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RESEARCH ARTICLE

BORON NEUTRON CAPTURE THERAPY – REDEFINING RADIOTHERAPY

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ABSTRACT

Boron neutron capture therapy (BNCT) has been an uprising in the field of cancer therapy. It is based on the nuclear capture reaction and the fission reactions that occur when a non-radioactive element such as boron is bombarded with thermal neutrons. The primary concern in BNCT is the concentration of the boron compound within the tumor cells. More the concentration of boron compound within the tumor cells better is the action of BNCT. Thus, BNCT is considered to be a biologic mode of treatment rather than a targeted treatment modality. BNCT may be used as an adjunctive treatment or in combination with other modalities, including surgery, chemotherapy, and external beam radiation therapy, which, when used together, may result in an improvement in patient survival. This paper highlights on the principle of BNCT, its mechanism of action and its application in treatment of head and neck cancer.

INTRODUCTION

Dr. Lawrence in 1930s formulated a new form of radiation therapy for cancer's that is based upon the selective uptake of non-radioactive boron compounds. The boron compound is injected in the patient and when the required amount of boron reached the tumor site, the area could be irradiated with a neutron beam causing boron (^{10}B) to be transformed into ^{11}B, which would disintegrate releasing an α particle and 7Li, which have high linear energy transfer (LET), thus killing the cancer cells with almost no damage to the surrounding normal tissues. This idea was first applied by Dr. Swift at the MIT in Boston to patients with gliomas of the brain. (Mario A. Pisarev *et al.,* 2007)Boron neutron capture therapy (BNCT) is based on the nuclear capture and fission reactions that occur when ^{10}B, which is a non-radioactive constituent of natural elemental boron, is irradiated with low energy (0.025 eV) thermal neutrons. This results in the production of high linear energy transfer (LET) alpha particles (4He) and recoiling lithium-7 (7Li) nuclei. (Rolf F Barth *et al.,* 2012)

MATERIALS AND METHODS

Several relevant articles from 1991 to 2014 were electronically searched by typing 'neutron capture radiotherapy', 'Boron neutron capture radiotherapy', 'recent advancements in radiotherapy of oral cancer', etc. The searches were limited to articles in English to prepare a concise review on BNCT. Titles and abstracts were screened and articles that fulfilled the criteria of application of BNCT for head and neck cancer were selected for a full text reading.

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Mechanism of action

Non-radioactive boron compounds are injected systemically followed by neutron beam radiation to the tumor site. Boron neutron capture therapy (BNCT) is based on the nuclear reaction that occurs when ^{10}B is irradiated with low-energy thermal neutrons to yield high linear energy transfer alpha-particles and recoiling lithium-7 nuclei. Since these products have path lengths in water of 5–10 µm, the effect depends on the maintenance of relatively high concentrations of ^{10}B in the tumor compared with the surrounding normal tissue. Only tumor cells that incorporate ^{10}B are destroyed. (Rolf F Barth *et al.,* 2012) (Figure 1 and 2)There are three major factors in BNCT, (1) A non-radioactive boron compound, (2) Neutron Source and (3) Dose Calculating and Treatment Planning by using Monte Carlo

1. B^{10}compound

These are the types of tumor cell-finding boron 10-containing agent which are injected into the human body, which then accumulates in the tumor through blood transportation system within a period of time.

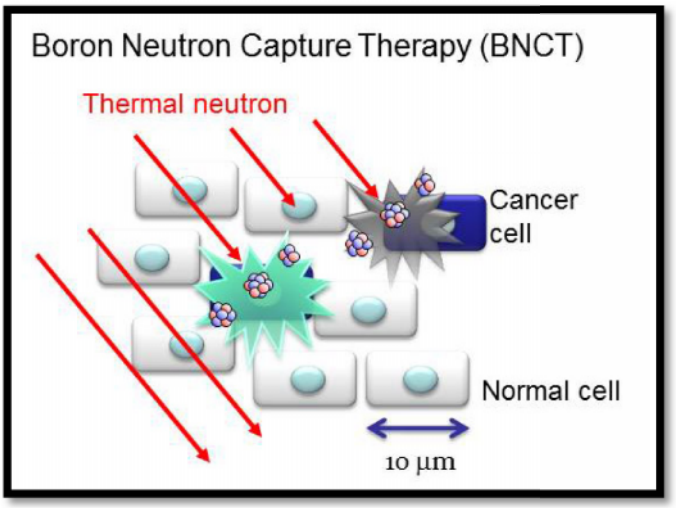

Figure 1. Principle of BNCT (Source: Kyoto University Research Reactor Institute)

