

Selective cancer treatment by Boron Neutron Capture Therapy (BNCT) – a review

Chiragkumar J. Gohil^{1,*}, Malleshappa N. Noolvi²

¹M.Pharm (Pharmaceutical Chemistry) & Junior Researcher of G.T.U and University of kwazulu Natal-Durban, South Africa

²Ph.D, Fast Track Scientist and Principal of Shree Dhanvantary Pharmacy College, Kim, Surat, Gujarat, India

*Corresponding Author:

E-mail: gohil2711@gmail.com

ABSTRACT

Cancer is the biggest question-mark for the medical science. However many effective drugs are available for the cancer treatment, the biggest obstacle is the selective targeting the drug to the cancer cells. Boron Neutron Capture Therapy(BNCT) is a selective therapy of the cancer, it may not affect or affect little to the normal cells,

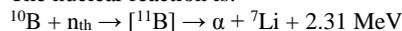
It works on 2 principles -

(1) Boron can capture the neutron & getting unstable.

(2) Subsequently nuclear fission of boron occurs via emitting radiation.

So, Delivered the required dose of boron to the cancerous cells and triggering it with the Neutron beam to this cancer cells which contain the boron, This neutron is capture by the neutron of cancer cells, getting unstable & subsequently nuclear fission is occur, this lethal radiation ultimately kills the cancer cells & normal cells are survive.

The nuclear reaction is:



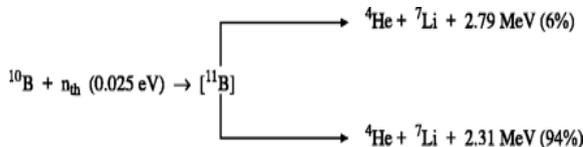
The future prospective are to limit the radiation to the cancer cells only & efficiently deliver the Boron to the cancer cell only, also evaluate the other radioactive materials like Gadolinium in place of Boron.

Keywords: Cancer, BNCT, Boron, Neutron, Nuclear Fission

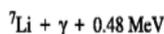
INTRODUCTION

Cancer is the second leading cause of death(42%) in the developed countries^[1]. Neutron capture therapy (NCT) is a non-invasive method for the treatment of the malignant tumors like primary brain tumor and recurrent head and neck cancer. It is a selective or near to selective treatment with compare to any other methods^[2].

In theory, boron neutron capture therapy (BNCT) selectively kills the cancerous cells and do not or little affect the normal cells. It works on the principle of the nuclear reaction, when the non-radioactive boron captures the neutron and getting unstable. In method, boron-10 (¹⁰B), which is a nonradioactive constituent of natural elemental boron, is irradiated with low-energy thermal neutrons to yield high linear energy transfer (LET) α particles (⁴He) and recoiling lithium-7 (⁷Li) nuclei:



↓



For the success of the method first of all we have to selectively deliver required dose of the boron to the cancerous cells and the enough thermal

neutrons must be absorbed by the boron, which is present in the cancerous cells. For the selective delivery of the boron we can use the antibody based selective drug delivery system or the any other selective drug delivery system^[3]. Because the high LET particles have limited path lengths in tissue (5-9 μm), the destructive effects of these high-energy particles is limited to boron containing cells.

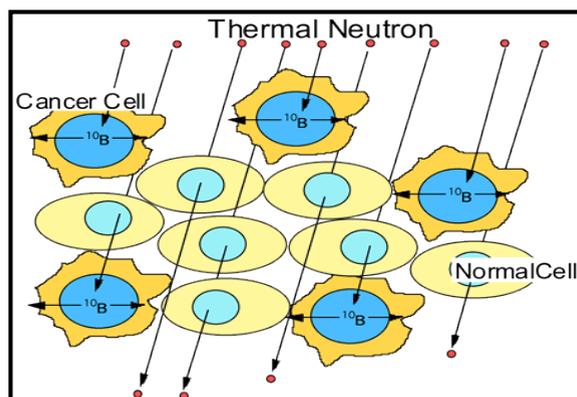


Figure 1: Effect of thermal neutrons and nuclear reaction in normal cells and Boron containing cancer cells

Since BNCT method requires the source of the neutrons it requires the nuclear reactor or it can be performed in the hospitals where the alternative source of neutrons is available. A beam of epithermal neutrons penetrates the brain tissue, reaching the

malignancy. Once there the epithermal neutrons slow down and these low-energy neutrons combine with boron-10 (delivered beforehand to the cancer cells by drugs or antibodies) to form boron-11, releasing lethal radiation (alpha particles and lithium ions) that can kill the tumor.

