CORRELATION OF CLINICAL OUTCOME TO THE ESTIMATED RADIATION DOSE FROM BORON NEUTRON CAPTURE THERAPY (BNCT)


1 Department of Radiation Oncology and 3 Neurosurgery, Beth Israel Medical Center, NY, 2 Medical Department, Brookhaven National Laboratory, Upton, NY

OBJECTIVES

A phase I/II trial delivering a single fraction of BNCT using 11-Boronophenylalanine-Fructose and epithermal neutrons at the Brookhaven Medical Research Reactor was initiated in September 1994. The primary endpoint of the study was to evaluate the feasibility and safety of a given BNCT dose. The clinical outcome from the disease was a secondary endpoint of the study. The objective of this paper is to evaluate the correlation of the clinical outcome of patients to the estimated radiation dose from BNCT.

MATERIALS AND METHODS

From September 1994 to July 1995, 10 patients were entered into the study. This analysis is limited to these subjects so that we may have a minimum of 1 year follow up on all patients. The details of the trial design have been described by Elowitz et. al, in this issue. All patients had unilateral, biopsy proven glioblastoma multiforme. The median age was 61 years, range 46-75 years. Nine patients underwent a BPA-F biodistribution study. All patients received BNCT ≤ 4 weeks from the biodistribution. For BNCT, patients received 250mg/kg of BPA-F as a 2 hour intravenous infusion just prior to the neutron exposure. The protocol specified the peak dose-equivalent as the dose to a 1cm^3 volume, along the center beam line axis, where the thermal neutron flux reaches a maximum. For estimation of the photon-equivalent dose delivered from the various BNCT radiation dose components the relative biological effectiveness (RBE) and compound biological effectiveness (CBE) factors shown in Table I were used. These factors were experimentally derived and data in support of these values have been published. The sum of each physical absorbed dose component times the biological effectiveness factor gives the total dose-equivalent in Gy-Eq. The peak dose-equivalent was 10.3 -10.9 Gy-Eq in 9 patients and 13.8 Gy-Eq in 1 patient. The peak dose rate was ≤ 27 Gy-Eq/min. The mean irradiation time was 45 min (range 42 - 61 min).

All patients underwent a treatment planning MRI with radiographic markers identifying the tattoos on the patients scalp. These tattoos provided a baseline coordinate system correlating the spatial distribution of the tumor to the external anatomy. They were also used for identifying the central axis entry point of the beam on the scalp, as well as, verifying the treatment position. This is discussed in more detail by Wielopolski et. al, in this issue. The Monte Carlo treatment planning programs developed at Idaho National Engineering Laboratory were used for treatment planning.

Address for correspondence: Manjeet chadha M.D. Department of Radiation Oncology, Beth Israel Medical Center, 10 Union Square East, New York, NY 10003

DISTRIBUTION OF THIS DOCUMENT IS UNLIMITED
The program provides a graphical environment for 3D modeling of structures of interest from the radiographs. The tumor volume was defined as the contrast enhancing lesion. The target volume was the tumor volume plus a 2 cm margin. For the radiation dose evaluation, isodose lines were displayed on the actual radiographs (Fig 1) and dose volume histograms were generated (Fig 2).

During BNCT, only the blood $^{10}$B concentration was measured before, midway and after the neutron exposure. The treatment plan defined the photon equivalent dose rate to the normal brain endothelium per unit concentration of $^{10}$B in blood per megawatt-minute of reactor irradiation. The blood $^{10}$B values were used to calculate the irradiation time. The average blood $^{10}$B concentration was $13 \pm 1.5 \times 10^{-10}$B/g. The $^{10}$B concentrations in the tumor and normal tissues were estimated from the known $^{10}$B concentration ratios measured at the time of the biodistribution study. The $^{10}$B concentration was greater in tumor than in the blood by a factor of at least 3.5 when corrected for cellularity, this is further elaborated by Joel et.al, in this issue. The $^{10}$B concentration in the scalp and normal brain was taken as $1.5 \times 10^{-10}$B/g and equal to that in the blood, respectively. The radiation dose summary is as follows: The peak tumor dose ranged from 47.6-64.4 Gy-Eq (mean 52.8 $\pm$ 4.2 Gy-Eq), the minimum tumor dose ranged from 19.8-32.3 Gy-Eq (mean 25.2 $\pm$ 4.23), minimum target dose ranged from 7.8-16.2 Gy-Eq (mean 12.3 $\pm$ 1.8 Gy-Eq). All critical CNS structures received < 6.5 Gy-Eq and the dose to scalp ranged from 10-15 Gy-Eq.

