Review paper

Boron neutron capture therapy – a brief review of principles and clinical applications

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Abstract

Boron neutron capture therapy (BNCT) exploits alpha and lithium particles produced in the boron-10 fission reaction (10B(n,α)7Li) with epithermal neutrons to inactivate cancer cells in the tumour volume ranges of produced alpha and lithium particles are limited to individual cells, so the boron-10 atoms should be located only in the target cancer cells. First, there is a need to administer to the patient the boron-10 carrier, which selectively deposits boron-10 atoms in cancer cells. Next, an external beam of epithermal neutrons must be delivered to the treated volume. BNCT is thus a bimodal method, combining epithermal neutron beam teletherapy with systemic therapy. Although BNCT is still under development, recent advances in boron-10 delivery agents and in accelerator-based epithermal neutron beam generation offer a new perspective for BNCT. These advances and some clinical applications of BNCT are briefly reviewed.

Introduction

Boron neutron capture therapy (BNCT) is based on the ability of alpha and lithium particles produced in the boron-10 fission reaction $^{10}B\ (n,\ a)\ ^{7}Li$ with epithermal neutrons (i.e. neutrons of energies 0.414 eV – 10 keV) to inactivate cancer cells in the target volume. The ranges in water of the high-LET alpha and lithium particles produced in this reaction are about 5 µm and 9 µm, respectively, and so are limited to volumes of single cells (Figure 1). For the $^{10}B\ (n,\ a)\ ^{7}Li$ reaction to occur, an external beam of epithermal neutrons must be delivered to the treated volume. The boron-10 atoms should be located only in targeted cancer cells but not in the healthy cells or critical organs. Prior to neutron beam irradiation, the patient should be administered a boron-10 delivery agent that selectively deposits boron-10 atoms only in cancer cells by exploiting the specific uptake properties of tumour cells [1, 2].

BNCT treatment is thus a bimodal method. It combines teletherapy – exposure of a patient to an external beam of epithermal neutrons – with systemic therapy whereby a boron-10–containing delivery agent selectively targets only tumour cells while avoiding normal cells surrounding the target volume [3–6].

There are several issues to resolve with respect to these two modalities of BNCT. Within its external

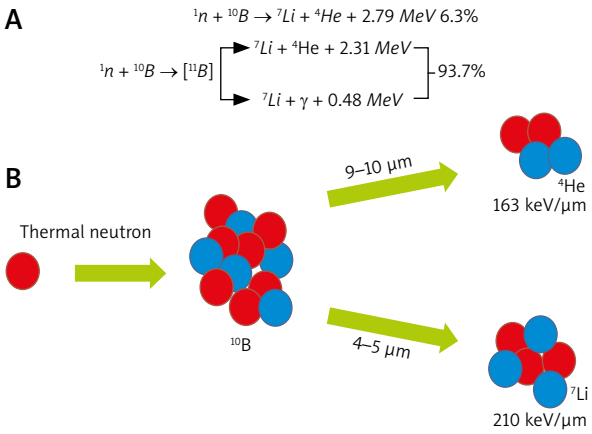

Figure 1. Scheme of nuclear reaction of boron-10 isotope with epithermal neutrons (**A**) and the principle of boron neutron capture therapy (**B**) (figure based on Wang *et al.* Boron Neutron Capture Therapy: Current Status and Challenges [2])

neutron beam delivery part, the dose delivered to the target (cancer) volume depends on the number of alpha and lithium particles deposited in cancer cells of the target volume, which in turn depends on the number of boron-10 atoms delivered by its carrier to these cancer cells, on the neutron beam flux (num-

