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Boron Neutron Capture Therapy

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BORON NEUTRON CAPTURE THERAPY

STATEMENT OF OBJECTIVES

The purpose of this continuing education lesson is to present the concept of Boron Neutron Capture Therapy and the potential role of this modality in Radiation Oncology. Aspects including mechanism, development, neutron production, boron delivery, and clinical outcomes will be discussed.

Upon completion of this continuing education lesson, the reader should be able to:

1. discuss the historical perspectives of boron neutron capture therapy (BNCT).
2. describe the concept and rationale of BNCT.
3. compare the various boron delivery agents under development.
4. compare different methods of neutron production for clinical use.
5. discuss the considerations of Relative Biological Effectiveness (RBE) in treatment planning.
6. explain the potential clinical role of BNCT.
7. discuss the results of clinical trials utilizing BNCT.
8. describe the potential side effects of neutron therapy.
9. explain how the pharmacokinetics of the various boron compounds affect the dosage, drug delivery and timing of neutron therapy.
10. discuss possible future roles for BNCT.
INTRODUCTION

In 1997, estimates predict that about 560,000 Americans will die of cancer - more than 1,500 people per day. Brain tumors in both adults and children are a relatively common form of cancer. In adults, there are approximately 17,000 new primary brain tumors diagnosed each year in the United States (a prevalence of 14.7 per 100,000 people), more than Hodgkin’s disease and almost as many as ovarian cancer (Table 1). If one includes metastatic brain tumors, the numbers swell to an estimated 100,000 patients per year with symptomatic brain tumors. In children, brain tumors are the second most common malignancy and are about as frequent as acute lymphoblastic leukemia.

Over the past decade there have been very few advances in the treatment of malignant cerebral gliomas, whose incidence in the United States is about four to six new cases per 100,000 inhabitants per year. The inability of cancer treatment modalities (chemotherapy, radiation therapy, surgery, and immunotherapy) to destroy malignant cells while minimizing adverse effects on normal tissue has been the limiting factor. As a result, the median survival time is less than 12 months. The overall prognosis for a patient suffering from glioblastoma multiforme (GBM) remains dismal. Boron neutron capture therapy (BNCT) represents a promising alternative for selective radiation therapy of such tumors and is being developed as a treatment for malignant melanoma and GBM.

TYPES OF BRAIN TUMORS

When discussing tumors of the brain, it is important to consider both the tissues that give origin and their particular environment within the brain. Neurons are the most common cells in the brain, but they have no significant capability for reproducing. Thus, they have little potential for the neoplastic changes that result in a tumor, and primary neuronal tumors are quite rare. The supporting cells of the brain, glial cells, are numerous and fulfill many structural and metabolic functions. The glial cells give rise to a variety of tumors, each dependent on the type of cell of origin, and each capable of behaving in
Table 1.
Estimated New Cancer Cases by Sex, United States, 1997*

<table>
<thead>
<tr>
<th>Primary Site</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Sites</td>
<td>785,800</td>
<td>596,000</td>
</tr>
<tr>
<td>Oral Cavity &amp; Pharynx</td>
<td>20,900</td>
<td>9,850</td>
</tr>
<tr>
<td>Digestive System</td>
<td>120,000</td>
<td>105,900</td>
</tr>
<tr>
<td>Respiratory System</td>
<td>111,400</td>
<td>83,200</td>
</tr>
<tr>
<td>Bones &amp; Joints</td>
<td>1,300</td>
<td>1,200</td>
</tr>
<tr>
<td>Soft Tissue (including Heart)</td>
<td>3,700</td>
<td>2,900</td>
</tr>
<tr>
<td>Breast</td>
<td>1,400</td>
<td>180,200</td>
</tr>
<tr>
<td>Genital System</td>
<td>343,000</td>
<td>81,800</td>
</tr>
<tr>
<td>Brain &amp; other CNS</td>
<td>10,100</td>
<td>7,500</td>
</tr>
<tr>
<td>Endocrine</td>
<td>5,530</td>
<td>12,030</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>34,200</td>
<td>26,900</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>7,900</td>
<td>5,900</td>
</tr>
<tr>
<td>Leukemia</td>
<td>15,900</td>
<td>12,400</td>
</tr>
<tr>
<td>Other &amp; Unspecified</td>
<td>16,500</td>
<td>19,000</td>
</tr>
</tbody>
</table>

* Excludes basal and squamous cell skin cancers and in situ carcinomas as well.

a benign or malignant fashion. Of all primary brain tumors, approximately 65% are gliomas (Table 2), which includes anaplastic astrocytomas and GBM. The overall incidence of GBM in the United States has been estimated to be approximately 7,000 new cases per year. Only a small number of these patients die for unrelated reasons, and about 90% of the deaths are directly related to the tumor. To date, the recovery rate for GBM is 0%. Surgery alone gives a median survival of 14 weeks; the addition of radiotherapy brings this figure to 36 weeks, and radiotherapy combined with
Table 2.

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Percent of Cases</th>
<th>Mean Age at Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glioblastoma</td>
<td>40</td>
<td>54</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>16</td>
<td>37</td>
</tr>
<tr>
<td>Meningioma</td>
<td>18</td>
<td>55</td>
</tr>
<tr>
<td>Schwannoma</td>
<td>2</td>
<td>57</td>
</tr>
<tr>
<td>Pituitary Adenoma</td>
<td>12</td>
<td>39</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>2</td>
<td>46</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>-</td>
</tr>
</tbody>
</table>

Chemotherapy increases it to only 51 weeks.

The treatment of GBM is problematic. Following pathological diagnosis, most patients undergo a surgical "debulking" followed by radiation therapy. Despite technical advances, a successful surgical approach is improbable in cases with diffuse and infiltrating growth of the tumor. Furthermore, conventional radiation therapy is limited by the dose that can be delivered to a tumor due to the intolerance of the surrounding normal tissue within the treatment zone. Chemotherapy has been shown to be ineffective in limiting tumor growth or in prolonging remission due to an inability to penetrate the blood-brain barrier and inherent toxicity to normal tissue. In addition, most gliomas have or acquire a drug resistant phenotype to chemotherapeutic regimens during the course of the disease.

Current research efforts to provide a more directed lethal event to malignant cells has included such modalities as high-linear energy transfer (LET) particle therapy, radiation sensitizers, radiation protectants, fast neutrons, interstitial brachytherapy, modified fractionation radiotherapy schedules, monoclonal antibody-mediated radionuclides, three-dimensional conformal therapy, and stereotactic radiosurgery. Additionally, to overcome the poor penetration of chemotherapeutic agents for brain tumors, a biodegradable wafer containing 7.7 mg of carmustine has been recently approved for patient use in the United States. The wafers are implanted into the brain during tumor resection to destroy residual brain tumor tissue. The reported median survival increased from 20 weeks with a placebo to 28 weeks with the carmustine wafers in patients treated for GBM. However, most of these therapeutic regimens employ a single mode of therapy which results in decreased effectiveness in
elimination of the cancer cells while attempting to minimize the side effects on normal tissue. The ability to combine two different modalities, which independently cannot effectively or selectively destroy malignant cells, but when combined as a bimodal therapy are capable of delivering a lethal event specifically localized in malignant tissue, is of great interest. Such a binary treatment system for the eradication of malignancy may provide the selectivity of malignant cells while at the same time sparing normal tissue through the ability to manipulate either modality separately.