METHOD

The BNCT is the mainly 2 step process:

- 1) Boron compound is selectively absorbed by or delivered to the cancer cell(s).
- 2) Neutron beam is aimed at cancer site, Boron absorbs neutron & Boron disintegrates via emitting cancer-killing radiation.

Boron neutron capture therapy (BNCT) non-radioactive Boron-10 is used, Boron-10 shares the 20 % of the natural elemental boron. When we irradiate this boron with the neutron, these neutrons will go to captured by the boron, so it is getting the unstable and the nuclear fission will occur which produce the high energy alpha particles, which rupture/destroy the cancerous cells^[4].

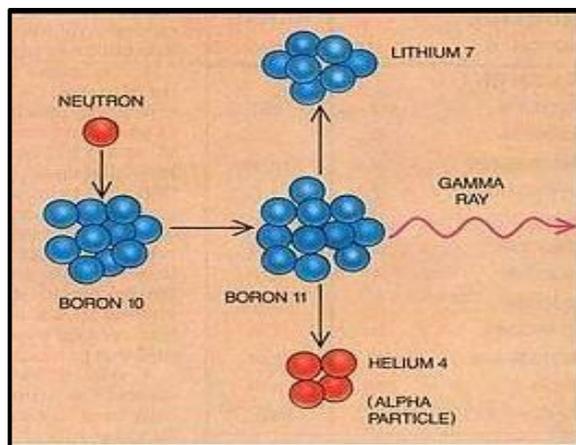


Figure2: Neutron capture by the boron and subsequent nuclear reaction and nuclear fission

Both the alpha particles and the lithium ions produce closely spaced ionizations in the immediate vicinity of the reaction, with a range of approximately 5–9 μm , or approximately the diameter of one cell. Their lethality is limited to boron containing cells.

BNCT, is both the physically and biologically targeted type of therapy, to selectively target the cancerous cells or tumor we have to selectively delivered the required dose of ^{10}B to the cancerous cells, we can also have the advantage of the natural tendency of the cancerous cell, cancerous cells have the tendency to absorbed more amount of material than normal cells^[1]. So normal cells doesn't contain the ^{10}B so they don't have the nuclear fission reaction, and if the normal cells absorbed the small amount of ^{10}B they will not affected by the minor

quantity of it and respective nuclear fission reaction^[6]. Normal tissue tolerance is determined by the nuclear capture reactions that occur with normal tissue hydrogen and nitrogen.

Clinically, Doses up to 60–70 Gy can be delivered to the tumor cells in one or two applications compared to 6–7 weeks for conventional external beam photon irradiation. However, the effectiveness of BNCT is dependent upon a relatively homogeneous distribution of ^{10}B within the tumor, and this is still one of the key stumbling blocks that have limited its success

Boron delivering agents:

In BNCT the major obstacle is to selectively delivered the Boron-10 to the tumor and achieve the required blood concentration of the boronated drug in the tumor cells. Because dose of radiation is based on concentration of Boron in blood. And it should have a minimum toxicity to the tissue. The list of Boron Delivering Agents are as below:-

Table 1: Details of the Boronated drugs

Sr. No	Boronated Drugs	Status about Clinical use
1	Boronophenylalanine ("BPA")	Clinically used
2	Dodecaborate cluster lipids and cholesterol derivatives	-
3	"GB10" ($\text{Na}_2\text{B}_{10}\text{H}_{10}$)	-
4	Cholesteryl ester mimics	-
5	Boronated DNA metallo-intercalators	-
6	Transferrin–polyethylene glycol (TF–PEG) liposomes	-
7	Unnatural amino acids	-
8	Dodecahyrido-closo-dodecaborate clusters	-
9	Sodium borocaptate ("BSH")	Clinically used
10	Carboranyl nucleosides	-
11	Carboranyl porphyrins	-
12	Boronated EGF and anti-EGFR mAbs	-
13	Boron-containing nanoparticles	-
14	Carboranyl porphrazines	-
15	Boronated cyclic peptides	-
16	Boron carbide particles	-

Neutron sources:

(1) Nuclear reactors

Reactor derived neutrons are classified according to their energies as:

- (a) Thermal ($E_n < 0.5 \text{ eV}$),
- (b) Epithermal ($0.5 \text{ eV} < E_n < 10 \text{ keV}$)
- (c) Fast ($E_n > 10 \text{ keV}$).

