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Opinion Article

Boron Neutron Capture Therapy: A New Chapter in the Treatment of Resistant Tumors

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Abstract

Boron Neutron Capture Therapy (BNCT) has emerged as a promising avenue for cancer treatment, leveraging the selective destruction of tumor cells while sparing healthy tissue. This opinion piece delves into the intricacies of BNCT, its potential benefits, challenges, and future directions. BNCT operates on the principle of utilizing boron-10 and neutron radiation to induce localized damage to cancer cells. The success of BNCT hinges on two main factors. A reliable source of in-hospital based low energy neutrons and selective drug delivery to malignant cells in high concentrations. So far, traditional reactor-based neutron sources have been used to demonstrate the clinical success of BNCT. Although the clinical results are highly encouraging, reactor-based neutron sources suffer from many challenges such as limited availability, high cost, safety concerns associated with handling radioactive materials, logistical challenges, and regulatory hurdles. Recently, many companies including- Neutron Therapeutics, USA; TAE Life Sciences, USA and Sumitomo Heavy Industries, Ltd. Japan, just to name a few have made significant efforts to design new accelerator-based neutron sources (ABNS) for BNCT, which are compact, affordable, and can be installed in hospitals, has significantly addressed the latter challenge. These neutron sources are more accessible and cost-effective compared to heavy ion accelerators, making BNCT more feasible and practical. While recent development in the ABNS has given new impetus to the BNCT, achieving selective delivery of boron-10 at high concentrations remains a major roadblock. Targeted drug delivery using nanotechnology offers a promising solution to enhance BNCT efficacy by enabling targeted drug delivery. Nanoparticles can improve tumor accumulation, penetrate the blood-brain barrier, and facilitate real-time treatment monitoring. Overcoming the remaining drug delivery challenge through nanotechnology-based approaches thus holds great promise for advancing BNCT as a potent cancer treatment modality.

Keywords: Boron Neutron Capture Therapy (BNCT); Glioblastoma Multiforme (GBM); Radiation Therapy; Nano-Boron; 4-Boronphenylalanine (BPA)

Introduction

Boron Neutron Capture Therapy (BNCT) stands as a cutting-edge approach to cancer treatment, offering a targeted method with minimal side effects. This innovative technique utilizes boron-10 and neutron irradiation to selectively destroy cancer cells while preserving healthy tissue [1,2]. The concept and principles of neutron capture therapy were initially elucidated by Locher in 1936 [3]. The inaugural clinical trial of BNCT was initiated by Farr and Sweet et al. in 1951, utilizing the Brookhaven Graphite Research Reactor to treat GBM [4]. BNCT operates on a simple yet ingenious principle, in which aboron-10, a non-radioactive isotope, accumulates in a target cell, and when exposed to low-energy neutrons, boron-10 captures a neutron and spontaneously undergoes a nuclear reaction, emitting high-energy alpha particles and recoiling lithium nuclei. Since the path length of these high LET

particles is around 5-9 microns, the damage remains in the targeted cell, sparing the non-boron-10-containing surrounding healthy cells. This targeted approach minimizes collateral damage to surrounding tissues, thereby reducing the debilitating side effects commonly associated with traditional cancer treatments such as chemotherapy and radiotherapy [2,5]. In this opinion piece, we explore the intricacies of BNCT, its potential benefits, challenges, and its future prospects.

One of BNCT's most compelling advantages lies in its ability to treat highly invasive and resistant tumors that have proven refractory to other therapies. Unlike conventional treatments, which often rely on the indiscriminate destruction of rapidly dividing cells, BNCT offers a precise and tailored approach that can effectively eradicate even the most aggressive cancerous growths [2]. Moreover, BNCT holds great promise for treating tumors located in critical or inaccessible areas of the body, such as the brain, spine, and head and neck regions, where surgery and conventional radiotherapy pose significant risks to surrounding healthy tissues and vital structures [2]. Furthermore, BNCT exhibits remarkable versatility, with the potential to be combined synergistically with other treatment modalities to enhance therapeutic outcomes. By exploiting the complementary mechanisms of action of different therapies, such as chemotherapy, immunotherapy, and targeted molecular agents, BNCT can potentially overcome treatment resistance and improve patient responses [6]. This multidisciplinary approach underscores the adaptability and efficacy of BNCT in addressing the complex and heterogeneous nature of cancer.