**Fundamentals of BNCT**

Boron neutron capture therapy is based on the nuclear reaction that occurs when a stable non-radioactive nuclide, $^{10}$B, is irradiated with low energy (0.025 eV) or thermal neutrons ($n_{th}$). The reaction yields intensively ionizing particles with high LET radiation, $^4$He (α particles) and recoiling $^7$Li nuclei (Figure 1). The $^7$Li atom and the stripped $^4$He atom (α-particle) have a maximum range in tissue of approximately 5 and 9 μm, respectively. Thus, in 93.7% of disintegrations, a total energy of 2.31 MeV is deposited within the range of one cell diameter (<10 μm). The nuclear fragments thus produced are highly cytotoxic, slow moving in tissues, and are closely spaced high LET ionizing events. To cause malignant cell death, the reaction requires that only a few of the 1.78 MeV α-particles produced actually dispense their average LET energy within the cell. As a result, the cells that have bound or taken up the $^{10}$B agent are preferentially destroyed.

**History of BNCT**

Neutron capture therapy was first recognized as a potential cancer treatment by Dr. Gordon Locher in 1936 just four years after the discovery of the neutron. Laboratory investigations during the 1940s by Conger at Oak Ridge National Laboratory confirmed at the cellular level the lethality of the neutron capture therapy reaction. Following initial experiments of boron compound localization by Sweet at Massachusetts General Hospital, the first clinical trial with BNCT was started in 1951 at Brookhaven National Laboratory with ten patients. From 1959 to 1961 an additional 18 patients were treated by Sweet's group using the Massachusetts Institute of Technology Reactor. Poor results were obtained during these clinical trials and the research treatment was discontinued in 1961. These clinical trials were unsuccessful for a variety of reasons including poor tumor selectivity of the boron compound, poor penetration of the neutron beam, and the lack of control of cerebral edema.

Subsequent to the failure of these clinical trials, there was renewed interest in BNCT due to a period of boron compound development highlighted by the synthesis of sodium borocaptate ($\text{Na}_2\text{B}_{12}\text{H}_{11}\text{SH}$) also know as BSH (Figure 2a) in the mid-1960s by Soloway and Hatanaka. Hiroshi Hatanaka, from Japan, had joined Sweet's research group where he became actively involved with Soloway on the evaluation of BSH. Sodium borocaptate demonstrated high tumor-to-brain and tumor-to-blood ratios following administration to tumor bearing mice.

Upon his return to Japan in 1968, Hatanaka began clinical tests using a combination of surgery and BNCT with borocaptate as the capture agent on patients with high grade gliomas. Between the years of 1969 and 1993, Hatanaka had treated approximately 120 patients, a significant subset of which had glioblastomas. The median life expectancy of patients having this type of tumor under conventional therapy is less than one year.
More than 100 patients with grade III-IV gliomas were treated with BNCT and the mean survival time was significantly improved. There were several long term survivors of periods ranging from 5 to 15 years with a trend towards increased survival in patients having more superficially located tumors. These encouraging results have revived the world's interest in BNCT despite the criticism of many clinicians based on the past clinical failures in the United States. Several patients with glioblastoma multiforme have been treated in the United States since September 1994.

Figure 2. Clinically used compounds in BNCT: (a) borocaptate sodium (BSH) and (b) p-boronophenylalanine (BPA).

**STRATEGIC DELIVERY OF BORON TO TUMORS**

Boron-10 constitutes about 20% of naturally occurring boron. Employing 10B-enriched compounds for BNCT is advantageous because 10B has a high cross-section for neutron capture (3838 barns, where 1 barn = 10^-24 cm^2). Other nuclides having large neutron capture cross sections include 155,157Gd, 6Li, and 235U. These nuclides are less attractive than 10B for neutron capture therapy because of their complex chemical synthetic requirements and they are not as available. However, 157Gd is of interest as a capture agent due to its neutron capture reaction 157Gd(n,γ)158Gd, which yields gamma rays as well as internal conversion and Auger electrons. Of clinical concern, capture reactions may occur with nitrogen [14N(n,p)14C] and hydrogen [1H(n,γ)2H] within tissues producing protons and gamma rays, respectively. Even though the neutron capture cross-reaction of these elements (1.82 and 0.332 barns, respectively) are several magnitudes lower than that of 10B, the simple fact that nitrogen and hydrogen are in such high abundance in normal tissue can make these capture reactions significant. Therefore, the amount of neutron irradiation that can be delivered depends on the tolerance of the surrounding normal tissues to these side reactions and their resulting radiation production. Thus, it is necessary to deliver relatively high amounts of boron to tumor cells to obtain a significant boron dependent radiation dose. Despite the fact that there is no exact concentration of 10B that must be delivered to the individual tumor cells, experimental data suggest that it should be at least 20-35 µg of 10B per gram of tumor. To minimize damage to normal tissue, the boron concentration in this tissue must be kept low with a minimum tumor-to-tissue ratio of 3:1. In order to achieve success with BNCT, the 10B content of both tumor and normal tissue, the neutron fluence, and the location and depth of tumor must all be taken into consideration during the treatment process.

The ability to design and synthesize boron-containing compounds capable of targeting tumor tissue and providing the characteristics necessary for BNCT is based on two concepts. First, the boron-containing compounds must have the capacity to provide tumor selectivity. Second, once in the desired target (malignant tissue), the compound must remain there at the appropriate tumor boron concentration. The design of such agents is not a modest task because there is the potential for wide variation in the cellular and subcellular concentration of these compounds and because there can be a notable biological heterogeneity of tumor cells with regard to characteristics such as their level of oxygenation, metabolic activity, and proliferative potential as well as variability in tumor vascularization and necrosis which affect the transport of low- and high-molecular weight compounds. As mentioned previously, published reports have suggested that the success of BNCT depends on a tumor selectivity of the boronated compound great enough to ensure a tumor-to-normal tissue boron ratio of at least 3:1. A number of boron-containing compounds have been synthesized for the purpose of targeting (see Table 3).

**Boronated Non-Biological Agents**

Shortly after the first clinical trials of BNCT, one group reported the favorable tumor-to-blood ratio of mercaptoundecahydrododecaborate (B11H11SH)-. Since then, the sodium salt of this compound, borocaptate sodium (BSH), has been widely used in
Table 3: Strategic Delivery of Boron to Tumors for BNCT

<table>
<thead>
<tr>
<th>Design: Synthetic Chemistry</th>
<th>Design: Biochemical Molecule</th>
<th>Boron-Encapsulated Carrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boronated Non-Biological agents</td>
<td>Boronated Biological Agents</td>
<td>Boronated Macromolecules</td>
</tr>
<tr>
<td>Sulfur Compounds</td>
<td>Amino Acids</td>
<td>Monoclonal Antibodies</td>
</tr>
<tr>
<td>Porphyrins</td>
<td>Ether Lipids</td>
<td>Growth Factors</td>
</tr>
<tr>
<td>Aziridines</td>
<td>Nucleosides</td>
<td>Polysaccharides</td>
</tr>
<tr>
<td>Nitroimidazoles</td>
<td>(Oligo)Nucleotides</td>
<td></td>
</tr>
<tr>
<td>Bibenzimidazoles</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. An overview of various boron delivery agents for BNCT. The synthetic chemical approach involves compounds capable of being completely synthesized.

BNCT, especially in Japan for the treatment of glioblastoma patients. In both experimental animals and samples from surgical patients, BSH has shown significant accumulation within malignant tumors and tumor-to-blood concentration ratios above 1.0 while appearing to be excluded by normal brain tissue. The Japanese treatment plan involved administration of the BSH approximately four weeks after surgical resection at a dosage of 30 to 80 mg/kg by intracarotid infusion, followed by neutron irradiation 12 to 16 hours later. The reported mean tumor-to-blood ratio was 1.69. No BSH toxicity was observed at these doses in over 100 patients. Thus, BSH has been one of the most widely used compounds for BNCT due to the low systemic toxicity profile and the ability to selectively localize in tumor.

