EDITORIAL

Boron neutron capture therapy of cancer: Critical issues and future prospects

Introduction

The role of radiotherapy in the management of cancer is well established. During the whole course of cancer treatment, more than 50% of all cancer patients need to undergo radiotherapy, which is always considered to be one curative treatment modality for localized cancers. However, radiotherapy may cause severe acute and late toxicities, especially in patients with recurrent cancer. With the development of physical and biological technology, some novel radiotherapeutic strategies have been developed which may address these issues.[1] One of these is boron neutron capture therapy (BNCT), a targeted radiotherapy for cancer cells that preferentially accumulate drugs carrying the nonradioactive boron-10 (^{10}B). It is based on the nuclear capture and fission reactions that occur when ^{10}B is irradiated with neutrons to yield linear energy transfer alpha particles (^{4}He) and recoiling lithium-7 (^{7}Li) nuclei.[2] The short range of this reaction limits the damage to only cancer cells without affecting normal cells, even if the two types of cells are mingled at the cancer margin. This property allows BNCT to be used to treat cancers without damaging the surrounding critical normal tissues.[3] Indeed, BNCT has been clinically evaluated as an alternative to conventional radiotherapy for the treatment of multiple cancers, including high-grade gliomas,[4] primaries or cerebral metastases of melanoma,[5] and head and neck cancer.[6] However, if BNCT can be used clinically as a modality for the treatment of cancers, several critical issues regarding boron-containing agents and their delivery strategies, neutron sources for BNCT and clinical studies of BNCT must be addressed. Here, we also provide several valuable clues that can be followed to solve these critical issues.

Boron-containing agents

Conventional boron-containing agent

The ideal boron-containing agent should fulfill the general requirements as follows: (i) low systemic toxicity; (ii) low normal tissue uptake with high tumor uptake (tumor/brain and tumor/blood boron ratios >3–4:1); (iii) tumor concentrations of approximately 20 μg ^{10}B/g tumor; and (iv) persistence in tumor tissues but rapid clearance from normal tissues during BNCT.

In the 1950s and early 1960s, the first-generation boron-containing agents, such as boric acid and some of its derivatives, were developed as delivery agents for BNCT. However, these chemical compounds are nonselective attaining low tumor/blood boron ratios and cannot achieve effective neutron capture therapeutic effects.[7,8] Therefore, the treatment of malignant tumors by BNCT using these agents has been proven to fail.

In the 1960s, the clinical trials of BNCT used two second-generation boron compounds. One of these was (L)-4-dihydroxy-borylphenylalanine (BPA), which is based on aryl boronic acids. Another boron-containing chemical is sulfhydrylboran (BSH), which is based on sodium mercaptoundecahydro-closododecaborate. In comparison with the first-generation boron-containing agents, the second-generation boron compounds have lower toxicity, higher tumor/blood boron ratios and persist longer in tumor xenografts. However, it should be noted that none fulfills the requirements for a successful boron delivery agent.

The third-generation boron-containing agents mainly consist of a stable boron cluster attached through a hydrolytically stable linkage to a tumor-targeting moiety, such as low or high molecular weight agents.[9] Low molecular weight agents include boron-containing amino acids, polyhedral boranes, biochemical precursors, DNA-binding agents, glucose, mannose, ribose, gulose, fucose, galactose, maltose, lactose molecules, phosphates, phosphonates, phenylureas, thioureas, nitroimidazoles, amines, benzamides, isocyanates, nicotinamides, azulenes, and dequalinium derivatives. High molecular weight agents include monoclonal antibodies, receptor-targeting agents, and liposomes, which have been shown to have better selective targeting properties compared to the first- and second-generation boron compounds.[2] However, the biological properties of these agents depend on the density of the targeted sites and very little biological data on the third-generation boron-containing agents have been reported to date.