Nuclear fission reaction produces the Neutrons. From the total number of neutrons, 50 % of the neutrons are required to sustain the chain reaction and the remaining 50 % of the neutrons are available for the use in BNCT, In the BNCT, the thermal neutrons are most widely use to start up the neutron capture reaction^[7]. Thermal neutrons are proffered because they have limited depth of the penetration.

(2) Accelerators/neutron generator

Accelerators are also used as a source of epithermal neutrons. In the accelerator generator, Neutrons are produced by Bombarding the high energy protons on the heavy nuclei^[5].

APPLICATIONS

- Treatment of malignant brain tumors (gliomas)
- Head and neck cancer
- Malignant melanoma (skin cancer)
- Lung cancer
- Liver cancer

CONCLUSION

The future scope of BNCT is for those malignancies, for which effective treatment is not available yet, the main advantages of BNCT therapy is (1) It can selectively delivered the dose of radiation to the cancerous cells with much lower dose to the normal cells. (2) It has the potential to more effectively target multi-centric deposits of tumor than is possible with stereotactic radio-surgery of primary and metastatic brain tumors. (3) 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.

Critical issues that must be addressed include:- (1) Development of selective as well as effective boronated drugs and their delivery should be optimise. (2) Improvement of methods to determine the boron dose delivered to the residual tumor volume on both macroscopic and microscopic levels to enable more accurate tumor dose assessment. (3) Be prepared to compete with or complement new therapeutic approaches.

This review will cover radiobiological considerations on which BNCT is based, boron agents and optimization of their delivery, neutron sources, which at this time are exclusively nuclear reactors and critical issues that must be addressed if BNCT is to be successful.

ACKNOWLEDGMENTS

**Dear god, I wanna take a minute,
Not to ask for anything from you,**

**But simply to say thank you for all I have.
“To mom and the dad, for their love, their
humour, their ethics, their inspiration but also for
their genes”**

I would like to thank my parents Mr. Jagdishchandra N. Gohil and Mrs. Vanitaben J. Gohil for their love and support. The spirit of kindness and forgiveness that you deposited in me will be kept in my heart for all of my life.

I am eternally grateful for the support given to me from my sweet younger sister Jigna Gohil. My heartfelt thanks to my guide Dr. M.N.Noolvi, for his support over the course of my study, Many thanks for your guidance, patience, trust, and provision of unconditional freedom throughout my academic progress.

I am lucky to have an opportunity to carry out my research project at University of Kwazulu-Natal, Durban-South Africa during my study and it is solely because of Dr. M.N.Noolvi sir and his sincere effort.

I sincerely thank to all my colleagues and friends.

Mr.Chirag J. Gohil



REFERENCES

1. Gohil et al. “Synthesis of new Diaryl Derivatives Comprising Imidazothiadiazole Moiety as Potential Anticancer Agents” *International Journal of Pharmaceutical Chemistry and Analysis*, **2015**, 2, 84-96
2. Rolf F Barth et al. “Current Status of Boron Neutron Capture Therapy of High-Grade Gliomas and Recurrent Head and Neck Cancer” *Radiation Oncology*, **2012**, 7, 1-21. <http://www.ro-journal.com/content/7/1/146>
3. Teruyoshi Kageji et al. “Boron Neutron Capture Therapy (BNCT) for Newly-Diagnosed Glioblastoma: Comparison of Clinical Results obtained with BNCT and Conventional Treatment” *The Journal of Medical Investigation*, **2014**, 61, 254-263
4. Kei Nakai et al. “Boron Neutron Capture Therapy for Glioblastoma: A Phase-I/II Clinical Trial at JRR-4” *European Association of Neurooncology Magazine*, **2014**, 4, 116-123
5. Zarma S.F et al. “Implementing BNCT through the use of an Electron Accelerator” *Romanian Reports in Physics*, **2014**, 66, 182-191
6. G. Randers-Pehrson et al. “A Practical Target System for Accelerator-based BNCT which may Effectively Double the Dose Rate” *Med. Phys.*, **1998**, 25, 894-896
7. Heikki Joensuu et al. “Boron Neutron Capture Therapy of Brain Tumors: Clinical Trials at the Finnish Facility using Boron phenylalanine” *Journal of Neuro-Oncology*, **2003**, 62, 123-134