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EDITORIAL

Boron neutron capture therapy of cancer: where do we stand now?

1 | INTRODUCTION

This is the *third* Editorial/Commentary that one of us (R. F. Barth) has written relating to boron neutron capture therapy (BNCT) [1, 2]. For those readers who are unfamiliar with BNCT we would refer them to several recent comprehensive reviews [3–5]. The *second* Editorial ended on a hopeful note that with the introduction of accelerator-based neutron sources (ABNSs), BNCT would enter into the mainstream of radiation therapy [2]. This indeed has happened most notably in Japan, where BNCT now is being used to treat patients with recurrent tumors of the head and neck region, high-grade gliomas, meningiomas and melanomas. Similarly, there has been great interest in China, as indicated by an impressive number of publications coming from both of them [4, 6, 7]. In contrast to the active programs in Asia, there has been no recent clinical activity relating to BNCT in the United States and Europe. Hopefully, however, after many delays, a clinical program will be initiated in the near future in Finland using an ABNS to treat patients with recurrent tumors of the head and neck region. The obvious question is why there hasn't been interest in BNCT by clinicians in the United States and Europe? In this Editorial, we will address this question and hopefully make a convincing case for the further development of BNCT as a cancer treatment modality.

2 | REQUIREMENTS FOR BORON DELIVERY AGENTS FOR BNCT

Why has it been so difficult to develop new boron delivery agents for BNCT? Very simply put, the requirements for such agents are very challenging [3, 5]. These include (1) delivery of ~20-30 μg ^{10}B/g tumor; (2) high (>1) tumor:normal tissue and tumor:blood boron concentration ratios during irradiation; and (3) rapid clearance of boron from normal tissues while persisting in the tumor during neutron irradiation. The intracellular localization of ^{10}B in tumor cells is also important, and ideally, the closer to the nucleus, the better. To date, only two boron delivery agents have met many but not all of these requirements: a boron-containing derivative of phenylalanine, known as boronophenylalanine (BPA), and a polyhedral borane, known as sodium borocaptate (BSH). Finally, a major challenge in the development of effective boron delivery agents is their localization in all parts of the tumor and within all tumor cells. As reported by Elowitz et al. [8] and Goodman et al. [9], there was considerable variability in the boron concentrations of both BPA [8] and BSH [9] in multiple tissue samples taken from the same tumor. This would be especially true in brain tumors, since the blood-brain barrier limits trans-vascular entry of high-molecular weight boron delivery agents (>100 Da) into the tumor.

Many classes of boron-containing delivery agents have been proposed, and these broadly can be divided into low-molecular weight agents, such as amino acids, peptides, polyamines, nucleosides, carbohydrates, and porphyrins, and high-molecular weight agents, such as liposomes, proteins, monoclonal antibodies, and nanoparticles [5, 10]. Between 2018 and 2023, many new boron delivery agents with different chemical characteristics have been reported in both the chemical [5] and biological literature [10]. Based on studies in mice, we believe that the most promising of these is the 3-isomer of BPA (3-BPA), which has 10-100 times greater solubility than that of the 4-isomer of BPA (4-BPA) which currently is being used clinically [3]. The tumor uptake of 3-BPA in B16F10 melanoma-bearing mice was equal to that of 4-BPA [11], which requires complexing with fructose or sucrose to increase its solubility. A second promising chemical modification of BPA has been described by Nomoto et al. [12], who have reported that poly(vinyl alcohol) (PVA) can form complexes with BPA, thereby producing reversible boronated

Abbreviations: ABNS, Accelerator-based neutron source; BNCT, Boron Neutron Capture Therapy; BPA, Boronophenylalanine; BSH, Sodium borocaptate; HER-2, Human epidermal growth factor receptor 2; KURRI, Kyoto University Research Reactor Institute; PVA, Poly(vinyl alcohol); TPS, Treatment Planning System.

esters. In vitro studies revealed that PVA-BPA attained 3.6 times higher intracellular boron concentrations than the fructose-BPA complex. In vivo studies were carried out with murine CT26 colon cancer cells, implanted subcutaneously into mice, followed by intravenous administration of PVA-BPA and neutron irradiation. This resulted in a highly significant reduction in tumor volume over a 60-day period compared to unirradiated controls [12]. The uptake and retention of high-molecular weight delivery agents [4, 5, 10], such as monoclonal antibodies, albumin, anti-angiogenic peptides, human epidermal growth factor receptor 2 (HER2)-targeting liposomes, and boron carrier exosomes modified with cell-penetrating peptides, recently have been evaluated, and further studies are warranted. However, none of these have, as yet, reached the stage of clinical evaluation.