ber of neutrons per unit area per time), and on neutron energy – as the cross-section (probability of occurrence) of the ^{10}B (n, a) ^{7}Li reaction strongly depends on the energy of the epithermal neutrons in the beam at the tumour site (this reaction occurs in resonance mode). Based on experience and calculations, the general requirements of a BNCT-applicable neutron beam at the target volume are as follows: epithermal neutron flux ≈ 10^9 neutrons/cm^{2}s, neutron energy range 1 eV–10.0 keV, gamma dose rate 1.0 Gy/h, fast neutron dose rate 0.5 Gy/h, and current flux (J/Φ) ratio ≥ 0.8 [3]. Beams of fast neutrons of energies above 10 MeV have also been applied in NCT-augmented fast-neutron therapy (NCT-FNT) [3, 4]. It is challenging to control the size and shape of a low-energy neutron beam due to the strong penetration of neutrons through collimating systems and to the accompanying gamma-ray background. Thus, in principle, only large target volumes can be irradiated.

Regarding the systemic part of BNCT, in general, the number of boron-10 atoms delivered to cancer cells depends on the effectiveness with which the boron carrier is able to transport boron-10 through cellular membranes and the vascular border, and on the (patient-weight and organ type-dependent) volume of the boron carrier administered, usually intravenously, to the patient [3]. Because the delivery of boron to the target area depends on the patient's physiology and the composition of the boron carrier compound, time considerations when applying external epithermal neutron beam exposure after carrier administration are also important.

Until recently, beams of epithermal neutrons could only be obtained at nuclear reactor facilities by applying specially designed neutron filters to transmit only epithermal neutrons of carefully selected energy. Clearly, it is difficult to arrange patient treatment conditions at a nuclear research centre where such neutron beams could be available for BNCT treatment. With new developments in accelerator technology it is possible to obtain such neutron beams using dedicated accelerators, so a BNCT facility can now be located within a hospital [2–5].

Although there has been a great deal of research and several BNCT treatments over the past 60 years, progress in clinical applications of BNCT has been rather slow, limited only to a few medical installations located at nuclear reactor facilities. Clinical applications of BNCT often concerned "last resort" cases, so results were not forthcoming, although quite spectacular in individual cases. Moreover, only one type of boron-delivery agent was used during these early years. Currently, the main criticism of BNCT is in the lack of results from systematic clinical trials involving larger numbers of patients [7]. However, with better understanding of the biology of the vascular barrier and cellular membranes and the technological advances in accelerator-based epithermal neutron beam production, it is now possible to install a BNCT facility on hospital premises. These are the main reasons for renewed interest in BNCT cancer therapy [2, 5].

Presently, there is no access to BNCT in Poland; however, some BNCT-oriented research concerning biological and physical aspects of this modality are being undertaken at the National Centre for Nuclear Research in Świerk [https://www.ncbj.gov.pl/en], using the MARIA research reactor. A few BNCT facilities are located in Europe (Germany, Finland), and several are under construction in China. Most of the earlier BNCT studies were carried out in Japan [2–7].

Here, a brief review is given of some more promising clinical results from recent studies. The current advances in the field of BNCT boron carriers are also discussed.

Boron delivery agents

The delivery agents used in BNCT must feature a low rate of normal tissue uptake with a high rate of tumour tissue uptake. The tumour/normal tissue and tumour/blood boron-10 isotope concentration ratios should exceed 3 and the carrier should have a low level of toxicity, present a stable concentration in the tumour during BNCT, and rapid clearance from normal tissue and blood post exposure. Currently, three groups of boron delivery agents, differing in specific uptake by tumour cells and toxicity, are in use [1].

The first group of boron-10 isotope delivery agents are based on boric acid and its derivatives. These compounds were initially used in the clinical BNCT trials. They had a low rate of specificity for tumour tissue, which caused many serious problems, such as skin burns, tissue necrosis, or deep ulceration.

