A Mini Review on Application of Boron Neutron Capture Therapy in Cancer Treatment

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Abstract. Nowadays, Cancer is undoubtedly a consequential and potentially life-threatening illness. In the U.S., Around 1.7 million people discerned with Cancer last year. The application of boron in cancer treatment is applicable as therapy known as Boron Neutron Capture Therapy (BNCT). It is an analeptic technique that depends on the nuclear capture and fission reaction that results in various particles such as Li, He nuclei with their kinetic energy and γ-radiation. These radiations kill the malignant cells in our body without damaging the normal tissue. Boron particles delivered selectively to only malignant cells by minimizing their concentration in normal cells.

In this article, The clinical trials, clinical investigation in Different countries with a different type of Cancer as Lung, Brain, Head/Neck, Hepatic and gastrointestinal. Various delivery methods of Boron agents in the tumor cells recently developed boron delivery agents, and different techniques of their dose distribution explain. In recent years, boron compounds were applied with porphyrin, copolymers, nanoparticles, other peptides, EGRF’s, and Liposomes to intensify their killer properties toward target cancer cells. BNCT is also effectively used for the medication of various kinds of Cancers explained. The purpose of this article is to indicate the intelligible way of BNCT(Reactor-Based) for the treatment of malignant cells.

Keywords: Malignant cell, Analeptic, Neutron capture therapy, Boron in cancer medication

1. INTRODUCTION

Boron Neutron Capture Therapy (BNCT) has an inventive form of radiotherapy that has the potential to treat various types of cancers. It depends upon the nuclear capture and fission reaction in which the boron’s stable isotope B-10 irradiated with the thermal neutron of low energy (0.002eV) [1] or epithermal neutron of high energy (10,000eV) Figure 1. The reaction results in the formation of boron B-11 isotope, which is unstable to give a high value of linear transfer energy (LET) of α-particles (4He) with recoiling lithium nuclei (Li+1) and γ-radiation. These radiations destruct the malignant cells selectively in our body that contains energetic and cytotoxic ions [2]. It liberates a high value of LET energy and the timid path length of α-radiation with a range of 4-10µm. The extensive amount of energy released in this reaction dispatch in a limited volume, approximately one cell diameter (0.01mm) [3]. So, these confine radiations only damaged the cells from which they arise without affecting those normal cells. The two main difficulties are recognized to carry out this therapy, the sufficient amount of boron atom (thousand) deposited in the cell and the balanced amount of neutron release per second (tens of millions) to target the tumor cell.

\[
^{10}B + ^1n \rightarrow ^{11}B
\]

\[
^{4}He + ^7Li +2.79 \text{ MeV (6%)}
\]

\[
^{4}He + ^7Li +0.48 \text{ MeV +2.31 MeV (94%)} \text{ (gamma rays)}
\]

Figure 1. Reaction of B-10 neutron to form Li and He nuclei [5]
Specifically, Boron utilizes as an anticancer agent in neutron capture therapy (NCT) due to its high nuclear cross-section value with a epithermal or thermal neutron, i.e., 3837 B (1B=10^{-24}cm^2) [4]. The term nuclear cross-section defines as the ability of atomic nuclei to interact with neutrons that depends upon the actual structure of the Nuclei. The following table shows the Nuclear cross-section value of different atoms concerning their abundance. The Boron atom proves the highest Barn value with sufficient presence in the earth’s crust.

Table 1. Different Elements' cross-section values concerning their abundance in our body [1][4]

| Serial No. | Element  | Abundance (%) | Nuclear cross section value (Barn) |
|------------|----------|---------------|-----------------------------------|
| 1.         | ^14N    | 99.6          | 1.8                               |
| 2.         | ^12C    | 98.9          | 3.4x10^{-3}                       |
| 3.         | ^16O    | 99.8          | 1.8x10^{-4}                       |
| 4.         | ^1H     | 99.8          | 0.33                              |
| 5.         | ^10B    | 99.8          | 3.8x10^{-3}                       |
| 6.         | ^32S    | 95.0          | 0.53                              |
| 7.         | ^4He    | 1.4x10^{-4}   | 5.3x10^{-3}                       |
| 8.         | ^157Gd  | 14.8          | 6.1x10^{-3}                       |

Table 1 also represents that Gd-157 is also suitable for nuclear capture reactions. But the application of Boron is wider than the Gd-157 isotope due to its less abundance. The main challenge is to achieve the desired effect of BNCT that is the delivery of the boron compound would be selectively within doomed cells and its concentration also adjust in our body. The study reported that the acceptance concentration of Boron (B-10) in malignant cells is 10µ to 30µ per gram tumor as it depends upon the position of B-10 mass in tumor cell structure [6]. It also depends on the location of boron nuclei for its drug dosage. If the isotope of B-10 Nuclei is bound to the cells' external membrane, a 30ppm concentration is required [5]. Otherwise, If B-10 nuclei located within the cells' cytoplasm having 10-12 ppm concentration requires only [7].

