progress in developing more effective treatments for this disease is part of the driving force that propels research in BNCT forward. BNCT may be best suited as an adjunctive treatment to be used in combination with other modalities, including surgery, chemotherapy and external beam radiation therapy, which, when used together, may result in an improvement in survival of patients with both primary and metastatic brain tumors. Clinical studies have demonstrated the safety of BNCT. The next challenge is an unequivocal demonstration of therapeutic efficacy in one or more of the clinical trials that either are in progress or are planned over the next few years.

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