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Chapter

Boron Compounds for Neutron Capture Therapy in the Treatment of Brain Tumors

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Abstract

Boron neutron capture therapy (BNCT), which uses the capture reaction between neutrons and boron-10, an isotope of boron, is rapidly gaining interest. The reason for this is the successful development of a compact accelerator-type neutron generator that can be installed in a hospital and launched into the clinical setting. BNCT, which provides selective radiotherapeutic effects at the cellular level, is expected to be effective against invasive cancer. We have been investigating BNCT applications in various types of malignant brain tumors, especially malignant gliomas, as medical applications. Recently, we have conducted clinical trials using the developed accelerator neutron source. Research on pharmaceutical applications of compounds that transport boron to cancer cells is expected to be in even greater need. Currently, the only boron agent used in cancer therapy is BPA (Borofaran 10B), which takes advantage of the demand for essential amino acids, but the research and development of boron agents are an absolutely key technology to further improve the precision of this treatment modality. This chapter summarizes and discusses the results of BNCT in the treatment of brain tumors.

Keywords: boron neutron capture therapy, Borofaran (10B), brain tumor, glioma, accelerator-type neutron generator, nuclear reactor

1. Introduction

Boron neutron capture therapy (BNCT) for head and neck cancer was approved in Japan in 2020, using the world's first accelerator-type neutron generator, (BNCT treatment system NeuCure® Sumitomo Heavy Industries, Ltd.) along with the boron drug for BNCT (Borofaran (10B), and Steboronin® Stella Pharma Co., Ltd.) [1]. It has attracted a lot of interest due to its potential for advancement and widespread use in general medical practice.

Recent developments in quantum-based medicine are remarkable worldwide, and representative particle therapy devices are expected to expand their application range
due to their excellent beam quality and biological effects, as well as technological improvements in disease adaptability such as beam shaping technology, rotation of gantry, and diagnostic image-guided irradiation and focal tracking irradiation, which precede X-ray therapy devices. Neutron capture therapy is a representative method for applying quantum to medical treatment using neutron capture reactions with atoms, in addition to therapies that control and apply direct cellular damage of these quanta to living organisms. Neutron capture reactions occur between various atoms, but the stable isotope of boron, boron-10 ($^{10}\text{B}$), which is the most suitable condition for medical applications, is used and is called boron neutron capture therapy. Since naturally existing boron consists of two stable isotopes ($^{11}\text{B}$ and $^{10}\text{B}$), where $^{11}\text{B}$ accounts for 80%, special technology and equipment are required to produce concentrated $^{10}\text{B}$ used for BNCT.

BNCT is a particle therapy that biologically targets tumor cells [2]. By selectively introducing boron drugs containing $^{10}\text{B}$ atoms into tumors and irradiating them with thermal neutrons, charged particles are generated by neutron capture ($^{10}\text{B} + n \rightarrow ^{3}\alpha + ^{7}\text{Li}$ or $^{10}\text{B} (n, ^{3}\alpha ) ^{7}\text{Li}$). The resulting alpha particles and recoil lithium (Li) nuclei are high LET (linear energy transfer) particles that emit all their energy over a short range corresponding to the size of a cell. If boron compounds are selectively introduced, the reaction occurs only in cancer cells and is an ideal “cell-selective treatment” in which surrounding normal cells are preserved. The characteristic of this treatment is that the boron compounds to be administered and the neutrons to be irradiated are non- to low-toxic, respectively, and the treatment is completed by a two-step approach, “neutron capture reaction,” in which the effects of both compounds are shown for the first time in vivo (Figure 1).