3 | NEUTRON SOURCES, TREATMENT DELIVERY, AND PLANNING FOR BNCT: CURRENT STATUS, ADVANCES, AND CHALLENGES

When reviewing the current status of treatment delivery options of neutrons and comparing them with competing radiotherapeutic modalities, great progress has been made with BNCT over the past five years. It is well on the way to becoming a mainstream treatment modality in Japan and China. Over the past few decades, design improvements in both reactor and accelerator neutron beams have made considerable progress. Up until 2015, clinical BNCT was totally dependent upon nuclear reactors as neutron sources, which, to say the least, were not patient-friendly environments. The first major advance was the introduction of epithermal neutron beams in the 1960s, which led to the treatment of more deeply located tumors. The Fukushima nuclear catastrophe in Japan in 2011 resulted in the shutdown of all Japanese nuclear reactors except for the one at the Kyoto University Research Reactor Institute (KURRI) in Kumatori, Japan. Subsequently, in 2015, the nuclear catastrophe led to the introduction of ABNSs, which could be sited in hospitals. Over the past decade, ABNSs have become the mainstay of clinical BNCT in Japan, with at least four of them located in hospital settings [13]. Their clinical use has led to several commercial efforts to provide "turnkey" systems for hospital-based ABNS systems in Japan [13], soon in Finland [14], and several others at different stages of development, such as the Neuboron system being developed in China (https://en.neuboron.com/bnct). This has been the single most important development for the acceptance of BNCT as a cancer treatment modality. However, this transition has not been so easy, as exemplified by the experience of Neutron Therapeutics Inc. in Finland. It has taken over 5 years from the installation of the ABNS in 2018 to the initiation of a clinical trial to treat patients with recurrent tumors of the head and neck region in the summer of 2024. In many countries, even the installation of ABNSs as investigational use devices would require that they meet stringent safety requirements and control systems, which will be the only way that BNCT could move forward.

The earliest BNCT treatment planning systems (TPSs) were developed by research groups at the Massachusetts Institute of Technology [15], the Idaho National Engineering Laboratory, and the Japan Atomic Energy Research Institute [13]. All these TPSs' were developed for reactor neutron sources. More recently, TPSs have been developed for ABNSs, and this could be an important step for the further advancement of BNCT as a cancer treatment modality. TPSs for BNCT have followed a similar trajectory as TPSs for conventional radiotherapy. For BNCT to be used in clinical trials, in the future TPSs will be required to comply with local regulations that are in effect. Along with commercially available ABNSs, TPSs' that are commercially developed and maintained [14] will be key to the next phase, in order for BNCT to gaining wider acceptance. Such systems must have planning tools that comply with data exchange standards developed in conventional radiotherapy for supporting clinical trials.

Significant technological advances have been made in radiotherapy delivery systems over the past few decades and these advances have provided a vast array of very precise treatment delivery options to radiation oncologists for both X-ray and charged particle-based therapies. The other key functionality that has developed over the past decade has been integrated image guidance systems and robotic treatment couches. These allow for very precise re-positioning of patients, thereby ensuring that the treatment target is accurately localized and monitored during treatment delivery. ABNSs that will be used for BNCT must integrate image guidance and robotic positioning systems in order to gain acceptance by the radiotherapy community. Furthermore, especially with commercially developed ABNSs, it is important to incorporate the features mentioned above, as well as advanced collimators, in order to optimize neutron beam delivery.

4 | CONCLUSIONS

Looking back over the past six years, there has been significant progress in several areas: first and foremost, the widespread clinical use of ABNSs in Japan with at least four BNCT treatment centers currently in operation and several others either under construction or planned; second, the introduction of standardized treatment plans for

patients with recurrent tumors of the head and neck region [16], the cost of which now is partially reimbursed by the Japanese National Health Care Agency; third, impressive clinical results that have been obtained in Japan for the treatment of patients with high-grade meningiomas [17], cutaneous [18], and extra-cutaneous melanomas and extra-mammary Paget's disease [19].

