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## BORON NEUTRON CAPTURE THERAPY OF MALIGNANT BRAIN TUMORS AT THE BROOKHAVEN MEDICAL RESEARCH REACTOR

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### INTRODUCTION

Boron neutron capture therapy (BNCT) is a bimodal form of radiation therapy for cancer. The first component of this treatment is the preferential localization of the stable isotope  $^{10}\text{B}$  in tumor cells by targeting with boronated compounds. The tumor and surrounding tissue is then irradiated with a neutron beam resulting in thermal neutron/ $^{10}\text{B}$  reactions ( $^{10}\text{B}(n,\alpha)^7\text{Li}$ ) resulting in the production of localized high LET radiation from alpha and  $^7\text{Li}$  particles. These products of the neutron capture reaction are very damaging to cells, but of short range (each less than  $10\text{ }\mu\text{m}$ ) so that the majority of the ionizing energy released is microscopically confined to the vicinity of the boron-containing compound. In principal it should be possible with BNCT to selectively destroy small nests or even single cancer cells located within normal tissue. It follows that the major improvements in this form of radiation therapy are going to come largely from the development of boron compounds with greater tumor selectivity, although there will certainly be advances made in neutron beam quality as well as the possible development of alternative sources of neutron beams, particularly accelerator-based epithermal neutron beams.

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Clinical trials of BNCT in the treatment of brain tumors were conducted at the Brookhaven Graphite Research Reactor between 1951 and 1959 (28 patients) and subsequently at the specially designed Brookhaven Medical Research Reactor (BMRR) between 1959 and 1961 (see review by Slatkin<sup>1</sup>). These early clinical trials were considered largely unsuccessful in that; there was no evidence of life extension; nonhealing ulceration of the skin developed in some patients; and in an effort to increase the radiation dose to deep seated tumors, four patients died as a result of the therapy.

It is generally believed that two major deficiencies led to the disappointing results of the first clinical trials. (1) The use of low-energy thermal neutron beams resulted in the peak neutron flux at the surface of the head, followed by an exponential decline so that the neutron flux at tumor depth was insufficient. (2) The compounds employed at that time did not provide the required selective accumulation of boron in the tumor. In this context, two important developments have occurred since 1961. First, through the use of appropriate filters and modulators the mean energy of the neutron beam at the BMRR was made slightly higher<sup>2,3</sup>, concurrent with the suppression of the thermal neutron flux. This modified beam, referred to as an epithermal neutron beam, results in a lower incident thermal neutron flux at the surface of the head, with increased thermal neutron fluxes at depth in the brain.

A second major advance has been the development of boron compounds which yield greater concentrations of  $^{10}\text{B}$  in the tumor as compared to those in surrounding normal brain tissues. Although several classes of boron delivery agents are in various stages of development (see review by Barth, et al.<sup>4</sup>), including boronated porphyrins, nucleosides, amino acids, polyamines, monoclonal and bispecific antibodies, liposomes, and growth factors, only two boron compounds currently are being used clinically, sodium borocaptate (BSH) and *p*-boronophenylalanine (BPA). BPA was originally synthesized in 1957 for potential use in BNCT of rapidly growing neoplasms<sup>5</sup>. It is an analog of the amino acid tyrosine, a precursor for melanin synthesis, and has been employed by the Japanese in the BNCT treatment of melanomas<sup>6</sup>. The use of BPA as a boron carrier for BNCT of malignant brain tumors was largely developed at Brookhaven using animal tumor models, particularly a transplantable malignant brain tumor in rats referred to as the 9L gliosarcoma<sup>7-9</sup>.

### **BPA-Based BNCT Preclinical Investigation**

BPA is a non-toxic, metabolic compound that is actively transported across the

blood-brain-barrier (BBB) and therefore has the potential for accumulation in islets or streamers of tumor cells that are otherwise protected by the BBB. It is thought that these islets of tumor cells lying outside the main body of the tumor are the sites of the majority of recurrences following conventional radiation and/or chemotherapy.

Because of its insolubility in aqueous solutions, BPA was first given orally. Later methods were developed, first by the Japanese<sup>10</sup> and then modified by scientists at Idaho State University<sup>11</sup> and Brookhaven<sup>9</sup>, to solubilize BPA by complexing it with fructose. Currently, the BPA-fructose complex (BPA-F) is administered systemically to both animals and humans.

When rats bearing intracerebral gliosarcomas are injected with BPA-F, tumor boron concentrations greater than 50  $\mu\text{g/g}$  are readily achieved with tumor-to-blood and tumor-to-brain ratios of about 4 to 1. The biochemical mechanism(s) responsible for the selective uptake of BPA in cells of primary brain tumors is not fully understood but may, in part, be related to their high metabolic activity. BPA, is an amino acid analog, and is actively transported across the tumor cell membrane by the neutral amino acid transport system.