Despite its immense therapeutic potential, BNCT faces several challenges that must be addressed to realize its widespread clinical adoption. Foremost among these is the development of optimized boron delivery agents capable of efficiently targeting tumor cells while minimizing off-target effects. Current strategies primarily rely on boron-containing compounds such as Boronophenylalanine (BPA) and sodium borocaptate (BSH), which exhibit varying degrees of tumor selectivity and pharmacokinetic properties [2]. Research efforts focused on refining the pharmacological properties, biodistribution, and tumor uptake of these agents are essential for enhancing the efficacy and safety of BNCT. In addition, the availability of suitable neutron sources represents a significant logistical hurdle for the widespread implementation of BNCT. While research reactors and particle accelerators capable of producing therapeutic neutron beams exist, their accessibility and cost-effectiveness limit the scalability of BNCT [5,7]. Collaborative initiatives involving government agencies, research institutions, and private sector stakeholders are needed to overcome these infrastructural barriers and establish dedicated BNCT facilities equipped with optimized neutron sources and treatment delivery systems. To effectively apply BNCT, it's crucial to address key factors throughout its design and implementation stages. These include factors like lesion location and depth, absorption of the boron-10 delivery agent, neutron beam irradiation cycle and intensity, and pharmacokinetics [8]. Previous studies by Joensuu and colleagues at the University of Helsinki have extensively investigated the metabolism and toxicity of various boron delivery agents. For instance, they controlled the concentration and injection rate of paraboron-phenylalanine (BPA)-fructose (BPA-F) below 500 mg/kg/h and gathered substantial clinical data, showcasing the therapy's feasibility and offering valuable insights for further research [9].

Despite many advancements, BNCT remains underutilized due to limited experience in drug utilization, challenges in patient recruitment, insufficient medical neutron sources, and other factors. Consequently, the development and clinical implementation of BNCT have progressed relatively slowly. The challenges remain on the path to widespread clinical adoption, ongoing research, and collaborative efforts are paving the way for the realization of BNCT's full potential in the fight against cancer.

Discussion

BNCT holds a great potential for enhancing the therapeutic efficacy of Radiation Therapy (RT) in the management of many cancers including radioresistant. By exploiting the synergistic effects of boron-10-mediated neutron capture and conventional photon or proton irradiation, BNCT can augment the DNA damage inflicted upon cancer cells, leading to enhanced tumor control rates and reduced risk of recurrence. This combination approach, known as Boron-enhanced Radiation Therapy (BERT), capitalizes on the complementary mechanisms of action of boron neutron capture and external beam radiation, thereby overcoming inherent limitations associated with each modality alone. The synergistic interaction between BNCT and RT underscores the versatility and adaptability of BNCT as part of a multimodal treatment strategy tailored to individual patient needs [10].

Moreover, BNCT holds promise for expanding the therapeutic armamentarium against metastatic cancers, which pose a significant clinical challenge due to their propensity for widespread dissemination and resistance to conventional therapies. The ability of BNCT to selectively target metastatic lesions while sparing normal tissues offers a unique opportunity to eradicate residual disease burden and prevent disease progression. Furthermore, BNCT is typically given as a single treatment vs multiple rounds of fractionated radiation dose in combination with systemic chemotherapy makes it an attractive option for patients with advanced-stage disease who may have limited treatment options and poor tolerance to aggressive therapies. This provides favorable toxicity profile of BNCT compared to conventional RT/chemo.

The development of drugs for Boron Neutron Capture Therapy (BNCT) is hindered by the scarcity of suitable boron delivery agents, notably limited to Boronophenylalanine (BPA) and Sodium Borocaptate (BSH). While these agents have shown efficacy, they possess shortcomings, prompting the search for alternative treatments. Current agents struggle with selective tumor accumulation, necessitating high doses that may increase toxicity. To address this, researchers around the world, and in our laboratory are exploring nanotechnology-based approaches for targeted drug delivery in BNCT [11-13]. Nanoparticles offer advantages like enhanced tumor accumulation and BBB penetration, crucial for treating central nervous system tumors such as glioblastoma. Nanotechnology enables multifunctional

nanocarriers for simultaneous imaging and therapy, aiding in real-time treatment monitoring. The development of nanomaterials with optimal properties for boron-10 enrichment is crucial. These nanomaterials should possess high boron loading capacities and excellent stability to ensure effective drug delivery to tumor sites. Additionally, the incorporation of targeting peptides into nanocarriers can enhance their specificity towards cancer cells, improving therapeutic efficacy while minimizing off-target effects. These peptides can selectively bind to receptors overexpressed on tumor cells, facilitating targeted drug delivery and reducing systemic toxicity [11,14]. Furthermore, overcoming the blood-brain barrier (BBB) represents a critical challenge in treating central nervous system tumors like glioblastoma. Nanocarriers engineered with BBB-penetrating capabilities, such as surface modifications with specific ligands or size optimization, can facilitate efficient drug delivery to brain tumors while minimizing systemic exposure.

Conclusion

In our opinion, Boron Neutron Capture Therapy (BNCT) holds significant promise for cancer treatment, offering targeted destruction of tumors with minimal side effects. Challenges such as optimized boron delivery agents and neutron source availability persist, but nanotechnology presents a hopeful solution. Combining BNCT with conventional therapies like radiation expands its potential, particularly in radioresistant and metastatic cancers. Despite hurdles, nanotechnology presents a promising solution to enhance BNCT efficacy by enabling targeted drug delivery. Nanoparticles offer advantages such as improved tumor accumulation, penetration of the BBB, and real-time treatment monitoring. Overcoming these challenges through nanotechnology-based approaches holds great promise for advancing BNCT as a potent cancer treatment modality.

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Conflicts of Interest

The authors declare no conflict of interest.

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