To answer the question posed at the beginning of this Editorial, "Why hasn't there been interest in BNCT by clinicians in the United States and Europe", there are a number of significant challenges counterbalancing the gains that have been made. *First*, at this time, there are only two boron delivery agents in clinical use, BPA and, to a much lesser extent, BSH [3]. The best chances to move forward at this time would be to focus on chemical modifications of BPA [11, 12] and BSH, which could make them more effective boron delivery agents. Equally as important is to develop more effective methods for their delivery, especially in the Japanese clinical trial for patients with recurrent tumors of the head and neck region (JNH0002) [16] and for patients with recurrent high-grade meningiomas. *Second*, is to further define other types of malignancies that might make BNCT their preferred treatment. Among these are genital malignancies such as recurrent and refractory high-grade meningiomas [17], difficult-to-treat cutaneous melanomas [18], and extramammary Paget's disease and melanomas of the vulva [19]. *Third*, it must be recognized that there are a limited number of nuclear reactors that can be used to conduct radiation studies in experimental animals. Only the Japanese nuclear reactor at KURRI is being used for animal irradiations, which must be scheduled almost one year in advance since the reactor also is being used for non-biologic studies. In the United States, to the best of our knowledge, at the present time, there are only two nuclear reactors that can be used for animal irradiations, and these are the University of Missouri Research Reactor (Columbia, MO) and the Massachusetts Institute of Technology Reactor (Boston, MA). In contrast, in China, there are at least four neutron sources that could be used for this purpose and at least two of them that could be used for the irradiation of large animals. Among these is the In-Hospital Neutron Irradiator-1 in Beijing, which has been used for both human and animal irradiations. This, together with the robust basic research programs in Japan and China, bode well for the future of BNCT. One of the significant advantages that we had in the United States, which sadly no longer exists, was the availability of the Brookhaven Medical Research Reactor that was decommissioned over 20 years ago. *Fourth*, there has been almost a complete lack of funding for BNCT-related research by the National Institutes of Health in the United States, while in contrast, there is significant funding for BNCT in several other countries. From all the above, it should be apparent that BNCT as a cancer treatment modality has had a number of successes but also is facing significant challenges. However, ending on an optimistic note, this is about to change with the possible siting of an ABNS [20] by TAE Life Sciences in the United States.

AUTHOR CONTRIBUTIONS

Gong Wu participated in the writing of the first draft of this Editorial. Maria da Graca H. Vicente participated in the writing of text related to Requirements for boron delivery agents for BNCT. John Grecula and Nilendu Gupta contributed to the text relating to the Neutron sources, treatment delivery and planning for BNCT. Rolf F. Barth wrote the text in the Introduction, Requirements for boron delivery agents and Conclusions.