The mechanism of selective uptake of BSH into tumor tissue is not clearly understood. However, BSH has the potential to interact with plasma proteins through the sulfhydryl group. In addition, research has demonstrated selective uptake of such boronated proteins in cancer cells. Although the interaction with plasma proteins has been suggested as an important pathway for the selective localization of BSH, the interaction with tumor cell proteins has not proven to be the selective localization mechanism for BSH.
An analog of BSH, a dimer (B$_{12}$H$_{11}$S-SH$_2$B$_{12}$)$^+$ known as BSSB, was also evaluated as a potential agent for BNCT. Even though the results showed a higher ratio of tumor-to-blood and tumor-to-normal brain boron concentrations than BSH, BSSB had higher liver and kidney levels which resulted in elevation of hepatic enzyme levels in animals. The hepatotoxicity could be limited by a slow infusion of BSSB and appeared to be reversible. The exact mechanism for the selective uptake of BSSB is unknown but incorporation into tumor cell proteins was thought to play a role. In addition, an iodinated analog of BSSB has been synthesized for the purpose of serving as a boron-10 carrier as well as an iodinated contrast agent. This dual functionality would allow for the non-invasive quantification of boron in tumor by computed tomography (CT).

Boronated Biological Agents

Due to some success in clinical trials utilizing a ($^{10}$B) boronated phenylalanine derivative, $p$-boronophenylalanine (BPA) (Figure 2b), there has been an increasing interest in the development of amino acid derivatives containing boron. Since the initiation of clinical trials in 1987 by Mishima and his colleagues, more than a dozen patients have been treated with promising results for malignant melanoma as well as reported complete cures of melanoma with no sign of recurrence in some patients. Further evaluation of BPA demonstrated favorable tumor-to-blood and tumor-to-normal tissue boron ratios with tumor boron concentrations around 30 µg/g in experimental animals. Currently the dosage of BPA used in humans is approximately 250 mg/kg body weight. BPA's safety profile allows for the infusion of large doses of the boronated amino acid with no acute toxicity observed following a single dose of 3 g/kg infused over a one hour period. However, death was observed in experimental animals at a dosage of 4 g/kg infused over a three hour period. Despite this, it can be surmised that the dosage used clinically is well below the apparent toxic range.

The original concept behind the use of a phenylalanine derivative was based on the premise that the biosynthesis of melanin requires phenylalanine as a precursor. Thus, the boronated analog would be selectively taken up by melanoma cells. Research has proven that BPA is not selectively accumulated into melanoma cells or into melanin, thus resulting in only a temporary accumulation. Current studies have indicated that BPA is taken up by melanoma cells via an amino acid transport system where it forms a complex with some melanin-related compound, presumably L-DOPA. Thus, the transient accumulation of BPA in melanoma cells is due to the gradual decline in the BPA concentration as the complex dissociates.

Although BPA was initially used for the treatment of cutaneous melanoma, its preferential uptake in glioma has also been reported, allowing BPA to be used in the treatment of glioblastomas. The selective accumulation of BPA in glioma cells is believed to be based on the concept that BPA is a tyrosine analogue and gliomas exhibit elevated levels of the enzyme tyrosine hydroxylase.

One limitation to the use of BPA has been its poor water solubility making it cumbersome to administer large dosages through intravenous infusion. Even though the water solubility of the hydrochloride salt form of BPA is much improved, the solution has a pH of 1.5 thus causing pain and irritation upon administration. This has resulted in attempts to improve the aqueous solubility of BPA through complex formation with cis-diol sugars (e.g. fructose) and cyclodextran. The complex formation of BPA with both compounds has demonstrated improved bioavailability in experimental animals and has eased administration concerns.

BPA is not soluble at physiological pH because it exists as a neutral (zwitterionic) molecule. Yoshino et al. utilized the known ability of boronic acid to form an anionic complex with mannitol and reasoned that the boronic acid derivative of BPA might form a similar anionic complex with fructose. The equilibrium constant for the complex formation has been measured with a $^8$B NMR technique that quantified the $^8$B signal from the free BPA and the BPA-fructose (BPA-F) complex. The complexation with fructose increases the solubility of BPA in solution at pH 7.4 from 1.8 mg/mL to approximately 100 mg/mL. This has provided the opportunity for further evaluation of the BPA-fructose complex in clinical trials both in Japan and the United States. Currently, BNCT using 4-$^{10}$B$^8$B boronophenylalanine-fructose (BPA-F) is in Phase II clinical trials for the treatment of GBM and melanoma at Brookhaven National Laboratory.

Because of the promising results demonstrated by the use of the BPA-F complex, a variety of low molecular weight compounds have been
Many of the compounds have been biochemical precursors such as amino acids, pyrimidines/purines (peptide precursors of proteins), nucleic acid biosynthesis intermediates, and membrane lipid synthesis intermediates. Because these compounds may be considered cellular building blocks, their use is based on the fact that brain tumor cells undergo cell division, thus utilizing these compounds during S-phase prior to mitosis versus normal cells that are not dividing.

Attempts have been made to increase the boron load delivered to the tumor cells by attaching amino acids to a boron cage. A boron cage consists of ten boron atoms covalently linked in a polyhedral arrangement, thus delivering a higher boron content to tumor cells than BPA-F which only contains a single boron atom. The first such compound was carbornylalanine (CBA) which consists of a boron cage of ten boron atoms attached to the amino acid alanine. The in vivo uptake of CBA into tumor cells has been shown to be less than that of BPA even though CBA had demonstrated higher uptake than BPA in vitro. The reduced accumulation of CBA may be due to the highly lipophilic carboranyl group causing retention of CBA in the blood. To improve the biological distribution and reduce the lipophilicity of CBA, dipeptides have now been synthesized as well as efforts to attach more hydrophilic groups onto the compound.

Several other low molecular weight compounds have been prepared and evaluated. Of interest are the porphyrins, which are metal chelating agents capable of exhibiting selective affinity for malignant tumors. One boronated porphyrin compound, a tetrakis-carborane-carboxylate ester of deuteroporphyrin (BOPP) (Figure 3a), is highly water soluble and has reported selective localization in tumors at a ratio of 400:1 compared to normal brain tissue in animal models. BOPP has been shown to possess significant liver accumulation, which may not be a problem for localized neutron delivery used in the treatment of cerebral gliomas. However, more studies are needed to evaluate this compound's efficacy for BNCT and to better understand the selective uptake mechanism and toxicity profile. Huang et al. have reported on a manganese chelate of BOPP (Mn-BOPP) which has the potential to serve as a boron delivery agent with selective tumor uptake for BNCT and as a proton MRI contrast enhancement agent for glioma.

Because calculations have shown that the relative biological effectiveness (RBE) of a capture reaction occurring within the nucleus is 2.5 times higher than that in cytoplasm, containing the short pathlength of the high energy particles inside the nucleus would be advantageous. Since the mitotic index of malignant cells is several times higher than that of surrounding normal cells, boronated nucleic acid precursors could selectively accumulate in the highly proliferating tumor cells and be suitable agents for BNCT. Following entry into the cell, these low molecular weight nucleic acid precursors may get incorporated into DNA or at least get converted into the corresponding nucleotide and become trapped intracellularly. The boron-containing nucleotide, 5-dihydroboryl-2'-deoxyuridine (DBDu) (Figure 3b) has demonstrated the ability to destroy hamster v-79 cells in vitro following neutron irradiation. To further increase the boron concentration delivered within the tumor cells, carboranyl nucleosides have been synthesized which have shown both high in vitro and in vivo uptake. However, their mechanism for cellular uptake and retention has not been elucidated.