When the heads of tumor-bearing, BPA-F injected rats are exposed at the optimal post-injection time to neutron irradiation (BNCT), long-term survivals (cures) were obtained in the absence of demonstrable damage to normal brain, i.e., selective ablation of the malignant brain tumor<sup>12</sup>. The fraction of rats "cured" by BNCT (as high as 90%) was radiation-dose dependent, with a steep response seen between 22.5 Gy and 60 Gy-Eq (see Figure 1).

### Clinical Investigations

After extensive studies in animals on the efficacy and toxicity of BPA-F, an FDA-sanctioned protocol to study the biodistribution of BPA-F in human patients scheduled to undergo surgical debulking of their malignant brain tumor was initiated in January, 1994. These studies were done in collaboration with the Beth Israel Medical Center in New York City. Patients were infused intravenously with BPA-F

Figure 1. Survival of rats bearing intracerebral 9L gliosarcomas as a function of time after tumor implantation. The median survival of untreated controls ( $n = 18$ ) was 22 days. All irradiations were performed on day 14 after tumor implantation. Rats treated with 22.5 Gy of 250 kVp X rays ( $n = 55$ ) had a median survival of 35 days with 20% long-term survivors. Rats treated with 7.5 MW-min of reactor irradiation following oral administration of BPA (BPA + 7.5 MW-min,  $n = 12$ ) showed 50% long-term survivors. Rats treated with PPA-F and either 4.2 ( $n = 14$ ) or 7.8 ( $n = 14$ ) MW-min of reactor irradiation showed 85% and 93% long-term survivors.

\*Gy-Eq is equal to the physical absorbed dose (Gy) times an experimentally determined biological effectiveness factor for each dose component<sup>13</sup>, including boron capture [ $^{10}\text{B}(n,\alpha)^7\text{Li}$ ], fast neutrons [ $^1\text{H}(n,n')p$ ], nitrogen capture [ $^{14}\text{N}(n,p)^{14}\text{C}$ ] and gamma rays.

over the 2-hour period just prior to the beginning of surgery. Samples of tumor removed by the neurosurgeon were analyzed for boron content and sections of these specimens were taken for histopathology.

In the first group of subjects studied, it was observed that boron concentration in tumor samples varied considerably among patients and even within multiple samples from individual patients. Histologic sections prepared from specimens analyzed for boron suggested there was a correlation between the degree of tumor cellularity and boron concentration<sup>14</sup>.

This correlation was quantified in a total of 14 patients, receiving varying doses of BPA and the results suggested that the  $^{10}\text{B}$  uptake in the active part of malignant brain tumors was quite consistent from patient to patient<sup>15</sup>. From these data we

calculated that following the intravenous infusion of 250 mg BPA/kg (the dose currently used to treat patients), the  $^{10}\text{B}$  concentration in the most cellular regions of malignant brain tumors in humans is about  $50\mu\text{g/g}$ , with tumor-to-blood and tumor-to-brain concentration ratios of  $\sim 4$  to 1. These ratios are similar to those found in rats.

The first patient with glioblastoma multiforme was treated with BNCT in September, 1994 i.e., 33 years after the termination of the early clinical trials (Figure 2). After a four-month period of observation to verify the safety of the procedure, particularly with regard to the potential for early-delayed neurological problems, a multipatient protocol was initiated in February 1995<sup>16</sup>. The objectives of the first protocols (a slightly modified protocol was started in 1995) were: (1) to determine a

**Figure 2.** BNCT treatment room at the Brookhaven Medical Research Reactor. (A) Epithermal neutron beam port and collimator; (B) Patient gurney; (C) Laser beams for patient alignment; (D) Video monitoring; (E) Voice communication; (F) Observation window.

safe starting dose for BNCT; (2) to evaluate any adverse effects of BNCT and; (3) to evaluate the effectiveness of BNCT at a safe starting dose in patients with glioblastoma multiforme. These protocols were terminated in February, 1995, after 15 patients had been treated with BPA-based BNCT at the BMRR.

The major conclusions drawn from these 15 patients were: (1) BNCT, as administered to these patients, was safe. There were no adverse effects associated with the infusion of BPA-fructose at a dose of 250 mg BPA/kg body weight. There was no damage to the scalp other than focal alopecia and no damage to normal brain or other critical organs was observed; (2) tumor palliation was achieved with a median life span at least equal to that observed with conventional therapies; (3) almost all patients had local progression of the disease.

Based on this experience a follow-up protocol was activated in June, 1996. Under the new protocol, radiation doses to tumor and the surrounding target volume (2 cm envelop around the tumor) have been increased. To date, January 14, 1997, thirteen patients have been treated, however, it is too early to determine whether or not the increased radiation doses will result in increased life span. This study remains in progress.

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