Unlike other advances in radiotherapy that spatially add changes to the distribution of doses, it is necessary to note that there are different distributions of biological effects in the same irradiation field in BNCT. In the case of BNCT for glioma, we mainly examine the distribution dose of the tumor and the distribution dose of the normal brain for medical care. In the case of neutron irradiation, it is necessary to add and calculate other doses mixed in the neutron field to be irradiated, as well as the biological effects of the radiation quality and tissue reaction, respectively. There are

Figure 1.
In boron neutron capture therapy (BNCT), $^{10}\text{B}$ compounds are administered followed by low-energy neutron irradiation, which causes a nuclear reaction between the $^{10}\text{B}$ and the neutrons. The resulting helium nuclei (alpha particles) and lithium recoil nuclei selectively destroy tumor cells from within even in the infiltrated area.
some peculiarities in these calculations, but the results are easy to understand because they are visualized as X-ray equivalent doses (Figure 2).

The practice of providing medical care by considering the biological effects of radiotherapy is the same in the current general-purpose radiotherapy devices. The wide range of invasion areas of glioma is sometimes targeted as a tumor or as a risk organ, and different biological effects have been induced by the difference in the number of fractions and the dose at one time in the assumed tissues, which are each subject. For details, refer to the guidelines for radiotherapy and the Guidance on Evaluation of Accelerator Neutron Irradiation Device System for Boron Neutron Capture Therapy (BNCT Review Working Group, National Institute of Health.

Figure 2.
In BNCT, organ-specific dose distributions are calculated simultaneously (upper: Dose distribution, right: Lower: Dose volume histogram (DVH) for normal and tumor tissue). The SERA calculation engine used in many reactor-based BNCT facilities combines a proprietary Monte Carlo calculation code.
Characteristics and Applications of Boron

Sciences, Japan) [3]. This knowledge is necessary not only for BNCT, but also for conventional X-ray irradiation (2Gy 30 fractions) (for example, in combination with intensity-modulated irradiation, stereotactic irradiation, reirradiation at the time of recurrence, etc.), and is a sense to be acquired.

2. Background BNCT for brain tumors

In the 1950s, the first clinical trial was initiated at Brookhaven National Laboratory (BNL) in New York, and several low-molecular-weight boron compounds were tested as boron delivery agents [4]. Thereafter, it was progressed on to a full-scale clinical application using the Massachusetts Institute of Technology Nuclear Reactor (MITR), but the results of this study were unanticipated and clinical trials in the United States halted. In 1967, Hatanaka et al., who were deeply involved in research in the United States, launched a clinical trial using thermal neutrons and the boron drug sodium borocaptate (BSH) in Japan, with more than 200 cases treated. Although various tumor tissue types and patient backgrounds were mixed, leading to inconclusive conclusions about the effectiveness of the therapeutic effect on specific diseases and conditions, the results of the standard treatment of refractory malignant glioma at that time were as long as those of the standard treatment and have shown expectations for cure [5].

In the United States, BNCT of patients with brain tumors was resumed in the mid-1990s. Boronophenylalanine (BPA), a novel boron drug, was used in clinical trials for the first time, and BNCT in non-craniotherapy was achieved using epithermal neutrons with excellent tissue depth. BPA has been developed to target malignant melanoma with the essential amino acid phenylalanine in the skeleton, but it is a boron drug that exploits the amino acid requirements that are elevated in cancer cells and has been shown to be applicable to various cancer types. Clinical trials were conducted at Harvard University in collaboration with MITR to first treat patients with malignant melanoma of the skin, from which indications were expanded to patients with brain tumors (especially glioblastoma and metastatic melanoma). Twenty-two patients have been treated using BPA, five cutaneous malignant melanomas followed by brain tumor patients. Treatment was well tolerated, but did not outperform the results of conventional X-ray fractionated external beam radiation. A detailed review has conducted of BNCT using the nuclear reactor that has been implemented in Japan and overseas in the past [2].