Around 60 years, BNCT was performed with the help of two delivery agents such as (BPA) boronophenylalanine or a boron-containing amino acid (L)- 4-dihydroxy-borylphenylalanine and BSH sodium mercaptoundecahydro-closododecaborate (Na$_5$B$_{12}$H$_{11}$SH) or sodium boronate. Here, BPA is generally used to treat high-grade gliomas patients in Figure 2, and BSH is applicable for a wide range of cancer such as cutaneous melanomas, 9L gliosarcoma, etc. In recent years, to enhance the versatility of BNCT, several delivery agents were introduced as boron derivatives, boron compound fusion with nanoparticles, peptide, amino acid, polymers, etc [8].

Besides this, several new plans are introduced for the future development of BNCT. The researcher investigated that phenylboronic acid (PBA) performed the dual function (i.e., targeting effect and also contain the capacity to capture neutron) and formed with the fusion of nanoparticle, polymer. Further, this supramolecular structure act as a sialic acid-targeting agent to treat the B16 melanoma [9].

![Figure 2. Main Boron delivery Agents][5]
Transition metal carboranes that are based on photosensitizer were internalized in the SKBR-3 cells. Mono-carborane-phenanthroline complexes show low toxicity under photodynamic conditions. Thus, these complexes can be used for BNCT as anti-cancer agents due to the high content of the boron atom. In this paper, recent development in the boron anti-cancer agents for BNCT are explained with their clinical trials and clinical investigation [10].

2. HISTORY

In 1954, This therapy was introduced to 40 patients by using a simple inorganic boron compound. But their result gives severe side effects to the treated patient, such as scalp’s radio dermatoses, cerebral oedema. The two boron compounds are introduced as BPA (p-boronophenylalanine) and BSH (di-sodium mercaptopentacalcohol-hydro-closo-dodecaborate) to remove these side effects. These two delivery agents are used to treat severe diseases by targeting the damaged cell with the nuclear reactor at BNL and MIT [10]. Malignant melanoma was treated by using BPA in Japan in 1987. There are a lot of clinical trials and clinical investigations performed for BNCT in Finland [11], Sweden [12], Argentina [13], Japan [14]. This technique attracted the Researchers as the epithermal neutron is targeted the dead cell effectively. This therapy comes to an end due to a lack of facilities and equipment in hospitals and research centers. The presence of only two delivery agents for clinical trials also led to a drawback for BNCT. Remarkable progress was seen in this field in recent years that gives rise to the BNCT’s future. A short detail represents in the following (Figure 2) throughout the history of BNCT [4], [7]

![Figure 3. Historical Presentation of BNCT](image)

3. CLINICAL TRAILS

The capability of BNCT enhances with Several clinical trials contains new drugs. Further, these drugs were approved by the authority of national regularity for treatment purposes after a three-phase clinical trial. The first one is too concerned with the toxicity of the drug combination. The next one is to evaluate the effectiveness of the BNCT treatment, its dosage rate, its anti-tumor effect [12], and the third one leads to evaluate the therapeutic effect of the BNCT treatment on a large number of patients. These clinical trials would be held in various areas such as Finland, Japan, Taiwan. Here, Boron therapy proves by treating the maximum number of patients in glioblastoma [15], brain [16] and Head/Neck Cancer [17], Recurrent glioblastoma multiforme (GBM) [18], Malignant meningioma [15]. The most important use is that the damaged capability of normal cells and its side effect on the other parts of the cell are less. It is explained in the given (Table 2.) the clinical trial for different diseases in various areas.

| S.No. | Place     | Disease (number of patients)                             | Delivery Agent | Result                                                                 | Reference |
|-------|-----------|---------------------------------------------------------|----------------|------------------------------------------------------------------------|-----------|
| 1.    | Finland   | Head and neck tumor : (inoperable’s 30 patients, SCC’S 24 patient, T4 ’s 14 patient) | $^{10}$F BPA   | Median progressive-free survival (PFS) was 7.5 months in 27% patient had no clue of HN cancer within 2 years | [11], [17]|
|       |           | Recurrent malignant glioma: (GBM): 22 patients          | BPA            | Median survival time (MST) is 7 months                                 | [11]      |
2. Japan Head and neck malignancies (HNM) : (26 patients) BPA, BSH Survival periods increase as MST (33.36 months), Overall survival (2 years) [14],[19] Newly diagnosed glioblastoma : (15 patients) BPA, BSH BNCT show positive result with mean and median survival rate of 20.7 and 15.6 months respectively [18] Malignant meningioma (19 patients) BPA-PET 18/19 patients shows positive result with survival period of 14.1 months. [14] 3. Taiwan Head and neck region : (10 patients) BPA-fructose MST of 11.3 months, it cure 3 patient fully, 3 partially anf other are in stable disease. [20]

4. CLINICAL INVESTIGATIONOF BNCT:
During medical research, Scientists were concern whether BNCT is promising for a different disease or not. Several investigations were performed to evaluate the versatility of BNCT. For this purpose, the Japanese medical framework performs BNCT for the treatment of different diseases. With their recent work, it has been found that BNCT exploits the medication of many types of cancer such as hepatic cancer [21], lung cancer [22], Recurrent gastrointestinal cancer [23]. In the clinical investigation of BNCT, it concludes that the treatment of a particular disease in BNCT required a specific technique and doses as described in (Figure 3)

