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Opinion

Emergence of Accelerator-Based Neutron Sources and Novel Boron-10 Drugs: A Renewed Hope for Boron Neutron Capture Therapy

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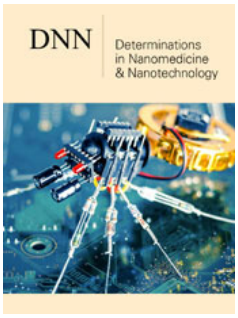

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Opinion

Boron neutron capture therapy (BNCT) is a clinical modality for treating locally invasive malignant tumors and has gained significant attention as a selective and non-invasive type of cancer therapy [1]. The results obtained from clinical trials from the USA, Japan, Finland, and other countries are highly encouraging and BNCT is going to be a part of treatment for patients with the therapeutically challenging malignancies that in the past have been treated with external radiation. Approximately 2,000 patients worldwide have undergone BNCT and shown favorable clinical outcomes in glioblastomas, head and neck cancer, lung cancers, breast cancers, hepatocellular carcinoma, sarcomas, cutaneous malignancies, extramammary Paget's disease, recurrent cancers, pediatric cancers, and metastatic disease. Approximately 2,000 patients worldwide have undergone BNCT and shown favorable clinical outcomes in glioblastomas, hepatocellular carcinoma, sarcomas, cutaneous malignancies, and various metastatic diseases, and head, neck, lung, breast, and pediatric cancer. BNCT is a binary therapy that utilizes ^{10}Boron(^{10}B) in combination with low energy neutrons to effectively eliminate targeted cells. The technology is based on the nuclear capture reaction of thermal (low energy < 0.5 eV, limited depth of penetration) and epithermal neutrons (>0.5eV<10keV, greater depth of penetration) using nonradioactive ^{10}B, which causes the production of a 7Li particle and an α particle with ~2.3 MeV thermal energy. The high linear energy transfer of charged particles is accompanied by a short spatial trajectory of 5-10μm, the approximate diameter of one cell. Consequently, radiation damage is selectively confined to the targeted cells containing ^{10}B, minimizing damage to surrounding tissue. Moreover, an effective therapeutic dose equivalent to 60Gy can be delivered to borated cells within one hour rather than the 5-6 weeks utilized for standard RT.

While BCNT represents a potentially ideal RT technique for glioma and many other tumors, the lack of suitable boron drugs and unavailability of hospital-based practical source of neutrons has constrained its clinical utility. Despite considerable effort by numerous investigators over the past 40 years, there are only two boron-containing drugs in clinical use: L-Boronophenylalanine (BPA) and Sodium Borocaptate (BSH). Nevertheless, even with available reactor-based neutron sources and low ratios of ^{10}B in tumor to healthy brain using a conventional small molecule-based approach, BNCT has been demonstrated to be an alternative treatment for newly diagnosed GBM that is as effective as conventional RT alone with just a single intervention compared to multiple rounds of radiation and chemotherapy. By solving these two critical issues, BNCT could become a practical therapy for treatment of multiple malignancies. Recently, Accelerator-Based Neutron Sources (ABNS) are rising in popularity and usage, especially in Japan, Finland, China and the USA [2]. Notably, Tokyo-Sumitomo Heavy Industries (Japan) obtained new medical device approval for manufacturing

and sales of accelerator based BNCT system and the dose calculation program from Japanese Ministry of Health, Labor, and Welfare. Kyoto University and Sumitomo Heavy Industries have developed an ABNS for BNCT at the Kyoto University Research Reactor Institute. Miyatake et al. published their findings from 167 cases of malignant brain tumors and high grade meningiomas treated with BNCT from 2002 to 2014 [3]. Phase II clinical trials are being carried out in Japan and a few trials will be carried out in Finland. Another company in the USA, Neutron Therapeutics, has developed an ABNS for in-hospital use as a replacement to the previously required nuclear reactor. The source is composed of a 2.6MeV electrostatic proton accelerator and a rotating, solid lithium target for generating neutrons. Neutron Therapeutics provides this neutron source as part of a treatment plan that can combine the necessary components for BNCT treatment.

While the development of new ABNS have given a new impetus to the BNCT, effective ^{10}B delivery remains a major roadblock that needs to be addressed. With the development of improved synthetic techniques and an increased awareness of the requisite biochemical properties, several new boron delivery agents have emerged. Various approaches have been employed for the targeting of ^{10}B atoms into the tumor region based on the concepts that include the use of macromolecules such as boron-conjugated dendrimers and biological complexes, dextran conjugates, and hyaluronan conjugates [4]. Nakamura et al. developed ^{10}B conjugated liposomes using lipids that link with ^{10}B-enriched BSH by covalent bonds to reduce the cytotoxicity of the boron-conjugated liposomes. In recent years, we have developed nanodrugs based on a natural biodegradable and nontoxic polymer Polymalic Acid (PMLA) that crosses Blood-Brain Barrier (BBB) for imaging and treatment of primary and metastatic brain tumors. Our novel method takes advantage of PMLA-based nanomedicine proven capable of intracellular delivery of various therapeutic and imaging agent across a formidable BBB to target glioma cells [5,6]. The prospect of new in-hospital based neutron sources becoming a reality for hospitals [1,7] has spurred a renewed interest in the development of novel boron drugs. This will fill the long-awaited void with new synthesis of targeted and BBB penetrable ^{10}Boron drugs, allowing clinical research to expand with the goal to have BNCT available as a new treatment option to improve the treatment outcome and the quality of life for suffering patients and families.

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