Recent treatment outcomes of BNCT using the nuclear reactor for glioblastoma (World Health Organization (WHO) Grade 4) have been reported by BNCT research groups in Japan, Sweden, and Finland. However, the background of the targeted cases according to patient selection criteria varied, making it difficult to make a simple comparison with other standard treatment groups. Therefore, there is a limitation of the interpretation of the analysis divided into historical control and recursive partitioning analysis (RPA) subgroup. In our report, we performed a clinical trial using the Kyoto University Nuclear Reactor with a protocol combining BPA (500 mg/kg) and BSH (sodium borocaptate) (100 mg/kg) as “multi-targeted type BNCT,” which uses multiple types of target boron drugs at once and irradiates a single neutron, with a median survival time (MST) of 15.6 months (n = 10) with BNCT alone and experiencing long-term survivors (>5 years) [6]. BSH can introduce a large amount of boron atoms, including 12\textsuperscript{10}B atoms, but its cell selectivity is low. However, in brain tumors, it remains tissue-selective by exploiting the breakdown of the blood-brain
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The MST of BNCT combined with X-ray fractionated external irradiation (20–30Gy) was 23.5 months. No significant toxicity other than hair loss was observed in this protocol, indicating that BNCT with cell selectivity remains highly tolerated in combination with existing radiotherapy (Figure 3).

The University of Tsukuba also reported that the median survival time was 27.1 months, the 1-year and 2-year survival rates after BNCT were 87.5% and 62.5%, respectively [7]. In Sweden, the dosage of BPA was increased to 900 mg, and the clinical trial was carried out [8]. BPA was administered over a duration of 6 h, and neutron irradiation was performed from two directions. The mean total brain dose was 3.2–6.1 Gy (X-ray equivalent), and the minimum dose to the tumor ranged from 15.4 to 54.3 Gy (X-ray equivalent). Progression-free survival and median overall survival were reported as 5.8 and 14.2 months, respectively. Adverse events associated with this protocol were only 14%, which was lower than the standard treatment with X-ray fractionated external beam radiation alone or with temozolomide. Our findings also suggested that the combination of BNCT with X-ray fractionated external beam radiation or temozolomide was tolerable and prolonged survival in primary gliomas [9].

Next, the treatment outcome of recurrent malignant glioma (of which the attention is especially high in BNCT of the brain tumor region) was introduced. The prognosis of recurrent malignant glioma is very poor, and especially in the case of radiotherapy, the treatment is difficult. Though surgery followed with radiotherapy has also been carried out, the survival time is approximately 6 months. A prospective trial of BNCT for recurrent malignant glioma has reported 22 treated cases from our institution and 19 cases of Phase I with increased dosage of BPA at the University of Helsinki. The median survival was 10.8 months and 7 months, respectively. Outcomes limited to recurrent glioblastoma included with survival of 9.6 months (n = 19) and 8.7 months (n = 12) after BNCT [10, 11]. To further improve the outcomes of these BNCT-alone treatments, we performed improved efficacy and safety validation when the angiogenesis inhibitor bevacizumab was also used after treatment and has performed very well at the pilot study stage [12].

Clinical trials for brain tumors using the accelerator as a neutron source have been performed for recurrent malignant gliomas, especially for refractory recurrent glioblastoma [13], and are ready for approval in the brain tumor area in addition to the preceding head and neck cancer.

Figure 3.
A case of reactor-based BNCT for malignant glioma with significant response. In this case, favorable boron drug distribution was observed on the pretreatment PET images. (left: FBPA-PET fusion, middle: Before treatment, right: After BNCT of contrast-enhanced MRI T1WI).
3. The practice of neutron capture therapy

3.1 Boron drugs

In many national and international BNCT clinical studies using BPA, neutron beam irradiation has been performed in many cases during the clearance phase after the intravenous infusion of BPA. This, however, required simulation of the in vivo dynamics of boron concentration during irradiation, resulting in an increased importance of subsequent evaluation. In promoting medical applications based on the idea of prescription dose, the accuracy of pre-prediction was pursued, and it was considered that the continuous intravenous infusion during the irradiation used in the clinical research of head and neck cancer using nuclear reactors could solve this problem, and we have taken this approach in our brain tumor treatment. To maintain the concentration of $^{10}$B in the tumor tissue that is expected to have a therapeutic effect during thermal neutron beam irradiation, it has been adopted as a dosage and administration method of BPA to maintain the concentration of $^{10}$B in whole blood at 20 ppm or higher.