Critical issues and future prospects

The development and synthesis of the third-generation boron-containing agents has been the subject of intensive investigation. The size of high molecular weight boron compounds has limited their usefulness as tumor-targeting agents. If they were administered by intracardiac injection or linked to an actively transported carrier molecule, they could be very useful delivery methods. Additionally, the use of multiple boron-containing agents is probably

required, especially for targeting of different cancer cell subpopulations and subcellular tumor sites. Furthermore, lower doses of each individual boron-containing agent would be needed which could reduce the toxicity and enhance tumor-localizing properties while resulting in improving the therapeutic ratio.

Delivery of boron-containing agents

Factors affecting the delivery of boron-containing agents

Delivery of boron agents to cancer tissues depends on a number of factors, including the route of administration, the ability of the agent to traverse the blood-brain barrier (in the treatment of brain tumors), nonspecific uptake and retention in adjacent normal tissues (in the treatment of extracranial tumors), tumor blood flow and the lipophilicity of the agent.[2] Intravenous administration currently is being used clinically, but it is not an ideal route and other strategies may be needed to improve the delivery of boron-containing agents.

Intra-arterial administration and direct intracranial delivery

As shown in experimental studies using F98 glioma-bearing rats, intracardiac injection of BPA or BSH doubled the tumor boron uptake in comparison with an intravenous injection of the same boron-containing agents. In addition, tumor boron uptake was increased four-fold by infusing a mannitol solution (25%) via the internal carotid artery.[10] A similar enhancement in tumor boron uptake was observed in F98 rat glioma model following intracardiac injection of Cereport (a bradykinin agonist).[11]

Different boron-containing compounds may require different strategies. For example, the uptake of boron-containing nucleosides is cell cycle dependent, thus, continuous administration may be required.[11,12] Some studies have demonstrated that direct intrathecal injection and convection enhanced delivery were necessary for a variety of high molecular weight agents, such as boronated monoclonal antibodies,[13] and epidermal growth factors,[14] as well as for low molecular weight agents, such as porphyrins.[15] These studies have shown that a significant therapeutic gain can be achieved by optimizing boron-containing agent delivery.

Critical issues and future prospects

The delivery of boron-containing agents must be optimized to improve both tumor uptake and cellular micro-distribution, especially to different tumor cell subpopulations. In addition, several studies have shown that there is a considerable difference among patients in the uptake of boron-containing agents.[16,17] At present, the dosage and delivery of these drugs have not been optimized. Most related studies are based only on animal experiments and relevant clinical data is required in the future.

Quantitative estimation of the boron content in tumor tissue

Existing quantitative estimation method

Radiation dosimetry plays an important role in BNCT. The successful implementation of BNCT is based on the cumulative amount of ^{10}B in the tumor tissue to give the corresponding neutron exposure. Therefore, methods that can measure the neutron fluence rate or provide semiquantitative estimates of the boron content in the residual tumor are required. The currently known calculation method of neutron fluence rate includes fiberoptic scintillation detector real-time measurement, three-dimensional direct measurement and indirect measurement.[18] The calculation of the boron dose in tumor cells is also crucial. BNCT needs to set the irradiation dose according to the dose of boron in the tumor tissue. Therefore, ^{10}B concentration is a key parameter in BNCT, which will provide the basis for dosimetry for the development of BNCT treatment protocols.

^{10}B concentration in blood and normal tissues is associated with that in tumor tissues. Therefore, ^{10}B concentration in tumor tissue can be estimated by measuring the blood ^{10}B concentration during BNCT.[19] However, this method will result in a certain error in the estimation. Currently, there are three types of estimation methods: (i) track engraved technology; (ii) inductively coupled plasma atomic emission spectrometry (ICP-AES); and (iii) prompt-gamma neutron activation analysis (PGNAA). Track engraved technology is highly sensitive. However, it cannot be used in real-time measurement. To date, ICP-AES is the most common method. Although its processing time is short, the sampling procedure of ICP-AES is complicated. PGNAA is accurate, fast, and requires no sample processing and has been successfully applied in China. Fluorine-p-borono-phenylalanine positron emission tomography (^{18}F-BPA PET) has also been used to estimate the cumulative dose of boron in tumor tissues before BNCT and applied to the treatment of various cancers, such as metastatic melanoma and recurrent oral cancer.