4.1. Treatment for Hepatic Cancer:
For the recurrent hepatic cancer investigation, Yanagie synthesized a technique in which BSH (B-10 isotope) contains WOW (water-in-ni-in-water) emulsion. It is applicable to treat recurrent hepatic cancer as previously Epitubic that containing WOW emulsion in hepatic arteries chemotherapy for patient treatment[24]. Here, SERA is using as Treatment planning has an equivalent dose of 12.044 Gy for mean tumor, 19.0 Gy for maximum, and 5.044 Gy Doses for normal mucosa uses in 56 minutes irradiation. The result shows that BSH -WOW emulsion is applicable for an intraarterial boron carrier in recurrent hepatic cancer with no side effects [21].

4.2. Treatment for Gastrointestinal Cancer:
In gastrointestinal cancer, BPA can decrease the tumor size when a severe lymph node is observed. It gets a high accumulation of 10B with left metastasize. After, the surgery it regrew again. But, in this case, we use the 18F-BPA as a delivery agent, and SERA is used as treatment planning and represents a comparable dose of 20 Gy in more than 4:5 ratios of the tumor. Its highest Dose is delivered 5.6 Gy in the ordinary case. The result shows a high suppression in tumor growth after two months of BNCT treatment [15].

4.3. Treatment for Lung Cancer:
In 2006, the Research Team of the Kyoto University investigated all the viability of BNCT for doomed pleural mesothelioma. The results are in favor of BNCT without any side effects. The Neutron source energy proposed for the treatment of lung cancer in BNCT. The oncology Institute Roff (University of Buenos Aires) and the University of Pavia Collaborated with R. Farias from the commission Nacional de Energia Atomica. During BNCT, the Dose distribution in lung cancer treatment effected by the respiratory system [25]. The Change in tumor location affects the neutron flux distribution where the tumor locates. It may also affect the patient dose distribution in BNCT. In 2018, Lee et al. Verified the dose distribution result from the different amplitude of motion with tumor movement. The difference between the end-inhaled and ex-haled phases represents the mean tumor dose distribution difference of the virtual respiratory patient model. The radial direction of the neutron beam causes the dose change by tumor movement [26]. To solve this, researchers evaluated the technique, and LDL is also used as a
delivery agent. Throughout the respiratory cycle, the anatomy of a patient represents by six phases at different moments. The Monte-Carlo tool kit exploits to calculate the tumor-related dose-volume histogram (DVH) indices at different Phases. Under the treatment planning Configuration, the movement in the anterior-posterior (AP) direction caused the Dose to change intensively with the increase of respiratory motion amplitude. the dose difference ranges from -13.8% to 15.8% increased [27].

An innovative approach for lung cancer is that a low-Density Lipoprotein (LDL) as a carrier used to increase the selective update of tumor cells, and magnetic resonance imaging (MRI) could quantify the boron distribution.

![Diagram](image_url)

**Figure 4.** Clinical Investigation on Treatment of Cancer with Technique and Doses [21],[25],[12]

### 5. OTHER BORON DELIVERY AGENTS

Several new boron delivery agents have come to enhance this synthetic technique and raised several necessary biochemical properties. The main challenge to synthesize a new delivery agent is the specification of tumor cell killing and the process of delivering the drug with a minimum concentration in undoomed tissue [8]. For the synthesizes of the delivery agents, the boron compound undergoes fusion with nanoparticles, biomaterials (lipids, peptides, carborane, etc.). It contains three main parameters such as boron presence in the tumor should be 20-35 mg, the ratio of tumor to normal tissue should be more than 3 with less toxicity. The molecular weight should be at a particular range for the synthesis of new delivery agents because Glioma cells have a high infiltration capability. Thus, the blood-brain barrier (BBB) and their genomic heterogeneity are responsible for excluding the molecular weight agents greater than 200Da [28][29]. Tumor targeting moieties use to enhance the selectivity of boron delivery agents.

Many boron anti-cancer agents are currently under evaluation with lower and higher molecular weight. Boric acid, Boron containing immuno-liposomes, Boron containing Lipiodol, Boronated Co-polymers, Boron nitride nanotubes Boronated cyclic peptides, Boronated DNA intercalators, Boronated EGF/anti-EGFR monoclonal antibodies, Boronated polyamine, Boronated porphyrines, Boronated sugar, Boronated unnatural amino acid, Boronated containing thymidine, analogs Decacaborane (GB10). Dodecahydro-closo-dodecaborate clusters, linear and cyclic peptides, Transferrin-polyethylene glycol liposomes, and Polyamionic polymers are some examples of boron delivery agents [29].
5.1. **Boron containing amino acid**