The group of second-generation boron compounds includes disodium mercaptoundecahydro-closo-dodecaborate ($Na_2B_{12}H_{11}SH$, BSH) and L-boronophenylalanine (L-BPA), which is an amino acid derivative. These compounds are also currently used in many other studies [8]. In BNCT, L-BPA is used as a fructose complex (BPA-F), a combination of BPA and BSH, or (18) F-BPA, applying positron emission tomography (PET) to determine the cellular uptake of the boron-10 isotope. Because BPA is an amino acid derivative, its cellular uptake is maintained by the L-amino acid transporter system (LAT-1). In the case of BSH, it is claimed that the compound uses passive diffusion across the cell membrane to enter cancer cells. BSH contains 12 boron-10 isotope atoms and is an anionic polyhedral borane icosahedron [3].

The third group of boron delivery agents are the so-called third-generation boron compounds. These boron agents are still under investigation and have not been used in clinical trials yet. Third-generation agents include, e.g., boronated amino acids [9], boronated peptides and lipopeptides [10], monoclonal

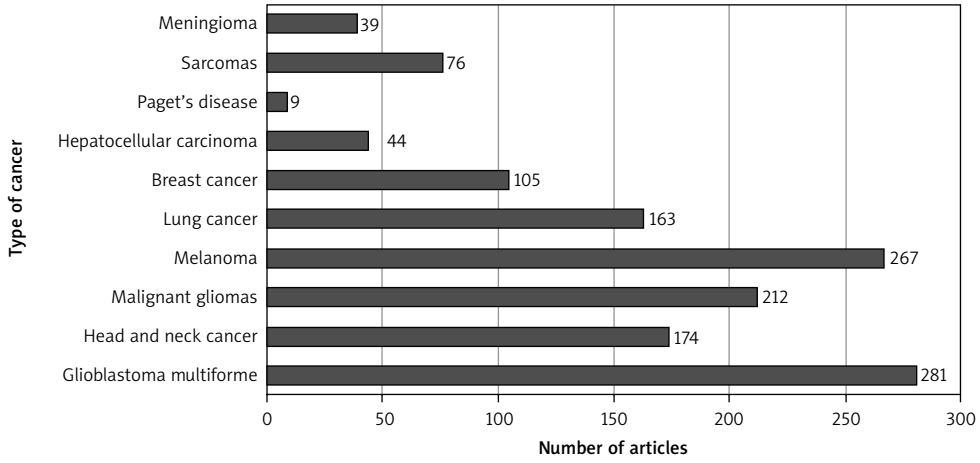

Figure 2. Numbers of articles on clinical trials for specific sites of cancer (based on PubMed and Science Direct data)

antibodies containing boronated epidermal growth factor (EGF) [11], immunoliposomes containing boron-10 [12], modified liposomes [13], or boron-containing nanoparticles [14]. Third-generation boron components are promising compounds due to their higher specificity for tumour cells, their nuclei, or DNA, which offers the possibility of enhancing the effectiveness of BNCT.

Clinical BNCT trials

BNCT has been performed as a treatment for the following cancers: multiforme glioblastoma [15], head and neck cancers [16, 17], recurrent lung cancer [18], recurrent malignant meningioma [16], and multifocal hepatocellular carcinoma [19].

In recent years, there has been a marked increase in the number of published articles on clinical BNCT trials. The highest increase in published articles about BNCT was in years 2011–2020 when almost 300 papers were released, according to PubMed and Science Direct.

Research on BNCT is growing rapidly, with significantly more clinical trials being performed for the treatment of gliomas (glioblastoma multiforme and malignant gliomas), as shown in Figure 2. A high number of clinical trials concerned head and neck cancers and melanoma.

Glioblastoma multiforme

Since its start, boron neutron capture therapy has been used primarily to treat glioblastoma multiforme (GBM). GBM is the most common brain tumour in adults and is classified as a neuroepithelial tumour. Due to its poor prognosis and lack of effective treatment, there is an urgent need to develop more effective therapies [20].