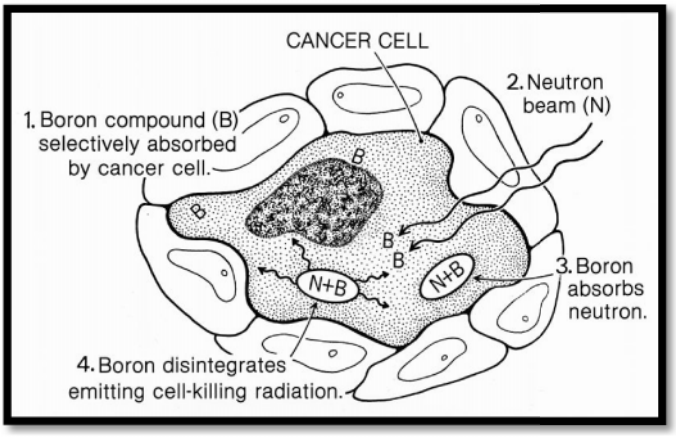

Figure 2. Illustration of BNCT intracellularly (Source: National Cancer Institute, image ID 2508)

Requirements for BNCT delivery agent: (Mario A. Pisarev *et al.*, 2007; Barth *et al.*, 2005; Soloway *et al.*, 1998)

a. Low toxicity and normal tissue uptake, with a tumor: normal tissue and tumor: blood (T:Bl) boron concentration ratios of ~3
b. Tumor boron concentration of ~20 µg 10B/g tumor
c. Relatively rapid clearance from blood and normal tissues, and persistence in tumor during neutron irradiations
d. Boron compounds should have no side effects
e. Boron compounds should remain in the tumor enough time to allow an appropriate time of irradiation
f. Chemical stability
g. Water solubility
h. Lipophilicity

Only two BNCT delivery agents currently used in clinical trials are sodium mercaptoundecahydro- closo-dodecaborate ($Na_2B_{12}H_{11}SH$), commonly known as sodium borocaptate (BSH), and the boroncontaining amino acid (L)-4-dihydroxy-borylphenylalanine, known as boronophenylalanine or BPA [10]. (Soloway *et al.*, 1998) BPA was infused at a dose of 500 mg/kg over 3 h at a rate of 200 mg/kg h for the first 2 h, and then at a rate of 100 mg/ kg h for the final hour during which time the patient received BNCT. (Rolf F Barth *et al.*, 2012)

Newer third-generation boron delivery agents comprise of cluster of stable boron that is attached to a tumor targeting agent such as monoclonal antibodies (mAb). For example, Epidermal Growth Factor Receptor (EGFR) in gliomas and head and neck cancer, also has been one such approach. (Olsson *et al.*, 1998)

2. Source for neutron beam

Neutrons that are derived from the neutron reactor can be classified based on their energies. If the energy of the neutrons is less than 0.5 eV, it is termed as thermal neutrons and if the energy of the neutron exceeds 10 keV it is termed as fast electrons. Similarly, if the energy level of the neutrons falls on the range of 0.5 eV to 10 keV it is termed as epithermal neutrons. In BNCT only thermal neutrons have the capacity to initiate the boron capture reaction. However, epithermal neutrons have been used clinically in BNCT, as it penetrates the tissue it loses its energy and is converted to thermal neutrons that initiates the further reaction. (Barth *et al.*,2005)

3. Dose Calculating and Treatment Planning by using Monte Carlo

Types of radiation delivered. The radiation doses delivered to tumor and normal tissues during BNCT are due to energy deposition from three types of directly ionizing radiation that differ in their LET characteristics: (Barth *et al.*, 2005)

(a) Low LET gamma rays, resulting primarily from the capture of thermal neutrons by normal tissue hydrogen atoms
(b) High LET protons, produced by the scattering of fast neutrons and from the capture of thermal neutrons by nitrogen atoms
(c) High LET, heavier-charged alpha particles (stripped-down 4He nuclei) and 7Li ions, released as products of the thermal neutron capture and fission reactions with boron compound.