Boron-containing unnatural amino acids have high metabolic stability as compared to natural ones. For example, (ABCHC)1-aminoacyclobutane-1-carboxylic acid, the 1-amino-3-boronoacyclo-pentane carboxylic acid (ABCPC) [30]. Dodecaboratethio-1-amino acid has been synthesized by S-alkylation from Bromo-1-α-amino acids and (S-cyanoethyl-10BSH, [10H12H11]2–SCH2CH2CN) S-cyanoethylthioundecahydro-closo-dodecaborate [31]. Boron-containing amino acids contain non-immunogenic properties, are easy to synthesize, are low Noxious, and have high tissue pervasive properties. The boron-containing peptides and linear conjugated bonds with boron captales have been studied. Phenylboronic acid-enhanced its functionalities, i.e., containing a capacity to capture a neutron toward itself and highly erect the activated BNCT drugs and kill the malignant cells within a particular range [32]

5.2. **Boron containing Thymidine**

3-Carboranyl thymidine analogs (3CTAs) are compounds of Boron-containing purines, Pyrimidine, thymidine. It uses for targeted thymidine kinase-1(TK1) especially. For example, N5-2OH represents the selective tumor uptake due to its low toxicity and high phosphorylation. (CED) Convection enhanced delivery which delivered the therapeutic agents to the brain directly and bypassing the Blood-brain barrier (BBB) completely [33]. Rats bearing RG2 gliomas treated by CED of N5-2OH show an effective result. In F98 glioma, N5-2OH is not promising as a boron delivery agent by producing a modest increase in MST [34].

5.3. **Boron containing porphyrin**

BOPP, Cu TCPH, and H2OCP are boron-containing porphyrins that investigate due to their low Noxious, natural empathy for tumors. Octa-anionic 5,10,15,20-tetra[3,5-(Nido-carboranymethyl)phenyl] porphyrin (H2OCP) accelerated within the cells to a greater extent than BSH/BPA, and the median survival time with H2OCP treated patients is greater than the untreated patients. They show similar characteristics as BPA and localize in macrophages rather than the tumor cells. β-carboranyl porphyrins show great potential in the treatment of BNCT because it contains (32-43%) boron content. It concluded that boron-containing porphyrin use as boron drug delivery agents by specifically localized the compound within the tumor cell rather than macrophages [35].

5.4. **Cell membrane penetrating peptide**

Amino acid Transporters are also proposed to kill the malignant cells as the cell membrane permits it to pass through the tissue. But the cell membrane doesn’t permit BSH to pass through the tissue. At the distinct location of Boron, the energy transfer simulated and showed a different mark between outside the cell and the inner nucleus [28]. This drawback of BSH in BNCT is deduced by using a cell
pervasive peptide system for transduction. Here, CPP (Cell membrane penetrating peptide) is a simple peptide contains various biological properties that transduces Biological active substance into cells or tissue by fusing with BSH. For example-8BSH fuse with 11R contains a dendritic lysine structure localized in the cell and shows as a killing agent to the doomed cell with neutron irradiation. Its effect is 100 times better than the high concentration dose of BSH. These results show its promise value for another stage trial of BNCT [7].

5.5. Boron containing Nanomaterials
In Biomedical sciences, Nanomaterials play a notable role in the medication of severe disease because the fusion of the nanoparticles with the organic or inorganic compound gives rise to explore innovative techniques. Here, Boron compounds get composed with the nanoparticles to form several delivery agents such as nanotubes, nanofibers, nanoparticles, Nanocapsules, etc. Several biological processes get influenced by the morphology of nanomaterials such as Cellular blood uptake, Blood circulation time, and the Biodistribution of drugs [36].

5.5.1. Boron nitride nanotubes: For the diagnostic purpose and drug delivery, Boron nitride (BN) shows a remarkable property such as a high value of thermal neutron capture cross-section of BN. It can be sufficient for interaction and absorption of B10 enriched atom with the thermal neutron. At Kyoto University, the Research reactor of Boron nitride was synthesized using an effective solvothermal method with the highest purity distorted electron cloud [57]. It forms by the distorted Boron nitride that forms the structural material becomes water dispersal and partial polar. Because of these properties, the formed nanosheets are less Noxious for the aggregation of Boron with cells in proper quantity for neutron irradiation and can easily replace the L-BPA. Effective anti-tumor neutron irradiation of 10B in 10BN is possible due to the high-water dispensability. 10BN can be used promisingly as a delivery agent for the medication of the doomed cell in BNCT [38]. The boron nitride nanotubes in which DSPE-PEG2000 are used to prepare BNNT’s in a suspended aqueous solution. It shows an anti-tumor effect against B16 melanoma cells, and the treated rate is three times higher than the BSH [39].