In the 1950s and 1960s, clinical trials related to the treatment of GBM were unsuccessful. No increase in survival rate was observed, and drastic side effects such as untreatable skin burns were noted. However, clinical trials with BSH administration have already begun in Japan and were performed in patients with GBM classified as G4 and anaplastic astrocytoma classified as G3. The results showed improved survival rates [3].

Miyatake *et al.* performed BNCT treatment in 167 patients with malignant brain tumours and high-grade meningiomas. In this case, p-boronophenylalanine was used as the boron delivery agent. The results of this study showed that the median survival for recurrent GBM was 10.8 months for BNCT with BPA. For BNCT with administration of BPA and BSH for newly diagnosed GBM, the survival time was 15.6 months without X-ray boost, and with X-ray boost it was 23.5 months. Consequently, there were some side effects of therapy, the most severe being necrosis [21].

In a clinical trial led by Yamamoto *et al.*, 7 patients were treated intraoperatively with BNCT using sulfhydryl borane. There was no difference in the median time to progression between the intraoperative and external beam (it was 11.9 months for all patients). Overall survival was 53.3% [22].

Kageji *et al.* conducted another study in 23 patients with newly diagnosed glioma. Patients were treated with BNCT without additional treatments, and BSH was used. The median survival was 19.5 months [23]. For recurrent GBM, Kankaanranta *et al.* conducted a study on the use of L-BPA-fructose as a boron agent. Median survival was 7 months. More detailed information can be found in the article by Kankaanranta *et al.* [24].

For the treatment of GBM, the main problem with boron-neutron therapy is the high degree of radiation-induced necrosis and symptomatic pseudoprogression. Due to the problem with radiogenic necrosis after BNCT, researchers in Japan started a pilot study using BPA in combination with bevacizumab. Seven patients were treated with BNCT and bevacizumab,

and the overall survival time was 15.1 months. Based on this study, the authors concluded that bevacizumab prevents radiation necrosis and prolongs overall survival [25].

Two current phase II clinical trials were conducted in Osaka and Tsukuba, Japan. The Tsukuba BNCT trial involves a combination of photon irradiation with concomitant temozolomide in combination with BNCT that uses BPA. The Osaka trial ended in 2018 with an overall survival of 25% [26].

Meningioma

In one study, Miyatake *et al.* performed BNCT in seven patients with different types of malignant meningioma. In this case, 18F-BPA PET was used before BNCT for 6 patients, and methionine PET was performed in the last patient. Six patients showed radiographic improvement [27]. Another study described 2 patients with recurrent meningeal tumours, who were treated with BNCT with BPA-F. Based on this study, they concluded that BNCT is a moderately effective treatment for malignant meningeal tumours [28]. In the study by Kawabata *et al.* BPA was used before neutron irradiation, and another dose of BPA was administered during irradiation. In this case, the median survival time was 14.1 months [29].

Head and neck cancer

Head and neck squamous cell carcinoma (HNSCC) is one of the most common malignancies, with high morbidity and mortality. Tumours of this type arise from squamous cells that line the surface of head and neck organs [4].

For the treatment of HNSCC, surgery, radiation therapy, and platinum-based chemotherapy are used. Regarding targeted therapy, only cetuximab is used, due to its approval by FDA. Therefore, it appears that BNCT may be a good option for treating HNSCC.

In vitro studies have shown that BNCT inhibits oral squamous cancer cells in a p53-dependent or independent manner. Additionally, subsequent apoptosis and lack of arrest in the G1 phase of the cell cycle contribute [30].

In 2007, Kankaanranta *et al*. treated 12 patients with head and neck cancer by BNCT. As a result, 10 of the 12 patients achieved a partial response rate (PR) of 83%. Thirty more patients with head and neck cancer were later recruited [31]. The median survival in this study was 7.5 months. In a study conducted in Finland, 79 patients with inoperable recurrent squamous cell carcinoma were treated with BNCT. Here, L-BPA-fructose was administered as the boron carrier. 68% of the treated patients showed some response, of whom 36% had a complete response to treatment. The overall survival was 21% in the Finnish clinical trial [16].