Another class of compounds for BNCT is the boronated antisense oligonucleotides. These compounds are in the early stages of development and still need to overcome the problem of poor cell membrane permeability and tumor selectivity. Other miscellaneous low molecular weight compounds include boronated ether lipids, carboranylaziridines, boronated nitroimidazoles, and boronated bibenzimidazoles. Natural and artificial derivatives of ether lipids have been shown to possess selective uptake in various tumors due to
the absence of \(\omega\)-alkyl glycerol mono oxidase (the enzyme responsible for the cleavage of these compounds) in the tumors of interest. The carboranylaziridine compound has the potential to alkylate DNA via the aziridine group resulting in the breakdown of DNA strands, thus placing boron close to nucleic acids. An advantage of boronated nitroimidazoles is their ability to selectively target the hypoxic cell fraction in tumors that may contain radiation resistant cells capable of repopulating the tumor following therapy. Boronated bibenzimidazoles have been widely used as fluorescent DNA stains through the binding of the minor groove of DNA and further studies are underway to evaluate their biodistribution.

Due to the fact that polyamines are known to be involved in DNA packaging and that tumor cells have an up-regulated polyamine transport system, polyamines have become an attractive boron delivery agent. Hariharan et al. have developed a spermidine analog [1,8-diamino-4-(4-o-carboranylbutyl)-4-azactaine (SPD)] and its spermine analog (SP4). Competitive uptake assays have demonstrated their utilization in the polyamine transport system as the boronated analogs. Further research evaluating their tumor selectivity and \textit{in vivo} toxicity are currently in progress.

**Boronated Macromolecules**

The third category for targeting the delivery of boronated compounds is based on one compound containing a large number of boron atoms being linked to a macromolecule as the target compound, resulting in a high molecular weight compound. In comparison to the low molecular weight compounds, the high molecular weight agents lack the ability to cross the intact blood-brain barrier. Therefore, many of these compounds have been developed for potential use in malignancies other than brain tumors. Over the last ten years, several researchers have tried to utilize monoclonal antibodies (MAbs) as boron delivery agents. Studies have reported that approximately 1000 \(^{10}B\) atoms must be carried by each antibody molecule to achieve an effective tumor concentration of boron. However, this results in a loss of immunoreactivity by the antibody due to the modification of a large number of chemical groups.

**Boron Encapsulated Carriers**

An alternate approach consisted of attempts to use boronated polypeptides and starburst dendrimers. Even though these agents kept their immunoreactivity, they possessed high uptake ratios for the spleen and liver as well as an alteration of their \textit{in vivo} biodistribution compared to their non-boronated analogs with large amounts accumulating in the reticuloendothelial system. Thus, to overcome these pitfalls, a new approach has employed bispecific antibodies (BsAb) that consist of one site which recognizes the tumor-associated antigen and another site capable of binding to the boronated polymer. One such BsAbs has been synthesized possessing the ability to recognize a tumor-associated proteoglycan expressed on human glioma and melanoma cells and bind to a variety of polyhedral borane anions including a boronated starburst dendrimer.

Due to receptor overexpression in 25-30% of highly malignant gliomas, epidermal growth factor (EGF), a 53-amino acid-containing polypeptide may serve as a potential boron delivery agent. Other peptides may also be used if their receptors are over-expressed in tumor cells. Efforts have been made to prepare radiolabeled MAbs directed against such EGF receptors for detecting human gliomas.

In addition, EGF has been labeled with radionuclides and boron to treat brain tumors. Capala et al. have synthesized and performed an \textit{in vitro} evaluation of a boronated starburst dendrimer linked to EGF. This biconjugate compound contained approximately 960 atoms of boron per molecule of EGF while retaining an affinity constant that was just one order of magnitude less than native EGF (8.6 x \(10^{-7}\) M\(^{-1}\) vs. 9.1 x \(10^{-8}\) M\(^{-1}\)). Further \textit{in vivo} studies are underway to evaluate the tumor-localizing properties of this compound.

**Other Boron-Containing Agents**

In contrast to the use of a tumor-specific macromolecules such as MAbs, the use of a boronated dextran conjugate for passive tumor targeting has been recently attempted. In theory, tumor vasculature has an increased permeability for macromolecules and poor lymphatic drainage resulting in prolonged retention of these molecules in tumors. This is known as the enhanced permeability and retention (EPR) effect. Water soluble BSH-dextran conjugates have been synthesized which contain more than 1000 boron atoms per conjugate. Further study is needed to evaluate the biological effectiveness of such conjugates. Both low-density lipoproteins (LDLs) and
liposomes are high molecular weight boron delivery mechanisms undergoing evaluation. They have the advantage of being able to handle large loads of boron to the tumor site. Liposomes containing a variety of boron compounds have been evaluated in experimental animals; the results have proven the ability of liposomes to selectively deposit boron quantities within murine tumors in the amount of 30-40 μg/g of tissue weight with tumor-to-blood ratios of about 5:1.

It has been shown in several studies that the uptake of intravenously administered drugs encapsulated in small liposomes was higher in tumors when compared to surrounding normal tissues. The proposed mechanism for the selective tumor uptake by liposomes is thought to be related to the increased extravasation of small liposomes in areas of leaky vasculature as in a rapidly proliferating tumor. Once in the tumor, liposomes are internalized by various pathways allowing for the delivery of their contents intracellularly.

Low-density lipoproteins have been proposed as tumor-specific boron carriers. The density of LDL receptors is much higher in tumor cells when compared to normal cells, allowing for the high capacity of carrying lipophilic boron compounds. Because of their relatively small size, LDL are able to diffuse from vascular to extravascular sites. Once they have bound with cell surface receptors, the LDL is internalized depositing its contents intracellularly. The synthesis and evaluation of carborane carboxylic acid esters of fatty alcohols have demonstrated the effective replacement of the cholesterol ester core in human LDL.

Other Neutron Capture Nuclides

Because of the large cross-section of ¹⁵Gadolinium (Gd), gadolinium neutron capture therapy is similar to BNCT except that ¹⁵Gd is used as the neutron capture agent. However, the resulting nuclear reaction produces Auger electrons and 'soft' x-rays. This requires the treatment regimen to target tumor DNA in order for the high LET particles to be effective. One proposed method for the delivery of high quantities of ¹⁵Gd to tumors is to infuse ¹⁵Gd in microcapsules via a feeding artery. This principle provides a temporary intratumoral embolization of the microcapsules leading to ¹⁵Gd retention in tumor. Such an approach could be applied to BNCT, but the size of the microcapsule, release of boron from the microcapsule, and the uptake and retention profile within tumor cells would need to be evaluated.

Because of the delivery route required and the inability to selectively target brain tumors in vivo, the use of these high molecular weight compounds have experienced several problems. Only a small percent (<0.005%) of the injected radioactivity of radiolabeled MAb has been demonstrated to localize in brain tumors. The quantity of MAb localized within tumor has been shown to increase following intracarotid injection; when combined with the blood-brain barrier disruption that is associated with many brain tumors, the uptake of MAbs can further be enhanced. BNCT will most likely not be employed as a single primary treatment modality for brain tumors, but rather used in combination with surgical intervention. Therefore, the ability to target residual brain tumor cells is vitally important for any BNCT agent.