These are then calculated using Monte Carlo's method – where in the neutron and the gamma fluxes are measured in a 5 to 10 mm resolution using MRI or CT. Thereafter, these fluxes are converted to doses using flux-to-kerma (kinetic energy released in matter) rate conversion factors. (Junjie Huang2009)

The large uptake by the tumor could be reflecting a more active metabolism. Mishima*et al.*(1997) showed with the use of 18-F labeled BPA a net incorporation rate for tumor 4 times higher than normal tissuesMishima*et al.*(1997).

DISCUSSION

It has been rightly quoted "BNCT is a biologically rather than physically targeted type of radiation treatment", as it destroys only the tumor cells that are dispersed in the normal tissue the potential exists to destroy tumor cells dispersed in the normal tissue. This is because of the concentration of the 10B

compound in the tumor cells and the thermal neutron beam targeting the specific area which helps to destroy the tumor cells in the tissue. (Barth *et al.,* 2005)

Treatment planning for NCT differs markedly from that of conventional radiotherapy and in some ways it is significantly more complex, requiring specialized software. (Zamenhof *et al.,* 1996; Palmer *et al.,* 2002; Nigg 2003; Kiger *et al.,* 2004) Relative biological effectiveness (RBE), which is the ratio of the absorbed dose of a reference source of radiation (e.g., Xrays) to that of the test radiation that produces the same biological effect. Because both tumor and surrounding normal tissues are present in the radiation field, there will be an unavoidable, nonspecific background dose, consisting of both high and low LET radiation even with an ideal epithermal neutron beam. However, a greater concentration of ^{10}B in the tumor will result in it receiving a higher total dose than that of adjacent normal tissues. This is the basis for the therapeutic gain in BNCT.(Barth *et al.*,2005)

There are a few merits of BNCT; firstly, distribution of high radiation dose only to the tumor cells while sparing the surrounding normal cells. This unique feature of BNCT makes it one of the primary modality of treatment in patients who have been treated to tolerance with photon irradiation. Second, it has the potential to more effectively target multicentric deposits of tumor than is possible with stereotactic radio surgery of primary and metastatic brain tumors. Third, although it may be only palliative, it can produce striking clinical responses, as evidenced by the experience of several groups treating patients with recurrent, therapeutically refractory head and neck cancer. (Rolf F Barth *et al.,* 2012) Thermal neutrons with energies of approximately 0.025eV are used in BNCT. They are well below the threshold of ionizing tissue components. (Zamenhof *et al.,* 1994)

thermal neutrons. Epithermal neutron (1 – 10,000eV) beams can deeply penetrate the tissue 3-6cm below the surface. (Soloway *et al.,* 1998) When an epithermal neutron enters a human body, it decelerates to a thermal neutron enabling easier boron neutron capture. In order to prevent the normal cells of patients from being irradiated by too much unwanted background radiation such as gamma rays and fast neutrons from the epithermal neutron beam port, patients must be irradiated with enough efficient doses and positioned as close to the beam port as possible within a period of time as short as possible. (Walker 1998)

Critical issues regarding BNCT: (Barth *et al.,* 2005)

First, there is a need for more selective and effective boron agents that, when used either alone or in combination. Furthermore, their delivery must be optimized to improve both tumor uptake and cellular micro-distribution, especially to different subpopulations of tumor cells. (Dahlstro *et al.,* 2004) Second, because the radiation dosimetry for BNCT is based on the micro distribution of ^{10}B, (Iwatsuki *et al.,* 1991 which is indeterminable on a real-time basis, methods are needed to provide semi-quantitative estimates of the boron content in the residual tumor. In the absence of real time tumor boron uptake data, the dosimetry for BNCT is very problematic. This is evident from the discordance of estimated doses of radiation delivered to the tumor and the therapeutic response, which should have been greater than that which was seen if the tumor dose estimates were correct. (Diaz 2003)Third BNCT has been totally dependent on nuclear reactors as neutron sources. These are a medically unfriendly environment and are located at sites at varying distances from tertiary care medical facilities, which has made it difficult to attract patients, and the highly specialized medical team that ideally should be involved in clinical BNCT.