Critical issues and future prospects

Although ^{18}F-BPA PET is effective in many types of cancers, its specificity of boron content using semiquantitative estimation in the inflammation site is not good enough, and there are still some limitations in its accuracy. Therefore, how to make it more accurate for the treatment of tumors needs to be further studied. The number and location of ^{10}B entering tumor cells vary with tumor grade and

biochemical properties. To make BNCT a more effective technique for radiotherapy, it is necessary to obtain more accurate and real-time data about ^{10}B concentrations from patients with different tumor stages. In this way, the dynamic dose distribution of the neutron irradiation of each target is accurately set, and it is required to be universally applicable to various cancers, thereby improving the therapeutic effect. Furthermore, magnetic resonance imaging (MRI), combined with positron emission tomography (PET), may become one of the future directions of BNCT.

Neutron sources for BNCT

The following are the requirements of BNCT for neutron sources. The first is neutron flux which should be more than 10^9 cm^{-2}/s at the beam aperture. The second is that it is necessary to generate $\geq 5 \times 10^{13}$ n/cm^2/s neutron flux at the point of neutron target. The third is neutron energy which should be high enough to penetrate tumors. Satisfactory neutron sources are produced only by nuclear fission reactors, which are not only costly, but also need to be considered operational and safe issues.[20] The neutron beam produced by the accelerator is not easy to meet the flux requirement. Furthermore, the pollution of neutron beam which include fast neutron and gamma ray pollution cannot be ignored.

High intensity neutron sources are warranted for highly efficient treatment. Nuclear reactor neutron sources have been used for BNCT for a long time since high intensity neutron beams have only been supplied by reactors. However, many of the reactors have been closed. Even in China, there is only one reactor constructed recently for BNCT. On the other hand, accelerator-based neutron sources are becoming popular in neutron application fields. To establish hospital-based BNCT as a general treatment, compact accelerator-based neutron sources are necessary to be developed around the world.[21]

Critical issues and future prospects

The photonuclear reaction which occurs in the electron accelerator generates high intensity X-rays which will contaminate the irradiation neutron beam. It is one of the problems to be overcome when using the electron accelerator.

Currently, neutrons are also produced from protons and their energies range from 1.45 to 30 MeV. An election accelerator for research on BNCT is still not producible. [21] Development of BNCT is constrained by the progress in neutron sources design. Creation of an enconomical and compact intense neutron source would significantly simplify treatments without using expensive and complicated nuclear reactors and accelerators. D-D or D-T neutron generator is one of alternative types of such sources.[2]

Clinical studies of BNCT

Recent clinical trials

BNCT has been used clinically for several decades for treatment of various cancers such as glioblastoma multiforme and head and neck cancers. Retrospective studies[22–24] have demonstrated the safety and effectiveness of BNCT, which has shown a promising treatment modality for cancer patients.

Miyatake *et al.*[24] treated 22 patients who had recurrent malignant glioma with BNCT. After BNCT, the median survival times for whole group and high-RPA group was 9.6 and 9.1 m, respectively. Compared to the historical data that the median survival time of high-RPA malignant glioma was 4.4 months, BNCT showed a survival benefit for recurrent malignant glioma, especially in the high-risk group. Furthermore, no serious adverse effects were observed in this study of BNCT for recurrent malignant gliomas. In the literature, hematuria has been reported to occur when large amounts of BPA in BNCT have been used.[25]

Recently, a prospective phase I/II trial investigated the efficacy and safety of fractionated BNCT for 17 patients with recurrent head and neck cancer following photon radiotherapy.[26] The median prescription dose for the first and second fraction was 19.8 and 14.6 Gy-Eq and median follow-up of 19.7 m (range: 5.2–52 m). The total response rate was 71%, including six complete responses. Two-year local control and overall survival was 28% and 47%, respectively. With regard to the acute toxicity, there were grade 3 mucositis in five patients and grade 4 laryngeal edema in one patient. Regarding the late toxicity, grade 3 cranial neuropathy occurred in two patients.