NEUTRON PRODUCTION FOR BNCT

In addition to a source of ¹⁰B that localizes in malignant tissue, the other main constituent for the bimodal treatment of BNCT is exposure of the tumor to a specified dose of neutrons. Neutrons with an energy of approximately 1 MeV and a mixture of gamma rays are produced in the fission reaction within a reactor core. Thermal, epithermal and fast neutrons can be extracted for use in radiation therapy by varying the amount of moderation (the slowing down of neutrons) through appropriate use of filter systems. Studies have demonstrated that thermal neutron fluences greater than 10¹⁶ncm⁻² along with approximately 10⁸⁻¹⁰B atoms are required. In order to overcome the dose-limiting factor of the unavoidable capture reactions with hydrogen and nitrogen in normal tissue, this high amount of ¹⁰B and neutron flux are required to produce an acceptable radiation dose from the resulting α-particles and Li nuclei.

In the 1950s, clinical trials of BNCT at the Brookhaven National Laboratory employed thermal neutrons from the Brookhaven Graphite Research Reactor (BGRR). The Brookhaven Medical Research Reactor (BMRR) was built and began operation in 1959. This reactor is capable of providing a higher flux of thermal neutrons for research applications. The BMRR facility is located in an 18.3 meter diameter gas-tight confinement building. There are two treatment neutron beam ports, each within a shielded room, on opposite sides.
of the reactor. At present, one is a thermal neutron beam and the other is an epithermal neutron beam. The emerging neutron beams at the patient irradiation ports are stopped by beam shutters with assemblies that can be raised or lowered hydraulically inside a vertical cavity to control the irradiation. When the shutter is down, a high-density concrete section of each shutter blocks the beam between the reactor core and the patient location. When the shutter is raised, the moderator section of the shutter is between the reactor core and the patient location. When the moderator is D$_2$O, a thermal neutron beam is produced and when the moderator is Al and Al$_2$O$_3$, an epithermal neutron beam is produced.

The neutrons produced in the core of the reactor by the fission process have a range in energy from thermal (approximately 0.025 eV), epithermal (0.4 eV to 10 keV), to fast (10 keV to 14 MeV). The thermal neutrons must be able to penetrate to the depth of the boron-containing tumor cell and be present in sufficient number (approximately 10$^8$/cm$^2$) to begin the $^7$B(n,$\alpha$)Li reaction.

After early clinical attempts, it was realized that in order to reach deep-seated brain tumors, a beam of epithermal neutrons was preferred over thermal neutrons. Excessive damage to the skin and skull occurs due to the limited depth of penetration of the thermal neutrons. Even though fast neutrons are able to penetrate to the desired depth of the tumor, they produce significant tissue damage to normal cells along the entire neutron beam path. By comparison, epithermal neutrons are relatively benign and are capable of passing through tissue. Epithermal neutrons pass through the outer skin and cranium, get moderated by the hydrogen present in tissue, and are deposited in the tumor as thermal neutrons. It is only these thermal neutrons that are captured by the $^10$B nucleus. In contrast, if only thermal neutrons were produced, they would interact with $^{10}$B present in the scalp producing radiation damage to the normal tissue. The epithermal neutron beam makes it possible to treat tumors with BNCT at a depth of 5 to 6 centimeters. In order to produce epithermal neutrons using reactors, a filter or moderator must be positioned between the patient and the primary source of neutrons. Such a moderator was placed in one of the beam shutters in 1988 at the BMRR$^{59}$ producing epithermal neutrons. The purpose of the moderator is to reduce the energy of the fast neutrons to the epithermal range while filters are able to absorb or redirect the undesired neutrons.$^{67}$ Currently, the neutron beam at the BMRR facility is produced by the use of a moderator composed of aluminum oxide. The subsequent epithermal neutrons produced are due to the filtering mechanism of aluminum and the moderating ability of oxygen which reduces the fast neutrons into the epithermal energy range but prevents the rapid transformation into the thermal range. To remove the thermal neutrons, a shield of cadmium was installed along with a layer of bismuth to aid in the reduction of the intensity of the $\gamma$-rays produced$^{69}$. In comparison, the Massachusetts Institute of Technology Reactor (MITR) utilizes a sulfur and aluminum combination as the filter and moderator while the reactor at Petten, Netherlands employs liquid argon and a titanium filter.

As an alternative to reactors, epithermal neutrons of the desired energy and fluence may be produced by accelerators. The reaction $^2$H(d,n)$^3$He (often called a d-d reaction) is exoergic, and good neutron yields can be obtained with deuteron energies as low as 100-200 keV. Using thick targets of solid D$_2$O, the yields are about 0.7, 3, and 80 neutrons per 10$^7$ deuterons at 100 keV, 200 keV, and 1 MeV deuteron energy, respectively. Preliminary designs have suggested that accelerators capable of producing proton beam currents in the range of 20 mA would be required on a suitable target, thereby generating a tremendous amount of heat. Thus, an effective and reliable target cooling system would be extremely important during the bombardment period. Another concern with accelerator production of neutrons is the choice of materials employed in the filtering and moderation of the neutrons to achieve the desired epithermal beam for treatment. The design and construction of a clinically practical accelerator for the production of epithermal neutrons has been evaluated by one group.$^{31}$ In addition to accelerators, researchers$^{73}$ have evaluated the use of californium-252 as a potential radioactive source for the production of epithermal neutrons. At present, $^{256}$Cf is the most practical source possessing a half-life of 2.64 years; decays 96.9% by $\alpha$-emission, 3.1% by spontaneous fission, and emits on the average 3.76 neutrons per fission (about 2.3 x 10$^3$ neutrons/mg·s$^{-1}$). Both accelerators and radioactive sources offer a potentially less expensive and more convenient alternative source of epithermal neutrons, but neither method has demonstrated a reliable production of the required scale of clinically-useful neutrons (Table 4).
Table 4.
Available Facilities with Epithermal Neutron Beams$^{(91)}$

<table>
<thead>
<tr>
<th>Location</th>
<th>Epithermal Neutron Flux $(x \times 10^9 \text{n/cm}^2\text{sec}^{-1})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brookhaven Medical Research Reactor (BMRR), Upton, NY</td>
<td>1.8</td>
</tr>
<tr>
<td>Massachusetts Institute of Technology Reactor (MITR), Cambridge, MA</td>
<td>0.21</td>
</tr>
<tr>
<td>High Flux Reactor (HFR-Petten), Petten, The Netherlands</td>
<td>0.33</td>
</tr>
<tr>
<td>Missouri University Research Reactor (MURR), Columbia, MO</td>
<td>9.5</td>
</tr>
<tr>
<td>Georgia Tech Research Reactor (GTRR), Atlanta, GA</td>
<td>2.5</td>
</tr>
<tr>
<td>Musashi Institute of Technology Reactor (Musashi I), Ozenji, Japan</td>
<td>0.5</td>
</tr>
<tr>
<td>Finnish Research Reactor (Fir 1), Otakaari, Finland</td>
<td>1</td>
</tr>
<tr>
<td>Japan Research Reactor (JRR-4), Toki, Japan</td>
<td>2</td>
</tr>
<tr>
<td>Taiwan</td>
<td>2</td>
</tr>
<tr>
<td>BMRR with Fission Plate Converter</td>
<td>10</td>
</tr>
<tr>
<td>MITR with Fission Plate Converter</td>
<td>18</td>
</tr>
<tr>
<td>Accelerator (Nigg design$^{(71)}$)</td>
<td>1</td>
</tr>
<tr>
<td>Accelerator at MIT$^{(90)}$</td>
<td>$3.58 \times 10^{12}$ neutrons/sec</td>
</tr>
</tbody>
</table>
### Table 5.
Radiation Dose (Gy-Eq) at depth from cortical surface

