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Protocols for BNCT of glioblastoma multiforme at Brookhaven: Practical considerations

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Introduction

Between September, 1994 and February, 1996 15 patients were treated with BPA-based BNCT at the Brookhaven Medical Research Reactor (BMRR) under two FDA-sanctioned protocols that differed primarily in the peak dose delivered to a volume of ~ 1 cm^3 of tissue 2 cm deep in the brain, generally located in the region of surgical debulking of the tumor, and in the average dose to ~ 16 cm^3 of brain (See Table 1). In this report we discuss some of the issues considered in the preparation of the initial clinical BNCT protocols and the rationale supporting the specifications adopted.

The first of these issues deals with tolerance of normal tissues within the radiation field, particularly the brain. The radiation dose limits established were based on results from both human and animal exposures to either single doses of photons [1-3] or single treatments with BNCT [4,5]. Collectively these studies suggest that the upper limit for a safe dose to the whole brain including the basal ganglia is between 10 and 11 Gy. Comparison of multiple fractions to a single fraction photon radiation using the brain tolerance unit formulation [6] supports this conclusion. Smaller volumes of brain (~ 14cm^3) were found to tolerate doses up to 20 Gy [7].

As shown in Table 1, the prescribed peak dose was 10.5 Gy-Eq in 11 patients and 12.6 Gy-Eq in 4 patients. The average calculated doses to the whole brain and basal ganglia were less than 3.0 Gy-Eq in all patients. In all BNCT treatments the dose rate was below 26 cGy-Eq/min. Although it was thought that these doses were conservative, it was considered advisable to initiate epithermal neutron-mediated BNCT as safely as possible while still delivering a potentially effective dose to the tumor.

Estimates of tumor control doses were based on the results of single-fraction photon therapy and single-fraction BNCT both in humans and in experimental animals [8-12]. The conclusion drawn from these studies was that 17 to 25 Gy-Eq should provide palliation and some prolongation of life in patients with glioblastoma multiforme but that higher doses may be required for long-term tumor control. In the patients treated with BNCT under these initial protocols, the nominal minimum tumor dose

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ranged from 20 to 37 Gy-Eq while the nominal minimum dose to the target volume (2 cm envelope around the tumor-enhanced MRI image) ranged from 8 to 17 Gy-Eq. In all patients tumor recurred between 3 and 9 months after BNCT.

Table 1. Radiation dose limits to the normal brain in the first BNCT protocols expressed as Gray-equivalent (Gy-Eq[1]). The number of patients is in parenthesis.

Brain Tissue	Gy-Eq.
Peak dose to ~ 1 cm^3 tissue	10.5 (11) 12.6 (4)
Average dose to ~ 16 cm^3 tissue	10.0 (11) 12.0 (4)
Average dose to whole brain	< 7.5 (15)
Basal ganglia	< 7.5 (15)

[1] Gy-Eq is equal to the absorbed dose (Gy) times an experimentally determined biological effectiveness factor for each dose component [13]

The decision to administer BNCT in a single fraction was based on the following reasons; 1) To date, all BNCT in humans has been delivered in a single fraction. 2) The distribution of BPA, particularly to normal brain, following more than one fraction of BNCT is unknown. 3) BNCT using BPA and the BMRR epithermal neutron beam allows a substantial tumor dose to be delivered without exceeding normal brain radiation tolerance. 4) Animal studies to date have not conclusively demonstrated that fractionation improves tumor control [14] nor have they shown that fractionation provides more than minimal protection to normal brain [15]. In the absence of experimental guidance as to the most effective method for fractionating BPA-mediated BNCT, we considered it prudent to start with single-fraction treatments.

Of the two boron compounds (BSH and BPA) potentially available, BPA was the rational choice since an FDA-sanctioned protocol for biodistribution in humans was in effect at the time the first BNCT protocols were written and therapy studies in experimental animals had shown it to be more effective than BSH [16]. Further, BPA is a non-toxic, metabolic compound that is actively transported across the blood-brain-barrier (BBB) with the potential for accumulation in islets or streamers of tumor otherwise protected by the BBB.

Other issues were less controversial. Prior debulking was deemed necessary to reduce tumor mass and to minimize the impact of post-BNCT cerebral edema. Maximum tumor depth was determined based on the limited thermal neutron flux to sites deep (> 6 cm) in the brain. A Karnofsky performance status (KPS) score of ≥ 70 was chosen to minimize potential problems associated with the requirement that patients be able to remain totally still during an exposure period of ~ 45 minutes without anesthesia. Also, this KPS score is used as a partitioning prognostic factor in analyzing patient survival [17]. Patients with a histopathologically confirmed diagnosis of glioblastoma multiforme were selected because their extraordinarily poor prognosis

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justifies their inclusion in an unproven experimental therapy. Patients with prior radiotherapy and/or prior chemotherapy were excluded because of the unknown degree of increased susceptibility of normal brain to BNCT resulting from these treatments.

These protocols were closed to patient entry in February, 1996. 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 approximately equal to that observed with standard therapies [18]. 3) Tumor recurrence was usually deep in the target volume, an area that received the lowest dose of radiation. 4) A simulation room outside the reactor for patient positioning is very advantageous.

Based on this experience a follow-up protocol received FDA sanction in June, 1996. Under the new protocol, radiation doses to tumor and target volume will be increased to 30 Gy-Eq [goal] and 17 Gy-Eq minimum [requirement] respectively. The average dose to the whole-brain and basal ganglia will be maintained at less than 7.5 Gy-Eq. These radiation dose parameters will be achieved by; 1) increasing the aperture size (8 cm to 12 cm) and thickness (7.6 cm to 15.2 cm) of the neutron beam collimator [19]; 2) incorporating bilateral irradiations if necessary to achieve the required dose to the target volume, and; 3) redefining the peak-dose as 12.6 Gy-Eq to less than 1% of the normal brain volume.

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