In 15 patients with recurrent head and neck tumors, BPA (fructose solution) 500 mg/kg (400 mg/kg was administered at a constant rate of 200 mg/kg/hr. for 2 h, followed by reducing the infusion rate of the remaining 100 mg/kg to approximately 100 mg/kg/hr. at a constant rate until the end of the irradiation) was administered at the reactor of the Kyoto University Institute for Integrated Radiation and Nuclear Science [14]. In BNCT of malignant glioma carried out by Osaka Medical University adopting the same protocol, an average result of 27 ppm in the whole blood boron concentration was obtained. On the other hand, the whole blood boron level immediately after irradiation in patients treated with BPA (fructose solution) 250 mg/kg could not be maintained at 20 ppm, and even in patients treated with 500 mg/kg, the mean value of whole blood boron level immediately after irradiation decreased to 19.5 ppm, and the fluctuation before and after irradiation was greater compared with 30.4 ppm before irradiation [14]. These experiences suggest that a dose of BPA 500 mg/kg (200 mg/kg/hr. × 2 hr. + 100 mg/kg of BPA at a constant rate of approximately 100 mg/kg/hr. to match the end of irradiation time) is expected to exceed 20 ppm of whole blood boron concentration during irradiation, and that the method of administration that satisfies the conditions for maintaining stable concentrations before and after irradiation.

In a phase II clinical trial (BNCT) in Sweden, 30 patients with glioblastoma were treated with a 6-hour infusion of 900 mg/kg of BPA followed by irradiation 2 hours later. Although transient serious adverse events have been observed, irreversible events have not been observed, and the tolerability of BNCT at 900 mg/kg BPA and 2 hours after 6 hours of intravenous infusion was confirmed [14].

3.2 Dose prescriptions

Factors on the radiation side that generally govern the effects on normal tissue include radiation quality, distribution of dose in the tissue and size of the irradiated volume, and on the tumor side include the presence of a history of radiotherapy and the effect of the tumor on the surrounding normal tissue. It is required that the dose in the irradiated volume is as uniform as possible in order to accurately evaluate the relationship between the reaction of the tissue and the dose. In conventional X-ray or particle therapy, it is possible to irradiate evenly a certain volume of radiation,
including the normal brain around the brain tumor. However, for neutron radiation, the attenuation of neutron intensity in the tissue is large and delivering a uniform irradiation becomes difficult.

The skin is a thin layer of tissue that is not affected much by neutron attenuation, so it is possible to define the dose at the skin surface. It’s also regarded to be more versatile when it comes to expanding its indication to other organs throughout the body.

Skin dose and dose distribution in the normal brain (maximum dose) can also be associated, and the idea of limiting skin dose so that the maximum dose in the normal brain does not exceed the tolerable dose usually obtained from experience and knowledge of radiotherapy has been adapted. In the case of brain tumors, it has been reported by Mayer et al. that necrosis of normal brain tissue develops when the cumulative dose of initial radiotherapy and re-radiotherapy exceeds 100Gy

Figure 4. Example of dose calculation (dose planning for a simulated brain tumor) using the BNCT dose calculation program (NeuCure® dose engine Sumitomo heavy industries, Ltd.) the graphical user Interface (GUI) enables detailed visualization of dose distribution, dose volume histogram (DVH) plotting, and reference and modification of various parameters in one GUI.
fractionated irradiation) [15]. In clinical practice, the effectiveness and safety of BNCT are considered, and the eligibility is judged, and the plan is made using the skin dose as an index.

### 3.3 Treatment plan

The BNCT dose calculation program (NeuCure® dose engine Sumitomo Heavy Industries, Ltd.) was developed and approved as a medical device. The Monte Carlo code uses a simulation code called PHITS, which enables BNCT dose calculation, as well as additional functions such as external I/F including security checks, and is developed as a dose engine dedicated to BNCT dose calculation. RayStation (RaySearch Japan Co., Ltd.), a general-purpose radiotherapy program, is used for the user interface, and it has an improved drawing function and excellent operability similar to the state-of-the-art radiotherapy equipment (Figure 4).