<table>
<thead>
<tr>
<th>Radiation Component</th>
<th>2 cm</th>
<th>4 cm</th>
<th>6 cm</th>
<th>8 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{10}$B(n,α)$^7$Li ($^7$B conc. = 43 μg $^7$B/g)</td>
<td>34.0</td>
<td>14.6</td>
<td>6.3</td>
<td>2.7</td>
</tr>
<tr>
<td>Fast Neutrons</td>
<td>4.2</td>
<td>2.7</td>
<td>1.8</td>
<td>1.1</td>
</tr>
<tr>
<td>$^{14}$N(n,p)$^{14}$C ($^{14}$N conc. =22 mg $^{14}$N/g)</td>
<td>2.6</td>
<td>1.1</td>
<td>0.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Gamma</td>
<td>6.1</td>
<td>4.2</td>
<td>2.7</td>
<td>1.8</td>
</tr>
<tr>
<td>Sum of endothelial radiation doses (Gy-Eq)</td>
<td>46.9</td>
<td>22.6</td>
<td>11.3</td>
<td>5.8</td>
</tr>
<tr>
<td>% from $^{10}$B</td>
<td>73</td>
<td>65</td>
<td>56</td>
<td>47</td>
</tr>
<tr>
<td>% from gamma</td>
<td>13</td>
<td>19</td>
<td>24</td>
<td>31</td>
</tr>
</tbody>
</table>

Table 5. Estimates of radiation dose (Gy-Eq) to capillary endothelial cells in normal brain at the BMRR facility.\(^{(28)}\)

### BIOLOGICAL EFFECTS OF BNCT

The mixed radiation field produced during BNCT comprises radiations with different LET and different efficacies in biological systems. To express the total BNCT dose in a common unit, and to compare BNCT doses with the effects of conventional photon irradiation, multiplicative factors [referred to as compound-adjusted relative biological (radiobiological) effects (C-RBEs)], of the physical absorbed radiation doses from each high-LET component of the BNCT dose are generally added. The total effective BNCT dose is then expressed as the sum of RBE-corrected components with the unit Gy-Eq (Gray-Equivalent). Relative biological effectiveness is a complex factor which is dependent upon a number of parameters including radiation dose, dose rate, number of dose fractions, physical radiation quality (LET), the choice of biological system, and the radiation dose effect that is monitored in the biological system. Furthermore, in BNCT there is an additional component to be considered. The short ranges of the two high-LET products of the $^{10}$B(n,α)$^7$Li reaction (α particle, 1.47 MeV, range approximately 7.5 μm, average LET = 196 keV/μm, $^7$Li ion, 0.84 MeV, range approximately 5.2 μm, average LET = 162 keV/μm)\(^7\) make the microdistribution of the boron
relative to target cell nuclei of particular importance. Thus, there is a "boron localization factor" to be considered in determining the C-RBE factor for the $^{10}$B(n,α)Li reaction. The latter can be defined as the product of the true, geometry-independent, RBE for these particles times a "boron localization factor," which will most likely be different for each particular boron compound. Also, in principle, C-RBE will depend upon the particular route and timing of administration chosen for a particular study or a particular irradiation, since the route and timing of the boronated substance determines the intra/extravascular partition of $^{10}$B within the tissues. The RBE of the beam components at the BMRR and the C-RBE for BPA-based BNCT have been assessed in the rat brain tumor model and in the rat spinal cord model. Estimates for the radiation dose (Gy-Eq) to capillary endothelial cells in human normal brain tissue have been calculated at different depths from the cortical surface using the 1959 to 1961 BMRR thermal neutron beam (see Table 5). Table 5 summarizes the measured values for the biological effectiveness of the high-LET BNCT dose components. The relative biological effectiveness value reported in the literature for the α particles produced by the $^{10}$B(n,α)Li reaction have ranged from a factor of less than two up to approximately six depending on the boron agent used, the biological system evaluated, and the specific target tissue, creating a considerable degree of controversy. In the past, the determination of the intracellular concentration of boron within tissues has been virtually impossible, but recently the advancement of high-resolution quantitative autoradiography, secondary ion microscopy, electron energy loss spectroscopy/electron spectroscopic imaging and magnetic resonance boron spectroscopy and imaging have allowed for a better understanding of the intracellular distribution of a variety of boronated compounds.

Standard radiation therapy for GBM is usually delivered in daily fractions (5 days/week) of 180 to 200 cGy to a cumulative dose of 55 to 60 Gy. BNCT may be delivered in a single dose fraction. The considerations that justify fractionation of conventional therapy were originally thought not applicable to BNCT. Given the high expected boron concentrations, it has been estimated that 85% to 90% of the total Gy-Eq tumor dose is from high-LET radiations. As a result, tumor hypoxia, oxygen enhancement ratio, and tumor cell cycle dependent radiation sensitivity are of minor concern in BNCT. For the normal brain, conventional fractionation protocols allow for the repair of photon-induced sublethal damage (SLD) and potentially lethal damage (PLD). With BNCT, because of the expected high therapeutic gain, researchers hoped it possible to deliver a tumor control dose of radiation in a single fraction without exceeding the threshold for radiation tolerance of the normal brain. Thus, the concept of repair between each fraction of radiation would be thereby alleviated. This is in contrast to SLD and PLD that is produced by both γ-rays and x-rays and can repair between fractionated treatments. In actuality, fractionation of BNCT may provide an additional margin of safety to normal brain. Multiple dosing would permit repair of damage from low LET radiation, arising from both the in situ hydrogen capture reaction and the gamma radiation from the reactor core. However, when considering single dose fractionation by BNCT, one must also evaluate the role of the boron carrier itself. The presence of boron in brain parenchyma and the vascular bed could produce radiation-induced damage to normal brain tissue such as tumor necrosis, brain edema, and increased intracranial pressure. Prior surgical debulking is expected to diminish the consequences of rapid radiation necrosis around the tumor bed. In the current protocol used in the investigational study at Brookhaven, the neutron irradiation of the patient lasts for approximately 45 minutes. During BNCT, the total body dose from the radiation has been calculated to be relatively small due to the neutron scattering. The estimated total body dose in the study has been stated to be between 0.05% and 0.3% of the peak volume dose in the brain which will not exceed 10.0 Gy-Eq. Because of the differences between BNCT and conventional radiation therapy, the stated normal mammalian brain tolerance to photon radiation given in multiple fractions of 2 Gy or less, is of no relevance. Data from various animal studies delivering total body irradiation of differing radiation doses have confirmed the theoretical and clinical evidence of a single fraction dose of 10 Gy-Eq to brain is within the threshold of tolerance. Non-human primates which received a single dose of 10 Gy-Eq showed no CNS damage for 24 months following irradiation. The total estimated radiation dose limit to the tumor, depending on depth, has been set at 20-45 Gy-Eq. When BNCT was initially begun, there was some concern regarding the radiation dose received by the central nervous system.
during treatment. Morris and cohorts looked at the long-term effects on the skin and spinal cord of the rat from BNCT. A dose of 100 mg/kg of BSH was infused followed by a three to five hour exposure to thermal neutrons. The skin surface neutron flux was reported to be $4.8 \times 10^4 \text{n cm}^{-2} \text{s}^{-1}$. Exposure times of greater than four hours resulted in vigorous, biphasic skin reactions, indicative of long-term vascular damage in the dermis. The rats were monitored closely for 84 weeks following irradiation showing no evidence of abnormal neurological responses or histological evidence of lesions in the spinal cord at the completion of the study.