5.5.2. Liposomes: BNCT could make more effective with a greater concentration of Boron atoms in cancer cells. Boron-containing liposomes that have low bioavailability and poor tumor retention are used to enhance the efficiency of BNCT which also leads to the law of Therapeutic efficiency.
Polyborane has been synthesized from decaborane that is implanted in bare and pegylated liposomes. These liposomes contain a large amount of boron atom with a hydrophobic property and highly accumulated delivery agent. In the diameter range of 35–40 nm, these liposomes get Biologically distribution in the body after ejecting into tumor-bearing mice. A Certain condition is marked for the whole process as the tumor/boron ratio should be exceeding 5, and the concentration of boron in the tumor should be 30 μg/g of tissue. It has been found PEGylated liposomes having a diameter of 40nm were capable to achieve sufficient results without exchanging the 11B with 10B [40]. Incorporating active drugs of polymeric nanoparticles and PS offered the way to deliver drugs to the tumor selectivity due to its high permeability and retention effect. But during the blood circulation, the leakage of incorporative Drugs from the nanoparticles takes place to deduce this hydrophilic drug that loads in a large amount into phospholipid-based liposomes [29]. It improves bioavailability in the body and blood circulation based on selective tumor uptake. Folic acid enhances the functionalization of NPS. Water in oil strategy uses to create liposomes to increase the bioavailability of Boron. Folic acid is conjugated equally on two amino-functionalized PEG to produce the folate functionalized PEG polyethylene glycol [40], [41]. The water in oil emulsion-based liposomes containing poly (maleic anhydride-alt-1-octadecane) (PMAO) and PEG on the upper face. The Boron nanoparticles and the fluorescent dye cy5 near-IR region in the Core. The average diameter of these liposomes is about 100 to 120 nm, and the Zeta potential of liposomes -38.0 +1.5 mV are formed. Fluorescence microscopy monitored the cellular uptake for folic acid that is conjugated with the liposome’s capability. It also is noted that the aggregation of FA-conjugated liposomes was much more effective than non-effect conjugated liposomes in C6 brain tumor cells under the same conditions [42]. This boron delivery agent represents less toxicity and high stability under physiological conditions and the blood-brain
barrier. A significant concentration of intracellular Boron gets aggregated with the cancer cells. It contains four therapeutic benefits from BNCT that are confirmed by inductively coupled plasma mass spectroscopy (ICP-MS) [3].

5.5.3. **EGFR:** Some Special antibodies are used as a molecular target of EGFR/EGFRviii and EGF ligands due to their high specificity for the medication of F98 rat glioma. Monoclonal antibodies (MoABs) and L8A4 can identify their type in which it presents a class of tumor-targeting agents. In clinical research of Barth, Wu, Yang, and their coworkers propose that five dendritic generations use a heavily Boronated precision dendrimer. In this way, these are associates with using heterobifunctional agents to targeting the vehicles [43]. For example, EGFR chooses to target MoAbs, cetuximab, and EGFRviii targets MoAbs LSA4. These MoAbs give a promising result in F98EGFR glioma when these bioconjugates combine with BBA administration. But, the F98 wild-type tumor is ineffective as they can’t express the amplified EGRF [44]. Here the use of a combination of two drugs gives better results for the treatment of BNCT.

5.5.4. **Carbon nanotubes:** Carbon nanotubes are used in drug delivery due to their many pharmaceutical applications, highly developed cellular uptake, and large surface area, and they can also functionalize with other bioactive compounds. It shows effective results as a anti-cancer agent in BNCT. Due to its low toxicity and biocompatibility, Carbon nanotubes can also be used for treatment purposes in BNCT [45].

The specification for the delivery of CNT’s in targeted tumors is that Within 48 hours after administration, a hyper concentration of CNT’s compound 21.5 UG per gram tumor approached with high selectivity of greater than 3:1 of the tumor to blood ratio in patient body [45]. The result shows a better quality of water solubility and High retention in tumor tissue than normal tissue. By making a little associate of (SWCNT-C(CO)-O(CH2)2-O-[O(CH2)2]-metallaborane), a single world carbon nanotube functionalized with Cobalt polaroid and graphene-oxide-close-deca-carbonate non-hydrides [30]. When these single-walled carbon nanotubes (SWCNT’s) hybrid with dendrimer (SB12)4 contain the fluorescence of NIR-I/NIR-II [46]. That will prove boron clusters can be extensively usable in BNCT.

5.6. **Copolymers**

With the occurrence of Nanomaterials as a drug carrier, this technique faces a problem in penetrating the tissue within the cell membrane. Thus, to solve this problem Polymers, copolymers are used for the treatment process in BNCT. These copolymers help to penetrate the tissue deeply with homogeneous delivery of 10-B atom specifically. Based on the clinical uses of sodium Boro-captate (BSH), block copolymers conjugated with Boron cluster such as poly(ethylene-glycol)-b-poly(glutamine acid) copolymers[47]. The Boron cluster was synthesized to deliver into the tumor cell selectively without affecting the normal surrounding cells that also penetrate the tumor tissue. Higher cellular uptake and tumor accretion are biological functions. They were demonstrated by these PEGylated block copolymers Boron cluster (BSH) conjugate. These conjugates reached the intracellular space in the tumor due to the selective delivery with their superior intratumorally penetration. Block copolymers contain the Boron cluster has the potential to damage the tumor cell [48].
**Figure 6. Different Boron agent Conjugates Used in BNCT**

6. Conclusion

In this article, we have discussed the BNCT of Clinical trials for the treatment of therapeutic malignant cells in the human body. These Trials indicates positive results for Head/Neck and Brain tumor. The Clinical investigation shows promising outcomes for hepatic, Head/Neck, and Gastrointestinal Cancer through different techniques such as WOW emulsion, extra. That indicates that BNCT is applicable to attract the people of the Twenty Century for a reactor-based treatment. In this discussion, new types of Boron delivery agents give a clinical approach for the Evaluation. Other than simple boron compounds, Liposomes, Caron nanotubes are also introducing the best aspects for BNCT. In last, BNCT proves the best treatment therapy for various types of Cancers. But, the complication links with this process due to lack of equipment, the unreliability of neutron source accelerator. The future for the therapeutic agents of BNCT clear with a variety of boron compounds with sources of neutron-based accelerators.
References

