EARLY CLINICAL EXPERIENCE OF BORON NEUTRON CAPTURE THERAPY FOR GLIOBLASTOMA MULTIFORME


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Boron neutron capture therapy (BNCT) is a binary treatment modality that can selectively irradiate tumor tissue. BNCT uses drugs containing a stable isotope of boron, $^{10}$B, to sensitize tumor cells to irradiation by low energy (thermal) neutrons. The interaction of the $^{10}$B with a thermal neutron (neutron capture) causes the $^{10}$B nucleus to split, releasing an alpha particle and a lithium nucleus. These products of the $^{10}$B(n,$\alpha$)Li reaction are very damaging to cells but have a combined path length in tissue of approximately 14 $\mu$m, or roughly the diameter of one or two cells. Thus, most of the ionizing energy imparted to tissue is localized to $^{10}$B-loaded cells.

Biodistribution of the Boron Carrier

A Phase I/II clinical trial of BNCT for glioblastoma multiforme using the epithermal neutron beam at the Brookhaven Medical Research Reactor is underway. The boron compound tested in this initial trial is the amino acid analog p-boronophenylalanine (BPA). Prior to the initiation of Phase I/II clinical irradiations, the biodistribution of BPA was studied in patients with glioblastoma multiforme scheduled for debulking surgery. The BPA was solubilized for intravenous infusion by complex formation with fructose (1). The administered dose of BPA was escalated from 130 mg/kg body weight to 250 mg/kg body weight. All BPA-F infusions were 2 hours in duration. Figure 1 shows the boron concentrations in tumor and blood. Boron concentrations in the tumor samples are variable. Histologic examination of tumor sections adjacent to the samples used for boron analysis show areas of microscopic necrosis that vary from patient to patient and within multiple tumor samples from an individual patient. The boron analysis provides an average value for the entire sample. The tumor boron values shown in Figure 1 are mean values ($\pm$ sd) which underestimate the amount of boron in highly cellular areas of tumor. The average boron concentration correlates with the degree of cellularity measured in histological sections, indicating that tumor accumulates approximately three times more boron that is present in the blood. Boron concentrations in the normal brain have been equal to or less than the boron concentrations observed in the blood in all patients. Boron concentrations in scalp biopsies have been $\approx$1.5 times higher than those observed in blood. These results are consistent with data from Japan using 170 mg BPA/kg i.v. thermal neutron BNCT of malignant melanoma (2).

Radiobiological Considerations

The mixed radiation field produced during BNCT comprises radiations with different linear energy transfer (LET) characteristics 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, each of the high-LET dose components (physical dose in Gy) is multiplied by an experimentally determined factor to correct for different degrees of biological effectiveness. The total effective, photon-equivalent BNCT dose is then expressed as the sum of the RBE-corrected components with a unit named Gy-Eq (Gray-Equivalent). The short ranges of the two high-LET products of the $^{10}$B(n,α)Li reaction 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 biological effectiveness of the $^{10}$B(n,α) Li reaction. The dependence of the biological effect on variations in the microdistribution of different boron compounds, or the same boron compound in different tissues, makes the term RBE inappropriate in describing the biological effectiveness of the $^{10}$B(n,α) Li reaction. The term "CBE factor" is used and is defined as the product of the true, geometry-independent RBE for these high-LET particles multiplied by a boron localization factor, which will be different for each boron compound or for a given compound in different tissues. For BPA-based BNCT in tumor, the CBE-factor of 3.8 and the RBE for the high-LET beam components of 3.2 were determined from the results of in vivo/in vitro clonogenic assays in the 9L gliosarcoma rat brain tumor model (3). For BPA-based BNCT in normbrain, the CBE factor of 1.3 and the RBE for the high-LET beam components of 3.2 were determined from dose-response studies of the irradiated rat spinal cord with an endpoint of limb paralysis within 7 months (4).
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BNCT Clinical Trial: Study Design.
The objectives of the Phase I/II clinical trial are: 1) To determine a safe starting dose for BNCT using epithermal neutrons; 2) To evaluate adverse effects of BNCT; and 3) To evaluate the effectiveness of this starting BNCT dose level in patients with GBM. Patients receive BPA at the time of craniotomy for a biodistribution study. Three to four weeks later, the patients receive another BPA infusion and are irradiated with the BMRR epithermal neutron beam. The starting dose to the normal brain was chosen with primary consideration given to safety and possible adverse effects. The administered dose of BPA-F is 250 mg BPA/kg delivered as a 2 hour i.v. infusion. BNCT is delivered in a single fraction for about 40-50 min (with a pause for blood sampling) using a single field. The peak and average radiation doses to the normal brain are determined from the measured boron concentration in the blood during the irradiation. The prescribed absolute peak dose in a 1 cm³ brain volume is 10.5 Gy-Eq. The peak dose rate will be kept below 27 cGy-Eq/min so as not to exceed that used with photons in whole brain irradiation. The average dose to the whole brain volume will not exceed 7.5 Gy-Eq. The maximum dose to the scalp will not exceed 20 Gy-Eq. The deepest part of the contrast enhancing tumor must be ≤ 6 cm from the scalp surface. The target dose to the deepest part of the contrast-enhancing region of tumor is ≥ 20 Gy-Eq.