**HIGHLIGHTS OF CLINICAL STUDIES**

The early attempts utilizing BNCT for the treatment of brain tumors in patients were performed at Brookhaven National Laboratory (BNL) and at the Massachusetts General Hospital/Massachusetts Institute of Technology (MGH/MIT) during the late 1950s and early 1960s. The boron delivery agents that were employed at BNL were sodium pentaborate ($\text{Na}_2\text{B}_{10}\text{O}_{10}\cdot10\text{H}_2\text{O}$) and borax ($\text{Na}_2\text{B}_4\text{O}_5\cdot\text{H}_2\text{O}$) administered intravenously followed by irradiation of the patient for treatment of malignant gliomas and GBM. These early treatment protocols were a failure as the patients ultimately died without prolongation of survival time. The group at MGH/MIT treated 18 patients, most of them diagnosed with glioblastoma. They used $^{10}\text{B}$-paracarboxybenzene boronic acid intravenously in 16 of the patients while the other two patients each received sodium decahydrodecarbonate administered by intracarotid injection. Again, the trial resulted in poor results in which nine patients revealed extensive radiation necrosis while 12 patients presented with residual tumor in the 14 brains evaluated by neuropathologic examination. In both trials, the poor results were the result of the boron concentration in the vasculature, nonselectivity of the target tissue by the boron agent, and the poor penetration of the thermal neutrons being utilized.

Shortly after returning to Japan in 1968, Hiroshi Hatanaka and co-workers began using BNCT for the treatment of brain tumors. This group has treated over 160 patients using surgical debulking and infusion of BSH with a dosage range of 30-50 mg $^{10}\text{B}$/kg. The patients are then irradiated with thermal neutrons at the operative site of excision six to twelve hours following BSH administration. The initial reactor utilized (at the Musashi Institute of Technology) produced a low neutron flux ($1.5 \times 10^6 \text{n cm}^{-2} \text{s}^{-1}$) requiring irradiation times of three to five hours per single treatment. Since 1992, irradiations have been performed at the Kyoto University Reactor (KUR) and the Japan Research Reactor (JRR)-2 due to their reported higher flux of epithermal neutrons. The method employed at these facilities utilized a BSH infusion resulting in a mean $^{10}\text{B}$ concentration of 26.3 $\mu$g/g and a tumor-to-blood ratio of 1.69 in 48 patients after waiting 14 hours post infusion of BSH. The results reported are of particular interest due to the mean survival time of 44 months (median of 25.6 months) in 38 patients with grade III and IV gliomas. Of this group, one man is still alive 24 years following treatment with no evidence of tumor, and two other patients, a girl and a woman, appear to have been cured. Of equal importance, out of this group there appears to be no evidence of radiation injury to the normal brain in patients treated with the standard dose of neutrons.

Even though some researchers have contested the lack of reports offering sufficient detail to allow independent recalculation of the mixed field of radiation dose to the tumor and normal brain, these survival data are quite impressive when compared to the median survival of less than 12 months following conventional therapy.

Because of the clinical results reported in patients having cutaneous melanomas by other researchers in Japan such as Mishima and cohorts, several groups have concentrated on the use of BPA as a possible agent for BNCT. In seven patients diagnosed with GBM, BPA-Fructose was administered at a dose of 130 mg/kg two to three hours prior to surgical debulking. After tissue analysis, the normal brain tissue values for boron was <5 $\mu$g/g while the peak boron concentration within tumor tissue ranged from 11-26 $\mu$g/g, a ratio of at least 2:1. Twelve patients have been treated; the first six patients were given BPA as the hydrochloride salt (per tumoral injections) and the latter six patients were given intravenous infusions of BPA-Fructose. Complete local tumor regression was reported in four of the six patients receiving intravenous BPA-F.

As a result of these promising trials, an investigational new drug application trial was begun at Brookhaven National Laboratory/Beth Israel Medical Center in New York. The purpose of the Phase I/II clinical trial is to evaluate (1) the safety of stepwise increases in BNCT doses to the normal
brain using BPA-F and epithermal neutrons at the BMRR facility, (2) the adverse effects of BNCT at each dose level, if any, and (3) the therapeutic effectiveness of each BNCT dose level in patients diagnosed with GBM. The approved protocol uses a two hour infusion of 250 mg of BPA/kg of body weight and the neutron irradiation is started approximately 45 minutes after the BPA-F administration. The duration of the irradiation is determined from the boron content of the blood samples obtained at the end of the BPA-F infusion and at the beginning of the irradiation period as well as from a blood sample obtained during the irradiation midpoint. These values are used to calculate an estimated pharmacokinetic boron profile to insure a safe and effective neutron dose. As a result, the irradiation time may be adjusted to deliver the prescribed radiation dose to the normal brain (not to exceed 10.5 Gy-Eq). For shallow tumors, the epithermal neutrons are delivered in a single session lasting about 40-50 minutes using a single field. For deeper tumors, BNCT is delivered in a single session using two fields of epithermal neutrons with the exposure time for each being approximately 30-40 minutes. Results from the first 15 patients showed that the treatment allowed many of the patients to enjoy a better quality of life in their remaining months than would have been expected with daily sessions of conventional therapy. On average, patients have survived just over one year; two patients are still alive with no sign of recurrent tumor.

Currently, one problem with BNCT treatment planning is the necessity for estimating boron distribution within the target tissue by tumor tissue removal during the pre-BNCT surgical debulking process. As mentioned, some groups have determined the in vivo boron biodistribution using boron-MRI methods but this method experienced limited success. An alternative approach for the determination of the pharmacokinetics of BPA-F is using radiolabeled analogues of the boron agent in conjunction with positron emission tomography (PET). One group has used 4-[^3]B borono-2-[^15]F)fluoro-L-phenylalanine-fructose ([^15]F-BPA-Fr) for evaluating two patients diagnosed with GBM. Their results suggest that the optimal window for effective BNCT is 60-90 minutes post injection of BPA-F assuming a 30 minute infusion duration. In addition to evaluating BPA as the boron delivery agent, another group is studying the in vivo localization of epidermal growth factor radiolabeled with 99m-Tc-sodium pertechnetate.

CONCLUSION

Boron Neutron Capture Therapy holds a promising future as a therapeutic treatment modality for treatment of brain tumors. The complexity of BNCT as a bimodal treatment depends on the design of an optimal boron delivery agent coupled with the irradiation of the correct dose of epithermal neutrons at the optimal time of peak tumor-to-target boron concentrations. At present, patients diagnosed with primary as well as metastatic brain tumors are most likely to benefit from treatment with BNCT. While both BSH and BPA have shown promise, research efforts are continuing to develop new boron compounds based on biochemical properties of tumor cells while enhancing the boron load within the tumor. Increasing experience and knowledge with these agents may provide treatment regimens comprised of a combination of boronated analogs resulting in a synergistic therapeutic outcome while minimizing adverse effects. In addition, the continued efforts to design and implement clinically-useful reactors as well as accelerators may allow for the establishment of regional BNCT centers, thus allowing BNCT to be more available to the patients who could benefit from this treatment modality.