[1] Allen D A and Beynon T D 1995. A design study for an accelerator-based epithermal neutron beam for BNCT Phys. Med. Biol. 40 807

[2] Moss R L 2014 Critical review, with an optimistic outlook, on Boron Neutron Capture Therapy (BNCT) Appl. Radiat. Isot. 88 2–11

[3] Perl J, Shin J, Schümann J, Faddegon B and Paganetti H 2012 TOPAS: An innovative proton Monte Carlo platform for research and clinical applications Med. Phys. 39 6818–37

[4] Soloway A H, Tjarks W, Barnum B A, Rong F G, Barth R F, Codogno I M and Wilson J G 1998 The Chemistry of Neutron Capture Therapy Chem. Rev. 98 2389-2390.

[5] Wittig A, Michel J, Moss R L, Stecher-Rasmussen F, Arlinghaus H F, Bendel P, Mauri P L, Altieri S, Hilger R, Salvadori P A, Menichetti L, Zamenhof R and Sauerwein W A G 2008 Boron analysis and boron imaging in biological materials for Boron Neutron Capture Therapy (BNCT) Crit. Rev. Oncol. Hematol. 68 66–90

[6] Barth R F, Mi P and Yang W 2018 Boron delivery agents for neutron capture therapy of cancer Cancer Commun. 1–15

[7] Roesch S, Fermi V, Rominger F, Herold-Mende C and Romero-Cortés I 2020 Correction: Gold (I) complexes based on six-membered phosphorus heterocycles as bio-active molecules against brain cancer Chem. Comm. 5615088-15088.

[8] Hawthorne M F and Lee M W 2003 A critical assessment of boron target compounds for boron neutron capture therapy J. Neurooncol. 62 33–45

[9] Kaur M, Singh P, Singh K, Gaharwar U S, Meena R, Kumar M, Nakagawa F, Wu S, Suzuki M, Nakamura H and Kumar A 2020 Boron nitride (10BN) a prospective material for treatment of cancer by boron neutron capture therapy (BNCT) Mater. Lett. 259 126832

[10] Conway-Kenny R, Ferrer-Ugalde A, Careta O, Cui X, Zhao J, Nogués C, Núñez R, Cabrera-González J and Draper S M 2017 Ru (ii ) and Ir( iii ) phenanthroline-based photosensitisers bearing o-carborane: PDT agents with boron carriers for potential BNCT Biomater. Sci. 9 5691–702

[11] Savolainen S, Kortesniemi M, Timonen M, Reijonen V, Kuusela L, Uusi-Simola J, Salli E, Koivunoro H, Seppälä T, Lönnroth N, Välimäki P, Hyvönen H, Kotiluoto P, Serén T, Kuronen A, Heikkinen S, Kosunen A and Auterinen I 2013 Boron neutron capture therapy (BNCT) in Finland: Technological and physical prospects after 20 years of experiences Phys. Medica 29 233–48

[12] Capala J, Stenstrom B H, Sköld K, Rosenschöld P M, Giusti V, Persson C, Wallin E, Brun A, Franzen L, Carlsson J, Salford L, Céberg C, Persson B, Pellettiere L and Henriksson R 2003 Boron neutron capture therapy for glioblastoma multiforme: Clinical studies in Sweden J. Neurooncol. 62 135–44

[13] González S J, Bonomi M R, Santa Cruz G A S, Meena R, Kumar M, Nakamura H and Kumada H 2003 Assessment of the results from the phase I/II boron neutron capture therapy trials at the Brookhaven National Laboratory from a clinician’s point of view J. Neurooncol. 62 101–9

[14] Nakagawa Y, I K P, Kobayashi T, Kageji T, Uyama S, Matsumura A and Kumada H 2003 Clinical review of the Japanese experience with boron neutron capture therapy and a proposed strategy using epithermal neutron beams J. Neurooncol. 62 87–99

[15] Kawabata S, Miyatake S, Kuroiwa T, Yokoyama K, Doi A, Iida K, Miyata S, Nonoguchi N, Michiue H, Takahashi M, Inomata T, Imahori Y, Kitahata M, Sakurai Y, Maruhashi A, Kumada H and Ono K. 2009 Boron Neutron Capture Therapy for Newly Diagnosed Glioblastoma J. Radiat. Res. 50 51–60

[16] Diaz A Z 2003 Assessment of the results from the phase I/II boron neutron capture therapy trials at the Brookhaven National Laboratory from a clinician’s point of view J. Neurooncol. 62 101–9