Another clinical trial was conducted at the Tsing-Hua Open Pool Reactor (THOR) at Tsing-Hua National University in Hsin-Chu. The BNCT study of head and neck cancer was conducted in 17 patients with recurrent cancers. An L-BPA complex with fructose was used as the boron agent. Two fractions of irradiation were applied at 28-day intervals. Nine patients had an improved quality of life, the side effects of therapy being low-grade oral mucositis. The overall 2-year survival rate was 47% [32].

Other types of cancers

Clinical trials of BNCT are also being conducted for other types of cancer.

For lung cancer, there has been one study on the treatment of shallow lung tumours with BNCT. Treatment has been proposed for unresectable, disseminated, and unresectable lung tumours. Suzuki *et al.* performed BNCT in 2 patients. The patients were treated with a F-BPA complex. After treatment, the tumours were stable or regressed after 6 months, without any acute or toxic symptoms [33].

There are several studies on the use of BNCT to treat breast cancer, especially the HER-2 (human epidermal growth factor receptor 2) subtype. For this treatment, trastuzumab-labelled immunoliposomes have been proposed as boron carriers [7]. Emerging data from the BNCT clinical trials show that this type of treatment, with BPA as a boron carrier, has the potential to be used to treat breast cancer with LAT-1 overexpression [34].

In the case of hepatocellular carcinoma, two studies on BNCT were carried out. In the first case, the patient suffered from Child-Pugh grade B cirrhosis. One month after BNCT treatment, the tumours remained stable, but disease progression occurred after 3.5 months [35]. In the second case, BNCT was performed in a 63-year-old patient with hepatocellular carcinoma. The boron carrier, BSH, was injected. The patient's condition was initially stable, although development of multiple nodules and metastasis to the lungs was later observed [36].

BNCT has also been used to treat osteosarcoma and has been shown to be safe and highly effective. In a study by Futamura *et al*., a 54-year-old woman was treated with BNCT for recurrent radiation-induced osteosarcoma. BPA was used as a boron agent. The only toxicity reported was alopecia [37]. High efficacy of BNCT treatment for clear cell sarcoma-type cancer was shown in animal models [38].

Another type of cancer that can be treated with BNCT is cutaneous melanoma. There are several clinical trials of BNCT for melanoma. Gonzalez *et al.* conducted a clinical trial of a group of 30 patients treated with BNCT. In this trial, they reported results from experiments carried out on a 54-year-old patient with cutaneous melanoma. After treatment of 25 skin nod-

ules in the patient, complete response 8 weeks after irradiation was achieved in 21 [39].

A more recent study of melanoma treatment was carried out at the Third Xiangya Hospital of Central University in China. The study included 22 patients with melanoma. The boron delivery agent was BPA-F. At 24 months after treatment, the pigment plaque in the affected cancer area was noticeably smaller in the case of all patients [40].

Conclusions

Boron Neutron Capture Therapy has potential as a highly promising cancer therapy modality. Results of clinical experiments to date, especially those recently reported, have shown the potential of BNCT in treating cancer cases that are difficult to manage using conventional therapy schemes of much higher complexity, with a higher propensity for various metastases. Furthermore, so far, full-scale development of BNCT has been hindered by the small number of patients currently receiving this therapy and by different procedures used at the few treatment facilities available. Nevertheless, as it matures by applying accelerator-based epithermal neutron beams, BNCT is becoming a promising and potentially successful treatment modality, possibly with reasonable safety and effectiveness in the treatment of patients with malignant or advanced tumours. Recent advances in computer technology are also helpful in the development of much faster Monte Carlo simulations of BNCT treatment situations. Moreover, BNCT may be effective not only in the treatment of cancer, but also in treating other conditions, such as Alzheimer's disease (proposed by the NECTAR project, cordis.europa.eu/project/id/964934).

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Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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