Critical issues and future prospects

To obtain satisfactory results with BNCT, it is crucial to identify the minimal dose required for the long-term survival of cancer patients. To address this issue, the correlation between and radiation dose and tumor control must be identified.[9,27] Furthermore, at present, the best way to improve the clinical efficacy of BNCT would be to optimize the dosing paradigms and delivery of BPA and BSH, either alone or in combination. Hopefully, future research will identify new and better boron delivery agents for clinical use.[9] Almost all major advances in cancer therapy have come from randomized clinical trials. However, until now, few randomized trials of BNCT have been conducted. It is a mistaken belief that the results of existing clinical trials of BNCT will be so clear-cut that the efficacy of BNCT can be clearly defined without randomized trials. Currently, more randomized clinical trials of BNCT which might best be accomplished through cooperative groups are required.

In conclusion, if BNCT is to become a useful treatment modality for cancers, there are several critical issues that

must be addressed: (i) there is a need for more effective boron-containing agents that could deliver the requisite amounts of boron to cancer cells when used either alone or in combination; (ii) the delivery of boron-containing agents must be optimized to improve both cancer cell uptake and cellular microdistribution, especially to different subpopulations of cancer cells; (iii) methods which provide semi-quantitative estimates of the boron content in the residual cancer cells are required; and (iv) randomized clinical trials to evaluate the safety and efficacy of BNCT are essential.

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Disclosure

The authors report no conflict of interest.

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References

1 Yan L, Zhang W. Precision medicine becomes reality-tumor type-agnostic therapy. *Cancer Commun* 2018; **38** (1): 6.

2 Barth RF, Coderre JA, Vicente MG, Blue TE. Boron neutron capture therapy of cancer: Current status and future prospects. *Clin Cancer Res* 2005; **11** (11): 3987–4002.

3 Barth RF, Zhang Z, Liu T. A realistic appraisal of boron neutron capture therapy as a cancer treatment modality. *Cancer Commun* 2018; **38** (1): 36.

4 Miyatake S, Kawabata S, Hiramatsu R *et al.* Boron neutron capture therapy for malignant brain tumors. *Neurol Med Chir* 2016; **56** (7): 361–71.

5 Hiratsuka J, Kamitani N, Tanaka R *et al.* Boron neutron capture therapy for vulvar melanoma and genital extramammary Paget's disease with curative responses. *Cancer Commun* 2018; **38** (1): 38.

6 Wang LW, Liu YH, Chou FI, Jiang SH. Clinical trials for treating recurrent head and neck cancer with boron neutron capture therapy using the Tsing-Hua Open pool Reactor. *Cancer Commun* 2018; **38** (1): 37.

7 Farr LE, Sweet WH, Robertson JS *et al.* Neutron capture therapy with boron in the treatment of glioblastoma multiforme. *Am J Roentgenol Radium Ther Nucl Med* 1954; **71** (2): 279–93.

8 Goodwin JT, Farr LE, Sweet WH, Robertson JS. Pathological study of eight patients with glioblastoma multiforme treated by neutron-capture therapy using boron 10. *Cancer* 1955; **8** (3): 601–15.

9 Barth RFMP, Yang W. Boron delivery agents for neutron capture therapy of cancer. *Cancer Commun* 2018; **38** (1): 35.

10 Barth RF, Yang W, Rotaru JH *et al.* Boron neutron capture therapy of brain tumors: Enhanced survival following intracarotid injection of either sodium borocaptate or boronophenylalanine with or without blood-brain barrier disruption. *Cancer Res* 1997; **57** (6): 1129–36.

11 Barth RF, Yang W, Bartus RT *et al.* Neutron capture therapy of intracerebral melanoma: Enhanced survival and cure after blood-brain barrier opening to improve delivery of boronophenylalanine. *Int J Radiat Oncol Biol Phys* 2002; **52** (3): 858–68.