[17] Kankaanranta L, Seppälä T, Koivunoro H, Saariluhtik K, Atula T, Collan J, Salli E, Kortesniemi, M. Uusi-Simola J, Välimäki P and Mäkitie A 2012. Boron neutron capture therapy in the treatment of locally recurrent head-and-neck cancer: final analysis of a phase I/II trial Int. J.
Vos M J, Turovski B, Zanella F E, Paquets P, Siefert A, Hideghéty K, Haselsberger K, Grochulla F, Postma T J, Wittig A, Heimans J J, Slotman B J, Vandertop W P and Sauerwein W 2005 Radiologic findings in patients treated with boron neutron capture therapy for glioblastoma multiforme within EORTC trial 11961 Int. J. Radiat. Oncol. Biol. Phys. 61 392–9

Leonetti E, Ricciardi W, Cadoni G, Arzani D, Petrelli L, Paludetti G, Brennan P, Luce D, Stucker J, Matsuo K, Talamini R, La Vecchia C, Olshan A F, Winn D M, Herrero R, Franceschi S, Castellsague X, Muscat J, Morgenstern H, Zhang Z F, Levi F, Dal Maso L, Kelsey K, McClean M, Vaughan T L, Lazarus P, Purdie M P, Hayes R B, Chen C, Schwartz S M, Shangina O, Koifman S, Ahrens W, Mates E, Lagiou P, Lissowska J, Szeszenia-Dabrowska N, Fernandez L, Menezes A, Agudo A, Daudt A W, Richiardi L, Kjaerheim K, Mates D, Betka J, Yu G P, Schantz S, Simonato L, Brenner H, Conway D I, Macfarlane T V., Thomson P, Fabianova E, Znaor A, Rudnai P, Healy C, Boffetta P, Chuang S C, Lee Y C, Hashibe M and Boccia S 2014 Adult height and head and neck cancer: A pooled analysis within the INHANCE Consortium Head Neck 36 1391

Barth R F, Vicente M G H, Harling O K, Iii W S K, Riley K J, Binns P J and Wagner F M 2012 Current status of boron neutron capture therapy of high grade gliomas and recurrent head and neck cancer Radiat. Oncol. 7 1–21

Yanagie H, Higashi S, Seguchi K, Ikushima I, Fujihara M, Nonaka Y, Oyama K, Maruyama S, Hatae R, Suzuki M, Masunaga S ichiro, Kinashi T, Sakurai Y, Tanaka H, Kondo N, Narabayashi M, Kajiyama T, Maruhashi A, Ono K, Nakajima J, Ono M, Takahashi H and Eriguchi M 2014 Pilot clinical study of boron neutron capture therapy for recurrent hepatic cancer involving the intra-arterial injection of a 10BSH-containing WOW emulsion Appl. Radiat. Isot. 88 32–7

Suzuki M, Suzuki O, Sakurai Y, Tanaka H, Kondo N, Kinashi Y, Masunaga S, Maruhashi A and Ono K 2012 Reirradiation for locally recurrent lung cancer in the chest wall with boron neutron capture therapy (BNCT) Int. Cancer Conf. J. 1 235–8

Farhood B, Samadian H, Ghiorbani M, Zakariaee S S and Knap C 2018 Physical, dosimetric and clinical aspects and delivery systems in neutron capture therapy Reports Pract. Oncol. Radiatother. 23 462–73

Ikushima I, Higashi S, Ishii A, Seguchi K, Iryo Y and Yamashita Y 2012 Ultraslective transcatheter infusion of epirubicin in water-in-oil- in-water emulsion for small hepatocellular carcinoma Brit. J. Radiol. 85 584-89.

Erridge S C, Seppenwoolde Y, Muller S H, Van Herk M, De Jaeger K, Belderbojs J S A, Boersma L J and Lebesque J V. 2003 Portal imaging to assess set-up errors, tumor motion and tumor shrinkage during conformal radiotherapy of non-small cell lung cancer Radiother. Oncol. 66 75–85

George R, Vedam S S, Chung T D, Ramakrishnan V and Keall P J 2005 The application of the sinusoidal model to lung cancer patient respiratory motion Med. Phys. 32 2850–61

Wu S, Geng C, Tang X, Bortolussi S, Han Y, Shu D, Gong C, Zhang X and Tian F 2020 Dosimetric impact of respiratory motion during boron neutron capture therapy for lung cancer Radiat. Phys. Chem. 168 108527

Miyabe J, Ohgaki R, Saito K, Wei L, Quan L, Jin C, Liu X, Okuda S, Nagamori S, Ohki H, Yoshino K, Inohara H and Kanai Y 2019 Boron delivery for boron neutron capture therapy targeting a cancer-upregulated oligopeptide transporter J. Pharmacol. Sci. 139 215–22

Thirumamagal B T S, Zhao X B, Bandypopadyaya A K, Narayanasamy S, Johnsamuel J, Tiwari R, Golightly D W, Patel V, Jehning B T, Backer M V., Barth R F, Lee R J, Backer J M and Tjarks W 2006 Receptor-targeted liposomal delivery of boron-containing cholesterol mimics for Boron Neutron Capture Therapy (BNCT) Bioconjug. Chem. 17 1141–50