Clinical BNCT: Case Example Summary.
The BNCT clinical trial is only recently underway and statistically valid clinical results are not yet available. Results from a representative case are presented to illustrate the approach. The thermal neutron fluence from the epithermal beam reaches a maximum at approximately 1 cm depth in the brain, or about 3 cm depth from the scalp surface. The average 10B concentration in the blood during the irradiation was 15 µg 10B/g. To reach the prescribed dose of 10.5 Gy-Eq to the peak dose volume (1 cm³ volume at 3 cm depth from the scalp surface) required a peak thermal neutron fluence of 3.3 x 10¹³ n/cm². The total irradiation time was 88 MW-min (or 44 min at 2 MW BMRR power). The absolute peak physical dose (1 cm³ voxel) to normal brain was 7.9 Gy (3.47 Gy from the 10B(n,α)Li reaction, 3.66 Gy gamma, 0.40 Gy from the 14N(n,p)14C reaction, and 0.33 Gy from fast neutrons). Using the RBE and CBE factor values listed above, the peak physical dose of 7.9 Gy corresponds to the 10.5 Gy-Eq prescribed maximum brain dose.

The estimation of tumor dose depends on the value assumed for the tumor/blood boron concentration ratio. Correlation of the measured boron concentrations with the degree of cellularity in histological sections taken from the same tumor samples indicate that non-necrotic, viable glioblastoma accumulates 3 times more BPA than is present in the blood. Thus, for 45 µg 10B/g in tumor, and 88 MW-min irradiation time, the peak dose (1 cm³ volume) was 47.8 Gy-Eq. The minimum dose to the tumor volume was 50% of the absolute peak dose. Examination of the normal brain isodose contours on MRI images at different levels in the brain allowed an estimation of the dose to other vital structures. Expressed as a percentage of the absolute peak dose, 10.5 Gy-Eq, these were: ipsilateral basal ganglia, 65%; hypothalamus, 50%; cerebral midline, 25%; optic chiasm, ≤ 20%; retina, ≤ 10%. The dose/volume relationships for the normal brain and the tumor are shown for this case example in Figure 2. The average dose to the entire brain volume was 2.8 Gy-Eq (ipsilateral hemisphere, 4.4 Gy-Eq; contralateral hemisphere, 1.2 Gy-Eq).

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Summary: Ten patients have received BPA-based BNCT under the protocol outlined above. There have been no unexpected acute effects in the normal brain. Several patients have been followed for greater than 4 months with no observed effects on normal brain. Scalp showed mild erythema in a few patients at = two weeks post BNCT. Epilation was observed in all cases within the 8 cm diameter treatment field. Tumor recurrence has been observed in several patients after intervals of 7.5, 6 and 4 months, respectively. Correlation of the site of the recurrence with the original treatment plan is in progress. It appears that tumor recurrence is at depths where the tumor dose falls below 20 Gy-Eq. Plans for dose escalation are in progress. This research was supported in part by U.S. DOE under Contract DE-AC02-76CH00016.

Figure 2. Dose-volume relationships for the tumor and the normal brain. The average blood-boron concentration during BNCT was 15 µg 10B/g. Based on correlations of the data from the biodistribution study with cellularity in histological sections, the average boron concentration in the tumor was assumed to be 3 x that in the blood, or 45 µg 10B/g.

REFERENCES