All patients have been followed with serial physical exams MRI/CT scans.

RESULTS

In all patients, in-field alopecia was observed. Mild erythema was noted in 3 patients. No CNS toxicity attributed to BNCT was observed. A transient drop in lymphocyte count that returned to normal range within 2 weeks was observed. One patient relapsed in the craniospinal axis within 2 months of BNCT. The other nine patients have experienced local disease progression at the primary site at a median follow up of 6 months, range 2.7-9 months. The local disease progression was documented radiologically in all patients. Five patients also had $^{18}$FDG PET scans. Five patients had a craniotomy at the time of recurrence and histologic documentation of the recurrence was obtained.

The time to local disease progression was correlated to a number of clinical and treatment variables, i.e. time from initial diagnosis to BNCT, target volume, tumor volume, tumor depth, minimum target dose, average tumor dose, peak dose and the minimum tumor dose. Subjects were divided into 2 groups by time to local failure ($\geq$ 6 mos.vs.< 6 mos). Given the limited number of subjects, the Wilcoxon Rank Sum test was employed to compare clinical variables between two groups. We noted a statistically significant difference with a higher median average tumor dose and minimum tumor dose in the late failures as compared to early failures (Table II). Further, it was noted that patients with minimum tumor dose $< 25$ Gy - Eq had a median time to local disease progression of 3 months as compared to 6 months in patients who received a dose of $> 25$ Gy-Eq ($p<0.05$).

SUMMARY

This study was the first contemporary series of BNCT in brain tumors using an
DISCLAIMER

Portions of this document may be illegible in electronic image products. Images are produced from the best available original document.
epithermal beam. The primary objective of the study was to evaluate the feasibility and safety of a single fraction of BNCT. No significant side effects from the BPA-F infusion were observed. The delivered dose as per protocol was noted to be safe. A delayed time to disease progression was noted with higher tumor dose. Although these conclusions are based on a small number of patients, these observations provide insight and direction towards the design of future clinical trials using the epithermal beam. These data warrant continued trials with dose escalation. Presently, there is an ongoing trial at BNL studying the efficacy and safety of a minimum target dose of 17 Gy-Eq and double neutron field exposures.

Acknowledgment:
This research was supported by the US department of Energy under contract DE-AC02-76CH00016

Reference


DISCLAIMER
This report was prepared as an account of work sponsored by an agency of the United States Government. Neither the United States Government nor any agency thereof, nor any of their employees, makes any warranty, express or implied, or assumes any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, apparatus, product, or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any specific commercial product, process, or service by trade name, trademark, manufacturer, or otherwise does not necessarily constitute or imply its endorsement, recommendation, or favoring by the United States Government or any agency thereof. The views and opinions of authors expressed herein do not necessarily state or reflect those of the United States Government or any agency thereof.
Table I: BIOLOGICAL EFFECTIVENESS FACTORS

<table>
<thead>
<tr>
<th>Dose Component</th>
<th>Biologic effectiveness factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{10}\text{B} (n_{th}, \alpha)^7\text{Li}$</td>
<td>3.8 for tumor</td>
</tr>
<tr>
<td></td>
<td>1.3 for the normal brain</td>
</tr>
<tr>
<td></td>
<td>2.5 for the skin</td>
</tr>
<tr>
<td>Gamma</td>
<td>1</td>
</tr>
<tr>
<td>$^{14}\text{N} (n_{th}, p)^{14}\text{C}$</td>
<td>3.2</td>
</tr>
<tr>
<td>Fast neutron</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Table II: CORRELATION OF RADIATION DOSE AND TIME TO PROGRESSION

<table>
<thead>
<tr>
<th>Time to progression</th>
<th>Median dose (Gy)</th>
<th>Minimum dose to Target Volume</th>
<th>Average dose to Tumor Volume</th>
<th>Minimum dose to Tumor Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&lt; 6 \text{ mo}$</td>
<td>10.6</td>
<td>39.9</td>
<td>21.7</td>
<td></td>
</tr>
<tr>
<td>$\geq 6 \text{ mo}$</td>
<td>12.9</td>
<td>46.2</td>
<td>27.8</td>
<td></td>
</tr>
</tbody>
</table>

NS p=0.0317 p=0.0317
Figure Legends

Fig 1 isodose curves overlay on radiographs for tumor

Fig 2 Dose Volume Histogram for brain, tumor and target volume
Nominal Effective Dose (Gy-Eq)

Fraction of Volume (%)

Target

Tumor

Normal Brain