Fatamuru G, Kawahata S, Nonoguchi N, Hiramatsu R, Toho T, Tanaka H, Masunaga S I, Hattori Y, Kirihata M, Ono K, Kuroiwa T and Miyatake S I 2017 Evaluation of a novel sodium borocaptate-containing unnatural amino acid as a boron delivery agent for neutron capture therapy of the P98 rat glioma Radiat. Oncol. 12 1–11

Kusaka S, Hattori Y, Uehara K, Asano T, Tanimori S and Kirihata M 2011 Synthesis of optically active dodecaborate-containing l-amino acids for BNCT Appl. Radiat. Isot. 69 1768–70
[32] Kim A, Suzuki M, Matsumoto Y, Fukumitsu N and Nagasaki Y 2021 Non-isotope enriched phenylboronic acid-decorated dual-functional nano-assemblies for an actively targeting BNCT drug Biomaterials 268 120551

[33] Al-Madhoun A S, Johanssone J, Barth R F, Tjarks W and Eriksson S 2004 Evaluation of human thymidine kinase 1 substrates as new candidates for boron neutron capture therapy Cancer Res. 64 6280–6

[34] Barth R F, Yang W, Wu G, Swindall M, Byun Y, Narayanasamy S, Tjarks W, Tordoff K, Moeschberger M L, Eriksson S, Binns P J and Riley K J 2008 Thymidine kinase 1 as a molecular target for boron neutron capture therapy of brain tumors Proc. Natl. Acad. Sci. U. S. A. 105 17493–7

[35] Hiramatsu R, Kawabata S, Miyatake S I, Kuroiwa T, Easson M W and Vicente M G H 2011 Application of a novel boronated porphyrin (H2OCP) as a dual sensitizer for both PDT and BNCT Lasers Surg. Med. 43 52–8

[36] Zhu Y and Hosmane N S 2018 Nanostructured boron compounds for cancer therapy Pure Appl. Chem. 90 653–63

[37] Datcu A and Ciobanu D 2020 Boron Nanoparticles Characterization 23 257–64

[38] Li L, Dai K, Li J, Shi Y, Zhang Z, Liu T, Jun Xie, Ruiping Zhang and Liu Z 2021 A Boron–10 nitride nanosheet for combinational boron neutron capture therapy and chemotherapy of tumor Biomaterials 268 120587

[39] Ferreira T H, Miranda M C, Rocha Z, Leal A S, Gomes D A and Sousa E M B 2017 An assessment of the potential use of BNNTs for boron neutron capture therapy Nanomaterials 7 1–11

[40] Takeuchi I, Ishizuka Y, Uchiho H and Makino K 2017 Detailed biodistribution of liposomes prepared with polyborane instead of cholesterol for BNCT: effects of PEGylation Colloid Polym. Sci. 295 1455–61

[41] Ueno M, Ban H S, Nakai K, Inomata R, Kaneda Y, Matsumura A and Nakamura H 2010 Dodecaborate lipid liposomes as new vehicles for boron delivery system of neutron capture therapy Bioorganic Med. Chem. 18 3059–65

[42] Singh A, Kim B K, Mackeyev Y, Rohani P, Mahajan S D, Swihart M T, Krishnan S and Prasad P N 2019 Boron nanoparticle-loaded folic-acid-functionalized liposomes to achieve optimum boron concentration for boron neutron capture therapy of cancer J. Biomed. Nanotechnol. 16 1714–23

[43] Yang W, Wu G, Barth R F, Swindall M R, Bandyopadhyaya A K, Tjarks W, Tordoff K, Moeschberger M, Sferra T J, Binns P J, Riley K J, Ciesielski M J, Fenstermaker R A and Wikstrand C J 2008 Molecular targeting and treatment of composite EGFR and EGFRvIII-positive gliomas using boronated monoclonal antibodies Clin. Cancer Res. 14 883–91

[44] Yang W, Barth R F, Wu G, Tjarks W, Binns P and Riley K 2009 Boron neutron capture therapy of EGFR or EGFRvIII positive gliomas using either boronated monoclonal antibodies or epidermal growth factor as molecular targeting agents Appl. Radiat. Isot. 67 328–31

[45] Bianco A, Kostarelos K and Prato M 2008 Opportunities and challenges of carbon-based nanomaterials Expert Opin Drug Deliv. 5 331–42

[46] Yamagami M, Tajima T, Ishimoto K, Miyake H, Michiue H and Takaguchi Y 2018 Physical modification of carbon nanotubes with a dendrimer bearing terminal mercaptopendecahydrododecaborates (Na2B12H11S) Heteroat. Chem. 29 1–7

[47] Mi P, Yanagie H, Dewi N, Yen H C, Liu X, Suzuki M, Sakurai Y, Ono K, Takahashi H, Cabral H, Kataoka K and Nishiyama N 2017 Block copolymer-boron cluster conjugate for effective boron neutron capture therapy of solid tumors J. Control. Release 254 1–9

[48] Yoneoka S, Park K C, Nakagawa Y, Ebara M and Tsukahara T 2018 Synthesis and evaluation of thermoresponsive boron-containing poly(N-isopropylacrylamide) diblock copolymers for self-assembling nanomiscellar boron carriers Polymers (Basel). 11