12 Barth RF, Yang W, Al-Madhoun AS *et al.* Boron-containing nucleosides as potential delivery agents for neutron capture therapy of brain tumors. *Cancer Res* 2004; **64** (17): 6287–95.

13 Yang W, Barth RF, Wu G *et al.* Development of a syngeneic rat brain tumor model expressing EGFRvIII and its use for molecular targeting studies with monoclonal antibody L8A4. *Clin Cancer Res* 2005; **11** (1): 341–50.

14 Yang W, Barth RF, Adams DM *et al.* Convection-enhanced delivery of boronated epidermal growth factor for molecular targeting of EGF receptor-positive gliomas. *Cancer Res* 2002; **62** (22): 6552–8.

15 Evstigneeva RP, Zaitsev AV, Luzgina VN, Ol' Shevskaya VA, Shtil AA. Carboranylporphyrins for boron neutron capture therapy of cancer. *Curr Med Chem Anticancer Agents* 2003; **3** (6): 383–92.

16 Goodman JH, Yang W, Barth RF *et al.* Boron neutron capture therapy of brain tumors: Biodistribution, pharmacokinetics, and radiation dosimetry sodium borocaptate in patients with gliomas. *Neurosurgery* 2000; **47** (3): 608–21.

17 Coderre JA, Chanana AD, Joel DD *et al.* Biodistribution of boronophenylalanine in patients with glioblastoma multiforme: Boron concentration correlates with tumor cellularity. *Radiat Res* 1998; **149** (2): 163–70.

18 Kono Y, Kurihara H, Kawamoto H *et al.* Radiation absorbed dose estimates for 18F-BPA PET. *Acta Radiol* 2017; **58** (9): 1094–100.

19 Hatanaka H, Nakagawa Y. Clinical results of long-surviving brain tumor patients who underwent boron neutron capture therapy. *Int J Radiat Oncol Biol Phys* 1994; **28** (5): 1061–6.

20 Kumada H, Naito F, Hasegawa K *et al.* Development of LINAC-based neutron source for boron neutron capture therapy in University of Tsukuba. *Plasma Fusion Res* 2017; **13**: 2406006.

21 Kiyanagi Y. Accelerator-based neutron source for boron neutron capture therapy. *Ther Radiol Oncol* 2019; **2**: 55–68.

22 Miyatake S, Kawabata S, Yokoyama K *et al.* Survival benefit of boron neutron capture therapy for recurrent malignant gliomas. *J Neurooncol* 2009; **91** (2): 199–206.

23 Kawabata S, Miyatake S, Hiramatsu R *et al*. Phase II clinical study of boron neutron capture therapy combined with X-ray radiotherapy/temozolomide in patients with newly diagnosed glioblastoma multiforme–study design and current status report. *Appl Radiat Isot* 2011; **69** (12): 1796–9.

24 Miyatake S, Kawabata S, Yokoyama K *et al*. Survival benefit of boron neutron capture therapy for recurrent malignant gliomas. *Appl Radiat Isot* 2009; **67** (7–8 Suppl): S22–4.

25 Henriksson R, Capala J, Michanek A *et al*. Boron neutron capture therapy (BNCT) for glioblastoma multiforme: A phase II study evaluating a prolonged high-dose of boronophenylalanine (BPA). *Radiother Oncol* 2008; **88** (2): 183–91.

26 Wang LW, Chen YW, Ho CY *et al*. Fractionated boron neutron capture therapy in locally recurrent head and neck cancer: A prospective phase I/II trial. *Int J Radiat Oncol Biol Phys* 2016; **95** (1): 396–403.

27 Kageji T, Nagahiro S, Mizobuchi Y, Toi H, Nakagawa Y, Kumada H. Radiation injury of boron neutron capture therapy using mixed epithermal- and thermal neutron beams in patients with malignant glioma. *Appl Radiat Isot* 2004; **61** (5): 1063–7.