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REFERENCES

1. Barth RF, Grecula JC. Boron neutron capture therapy at the crossroads - Where do we go from here? Appl Radiat Isot. 2020;160:109029.
2. Barth RF, Zhang Z, Liu T. A realistic appraisal of boron neutron capture therapy as a cancer treatment modality. Cancer Commun (Lond). 2018;38(1):36.
3. Barth RF, Gupta N, Kawabata S. Evaluation of Sodium Borocaptate (BSH) and Boronophenylalanin (BPA) as Boron Delivery Agents for Neutron Capture Therapy (NCT) of Cancer: An Update and a Guide for the Future Clinical Evaluation of New Boron Delivery Agents for NCT. Cancer Communications. 2024, doi:10.1002/cac2.12582 .
4. Cheng X, Li F, Liang L. Boron Neutron Capture Therapy: Clinical Application and Research Progress. Curr Oncol. 2022;29(10):7868–7886.
5. Oloo SO, Smith KM, Vicente M. Multi-Functional Boron-Delivery Agents for Boron Neutron Capture Therapy of Cancers. Cancers (Basel). 2023;15(13):3277.
6. Wang LW, Liu YH, Chu PY, Liu HM, Peir JJ, Lin KH, et al. Boron Neutron Capture Therapy Followed by Image-Guided Intensity-Modulated Radiotherapy for Locally Recurrent Head and Neck Cancer: A Prospective Phase I/II Trial. Cancers (Basel). 2023;15(10):2762.
7. Zhang Z, Chong Y, Liu Y, Pan J, Huang C, Sun Q, et al. A Review of Planned, Ongoing Clinical Studies and Recent Development of BNCT in Mainland of China. Cancers (Basel). 2023;15(16):4060.
8. Elowitz EH, Bergland RM, Coderre JA, Joel DD, Chadha M, Chanana AD. Biodistribution of p-boronophenylalanine in patients with glioblastoma multiforme for use in boron neutron capture therapy. Neurosurgery. 1998;42(3):463–468; discussion 8-9.
9. Goodman JH, Yang W, Barth RF, Gao Z, Boesel CP, Staubus AE, et al. Boron neutron capture therapy of brain tumors: biodistribution, pharmacokinetics, and radiation dosimetry sodium borocaptate in patients with gliomas. Neurosurgery. 2000;47(3):608–621; discussion 21-2.
10. Barth RF, Mi P, Yang W. Boron delivery agents for neutron capture therapy of cancer. Cancer Commun (Lond). 2018;38(1):35.
11. Kondo N, Hirano F, Temma T. Evaluation of 3-Borono-l-Phenylalanine as a Water-Soluble Boron Neutron Capture Therapy Agent. Pharmaceutics. 2022;14(5):1106.
12. Nomoto T, Inoue Y, Yao Y, Suzuki M, Kanamori K, Takemoto H, et al. Poly(vinyl alcohol) boosting therapeutic potential of p-boronophenylalanine in neutron capture therapy by modulating metabolism. Sci Adv. 2020;6(4):eaaz1722.
13. Matsumura A, Asano T, Hirose K, Igaki H, Kawabata S, Kumada H. Initiatives Toward Clinical Boron Neutron Capture Therapy in Japan. Cancer Biother Radiopharm. 2023;38(3):201–207.
14. Porra L, Wendland L, Seppala T, Koivunoro H, Revitzer H, Tervonen J, et al. From Nuclear Reactor-Based to Proton Accelerator-Based Therapy: The Finnish Boron Neutron Capture Therapy Experience. Cancer Biother Radiopharm. 2023;38(3):184–191.
15. Zamenhof R, Redmond E, 2nd, Solares G, Katz D, Riley K, Kiger S, et al. Monte Carlo-based treatment planning for boron neutron capture therapy using custom designed models automatically generated from CT data. Int J Radiat Oncol Biol Phys. 1996;35(2):383–397.
16. Sato M, Hirose K, Takeno S, Aihara T, Nihei K, Takai Y, et al. Safety of Boron Neutron Capture Therapy with Borofalan(10B) and Its Efficacy on Recurrent Head and Neck Cancer: Real-World Outcomes from Nationwide Post-Marketing Surveillance. Cancers. 2024;16(5):869.
17. Takai S, Wanibuchi M, Kawabata S, Takeuchi K, Sakurai Y, Suzuki M, et al. Reactor-based boron neutron capture therapy for 44 cases of recurrent and refractory high-grade meningiomas with long-term follow-up. Neuro Oncol. 2022;24(1):90–98.
18. Hiratsuka J, Kamitani N, Tanaka R, Tokiya R, Yoden E, Sakurai Y, et al. Long-term outcome of cutaneous melanoma patients treated with boron neutron capture therapy (BNCT). J Radiat Res. 2020;61(6):945–951.
19. Hiratsuka J, Kamitani N, Tanaka R, Yoden E, Tokiya R, Suzuki M, et al. Boron neutron capture therapy for vulvar melanoma and genital extramammary Paget's disease with curative responses. Cancer Commun (Lond). 2018;38(1):38.
20. Taskaev S, Berendeev E, Bikchurina M, Bykov T, Kasatov D, Kolesnikov I, et al. Neutron Source Based on Vacuum Insulated Tandem Accelerator and Lithium Target. Biology (Basel). 2021;10(5):350.