### 4. Future development of BNCT

At our institution, we have previously performed a clinical trial of reactor BNCT even for high-grade meningiomas and reported the results of BNCT for recurrent meningiomas [16, 17]. Prior to the treatment, ¹⁸F-labeled BPA positron emission tomography (FBPA- PET) was performed using a therapeutic agent, boron compound BPA, labeled with ¹⁸F as a tracer, and the tumor-to-normal brain (Tumor/Normal: T/N) ratio averaged 3.8. This value is equal to or better than the value experienced in glioma. The introduction of this PET study proved to be useful for the treatment of recurrent malignant glioma, but it was also indispensable for developing nuclear reactor BNCT for cancers of other organs of the whole body, as well as for the later expansion of indications for head and neck cancer. In high-grade meningiomas, although there was transient enhancement of contrast areas (pseudoprogression) in a few cases, all cases showed a reduction in tumor volume. These were all patients with recurrence after multiple surgeries and radiotherapy, and the treatment outcome after BNCT was generally good, but they are rare tumors, and there are few consolidated reports that can be compared. The major cause of death was metastasis to the whole

Figure 5.
A case of high-grade meningioma treated with reactor-based BNCT with significant response. The tumor in this case was located in the midline and was a recurrent case of refractory skull base meningioma, although a shrinkage effect was observed. (left: FBPA-PET fusion, middle: Before treatment, right: After BNCT of contrast-enhanced MRI T₁WI).
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Subsequent analysis showed that the method was effective in deep-seated tumors such as the skull base, where the dose is very low (Figure 5) [18]. The therapeutic effects of these cases treated using reactors have led to the development of physician-led clinical trials using accelerator-based neutron sources.

Even in situations where nuclear reactors have to be used as neutron sources, proposals for new indications and improved protocols have resulted in better treatment outcomes, and BNCT research has not been interrupted until now since the beginning of clinical research in the 1960s. Under such circumstances, Japan succeeded in BNCT using an accelerator-type neutron generator for the first time in the world [13]. Recently, the attention that exceeds the academic interest from all fields and industries around the world has also increased in keeping with the success of Japan. In the field of brain tumors, global standards are expected to be challenged in the future, such as
in combination with standard treatments for new diagnostic cases of glioma. However, improvements in the peripheral environment, such as the worldwide spread of approved devices and the approval of unapproved devices for medicine, are also awaited.

The “treatable” intracranial diseases on BNCT range widely and are absolutely not limited to gliomas. However, diseases such as “BNCT can be expected” are limited. In BNCT, it is one of the most important conditions for boron to maintain contrast with normal tissue and sufficiently accumulate in the tumor, and it is necessary to confirm that the boron drug to be administered shows high accumulation in the tumor using some technique before neutron irradiation. In the nuclear reactor BNCT, as described above, attempts to use PET examination with 18 FBPA have preceded, and clinical research has been conducted as “visible drug” (Figure 6). Although this idea is a pioneer in the field of “theranostics” that has been promoted recently, it is expected to expand the application of these combinations to new diseases and to tailor-made BNCT treatment.

5. Summary

Boron neutron capture therapy (BNCT) is a type of radiotherapy, but it has cell selectivity and can be used in combination with other radiotherapy for the treatment of recurrent and irradiated cases. The major adverse events are radiation-induced necrosis and brain edema especially for the patients with history of prior irradiation in the central nervous system.

BNCT using borofalan (10B) has become a general medical treatment by the development of medical equipment using the accelerator as a neutron source.

6. Conclusions

The current status of boron neutron capture therapy (BNCT) for brain tumors was reviewed, including recent advances in BNCT, which is still not mature, although its clinical application has begun following the successful launch of an accelerator-based neutron generation device. The contribution of “boron research” to the further development of BNCT will be important, and many researchers will be involved in the future progress of this field.

Research on the development of boron agents for treatment has also become active, and as introduced here, “multi-targeted BNCT,” which simultaneously combines multiple boron agents, is very promising for personalized cancer therapy and the extension of applications.

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Conflict of interest

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Notes/thanks/other declarations

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References