REFERENCES


49. Not used


QUESTIONS

1. According to estimates for 1997, which of the following statements is not true?
   a. more than 1,500 Americans are expected to die per day from cancer.
   b. in adults, there are about 17,000 new primary brain tumors per year.
   c. the mean age at diagnosis for glioblastoma is 71 years of age.
   a. glioblastoma compromises 40% to 60% of primary brain tumors.

2. Which of the following statements is correct regarding the prognosis of glioblastoma multiforme (GBM)?
   a. to date, the recovery rate for glioblastoma multiforme is 0%.
   b. treatment with surgery alone provides a median survival of 12 months.
   c. treatment with surgery plus radiotherapy gives a median survival of 24 months.
   d. treatment with radiotherapy and chemotherapy increases the median survival to 48 months.

3. All of the following are a single mode of therapy used in an attempt to deliver a lethal event to malignant cells except:
   a. high-linear energy transfer (LET) particle therapy.
   b. boron neutron capture therapy (BNCT).
   c. interstitial brachytherapy
   b. stereotactic surgery.
4. In the nuclear reaction that occurs when \(^{10}\text{Boron}\) is irradiated with thermal

a. slow protons  
b. fast neutrons  
c. beta particles  
d. alpha (\(\alpha\)) particles

5. During the production of the intensively ionizing particles, \(^{4}\text{He (}\alpha\text{ particles)}\) and recoiling \(^{7}\text{Li nuclei}, what energy is deposited within the range of one cell diameter?

a. 2.31 MeV in 93.7% of disintegrations.  
b. 0.511 MeV in 50% of disintegrations.  
c. 0.48 MeV in 98.1% of disintegrations.  
d. 3.22 MeV in 63.7% of disintegrations.

6. According to the early trials in the 1950s and 1960s with BNCT, all the following were reasons for unsuccessful treatment except?

a. or selectivity of the boron compound.  
b. poor penetration of the neutron beam.  
c. lack of control of cerebral edema.  
d. poor patient compliance.

7. The neutron capture cross-reaction for \(^{14}\text{Nitrogen}\) and \(^{1}\text{Hydrogen}\) is 1.82 and 0.332 barns, respectively. What is the neutron capture cross-reaction for \(^{10}\text{Boron}\)?

a. 3.8 barns  
b. 1.5 \(\times 10^{-23}\) cm\(^2\)  
c. 1500 barns  
d. 3838 barns

8. Experimental data suggest that the amount of \(^{10}\text{Boron}\) that must be delivered to the tumor must be at least __________ of \(^{10}\text{B}\) per gram of tumor.

a. 1,000 ppm  
b. 1 - 2 mg  
c. 20 - 35 mg  
d. 1,000 ppb

9. Borocaptate sodium (BSH) was used by Hatanaka in Japan for the treatment of glioblastoma at a reported intracarotid dosage of __________.

a. 250 mg/kg  
b. 30 to 80 mg/kg  
c. 12 g/kg  
d. 20 to 35 ug/kg

10. All the following compounds have been evaluated for use as a boron delivery agent in BNCT except:

a. borocaptate sodium (BSH)  
b. \(p\)-boronophenylalanine (BPA)  
c. cyclodextran (CCD)  
d. carboranylalanine (CBA)

11. Which of the following statement about BSSB, a dimer of BSH, is correct?

a. demonstrated a lower boron tumor-to-blood ratio than BSH.  
b. provided a lower boron tumor-to-normal brain concentration than BSH.  
c. resulted in increased hepatic enzymes.  
d. the exact mechanism of incorporation into tumor cells has been elucidated.

12. No acute toxicity has been observed following the administration of \(p\)-boronophenylalanine (BPA) as single dose of __________.

a. 4 g/kg infused over 3 hours intravenously.  
b. 3 g/kg infused over 1 hour intravenously.  
c. 250 mg/kg administered as rapid bolus intravenously.  
d. 35 \(\mu\)g/kg over 1 hour intravenously.
13. The selective accumulation of \( p \)-boronophenylalanine (BPA) in melanoma cells is thought to be by what mechanism?

a. the biosynthesis of melanin requires phenylalanine as a precursor.
b. through passive diffusion of the boron atom into tumor cells.
c. as a precursor to tyrosine production within malignant cells.
d. via an amino acid transport system through formation of a complex with L-DOPA.

14. All the following statement are correct regarding \( p \)-boronophenylalanine (BPA) except:

a. BPA possesses poor water solubility.
b. the pH of hydrochloride salt of BPA is 1.5.
c. BPA is soluble at physiological pH.
d. BPA has increased aqueous solubility as a complex with \( cis \)-diol sugars.

15. The proposed theory for the use of biochemical precursors such as amino acids, pyrimidines, and purines in BNCT is based on the fact that:

a. tumor cells are rapidly dividing and thus would incorporate these compounds during the S-phase.
b. amino acids are capable of chelating to tumor cells through disulfide bonds.
c. these compounds are hydrophilic allowing for intravenous administration.
d. both tumor and normal cells are rapidly dividing incorporating such "building blocks."

16. All the following statements regarding the boronated porphyrin compound, BOPP, are correct except:

a. is highly water soluble
b. reported tumor-to-normal brain tissue of 400:1
c. demonstrated low hepatic uptake.
d. a manganese derivative for proton MRI has been synthesized.

17. Which of the following cannot be used as possible method for the production of neutrons for BNCT?

a. fission reaction within a reactor core.
b. 11 MeV medical cyclotrons.
c. accelerators.
d. radionuclides.

18. Research has demonstrated that a thermal neutron flux greater than \( \text{n cm}^{-2} \) conjunction with \( 10^9 \) 10\(^9\) boron atoms is required.

a. \( 10^{12} \text{ cm}^{-2} \)
b. \( 200 \text{ cm}^{-2} \)
c. \( 10^{35} \text{ cm}^{-2} \)
d. \( 10^9 \text{ cm}^{-2} \)

19. What is the range in energy of an epithermal neutron?

a. 0.025 eV
b. 0.511 MeV
c. 0.4 eV to 10 keV
d. 10 keV to 14 MeV

20. The epithermal neutrons currently being produced by use of appropriate moderators and filters are capable of treating tumors with BNCT at a depth of \( \text{______} \).  

a. 9 micrometers 
b. 5 to 6 centimeters  
c. 1 inch 
d. 6 inches
21. Relative biological effectiveness (RBE) is a complex factor dependent on all the following except:

a. radiation dose.
b. the dose rate.
c. the physical radiation quality (LET)
d. the age of the patient during fractionated doses.

22. During treatment with BNCT, all the following are thought to be incorrect except:

a. fractionation therapy allows for the repair of sublethal damage to cells.
b. repair of sublethal damage and potentially lethal damage is prevented.
c. only repair of potentially lethal damage is obtained.
d. tumor hypoxia and tumor cell cycle must be determined prior to treatment.

23. According to the current investigational study of BPA-fructose by Chadha and cohorts at Brookhaven National Laboratories for BNCT all the following are true except:

a. the proposed maximal single fraction dose shall not exceed 10.5 Gy-Eq.
b. BPA-F is infused intravenously over 2 hours at a dosage of 250 mg/kg.
c. the patient is irradiated 14 hours post BPA-F administration
d. the irradiation period last approximately 40-50 minutes for a shallow tumors.

24. Possible side effects of the presence of $^{10}$Boron within the brain parenchyma and vascular bed during BNCT includes all the following except:

a. tumor edema
b. tumor necrosis
c. brain edema
d. increased intracranial pressure.

25. The approved indication for the use of BNCT during the Phase I/II clinical trial at Brookhaven is:

a. melanoma
b. meningioma
c. lymphoma
d. glioblastoma multiforme