Table: BNCT clinical trials using epithermal neutron beams for patients with recurrent or untreated unresectable head and neck cancer (Rolf F Barth *et al.,* 2012)

Author	Year	Type of Lesion	Partial Response	Complete Response
Kato *et al*	2001 – 2007	26 Recurrent Head and Neck cancer	39 %	46 %
Ariyoshi*et al*	2005 – 2008	6 Recurrent Oral Cancer	67 %	17 %
Kimura *et al*				
Suzuki *et al*	2001 – 2007	49 Recurrent Head and Neck cancer	29 %	28 %
Fuwa*et al*		13 Unresectable Head and Neck cancer		
Aihara*et al*	2003 – 2007	10 Recurrent Squamous Cell Carcinoma	35 %	55 %
		7 Recurrent Non-Squamous Cell Carcinoma		
		3 Non-Squamous Cell Carcinoma		
Fukutsuji*et al*	2005 – 2008	10 Head and Neck Malignant Melanoma	50 %	40 %
Kankaanranta*et al*	2003 – 2008	26 Recurrent Squamous Cell Carcinoma	31 %	45 %
		6 Recurrent Non-Squamous Cell Carcinoma		
Kankaanranta*et al*	2010	1 Poorly Differentiated Carcinoma	-	100 %
Wang *et al*	2010 - 2011	10 Recurrent Head and Neck cancer	40 %	30 %

However, thermal neutron beam cannot penetrate into deep tumors due to only 2.5cm penetration range of them within the tissue's surface. (Sweet *et al.,* 1960) Thus, thermal neutrons are suitable for superficial tumor treatments, such as BNCT treatment for melanoma which is a type of skin cancer. (Mishima *et al.,* 1989) However, substantial amount Japanese patients of malignant brain tumor have been treated with surgery of opening crania, followed by BNCT. In order to effectively treat the tumors deeply situated, epithermal neutrons have been used to treat these tumors instead of

Therefore, there is an urgent need for either very compact medical reactors.

Fourth, there is a need for randomized clinical trials. This is especially important because almost all major advances in clinical cancer therapy have come from these, and up until this time, no randomized trials of BNCT have been conducted. Finally, there are several promising leads that could be pursued. The up-front combination of BNCT with external beam radiation therapy or in combination with chemotherapy

has not been explored, although recently published experimental data suggest that there may be a significant gain if BNCT is combined with photon irradiation. (Barth *et al.*, 2004; Kato *et al.*, 2009) reported that they have treated a group of 26 patients (1 had a 4 salivary gland carcinomas, 3 had sarcomas, and 19 had squamous cell carcinomas) with BNCT since 2001. The whole group of patients had been treated by conventional therapy (chemotherapy, surgery and radiotherapy), and then developed recurrent tumors. During the trials, all of them were irradiated by epithermal neutron beams, and were injected with both BSH (doses: 5g) and BPA (doses: 250mg/kg). All patients survived 1-72 months after the treatments. The mean survival times were 13.6 months, with 6 patients having survival rate up to 6 years. The results indicated that BNCT had the potential to be applied to the tumors which recurred after the treatments of conventional therapies, such as head and neck recurrent cancers. (Kato *et al.*, 2009) Other studies of BNCT on Head and Neck cancer have been illustrated in the table. (Rolf F Barth *et al.*, 2012)

Conclusion

It is evident from this review that BNCT unites various branches of radiation biology to treat cancer. Recent developments of high-grade cancer in patients have been the driving force in the field of research towards BNCT. This evolving field of BNCT can be used as an adjunctive treatment modality or could even be combined with other forms of treatment such as surgery and chemotherapy. Clinical studies have shown the safety of BNCT. The challenge facing clinicians and researchers is how to get beyond the current impasse.

Conflict of Interest

None

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