BNL-65104
CONF-9709182--

Nominal Effective Radiation Doses Delivered during Clinical Trials of Boron Neutron Capture Therapy

Capala, J., Diaz, A.Z., and Chanana, A.D.
Medical Department, Brookhaven National Laboratory, Upton, NY.

RECEIVED
JAN 2 6 1998
OSTI

Introduction

Boron neutron capture therapy (BNCT) is a binary system that, in theory, should selectively deliver lethal, high linear energy transfer (LET) radiation to tumor cells dispersed within normal tissues (Barth et al. 1996). It is based on the nuclear reaction 10-B(n, α)7-Li, which occurs when the stable nucleus of boron-10 captures a thermal neutron (Byrne 1995). Due to the relatively high cross-section of the 10-B nucleus for thermal neutron capture (3838 barn) and short ranges (comparable to tumor cell diameter) of the products of this reaction, tumor cells in the volume exposed to thermal neutrons and containing sufficiently high concentration of 10-B ($\approx$ 10e9 10-B atoms/cell) would receive a much higher radiation dose than the normal cells contained within the exposed volume. Nevertheless, radiation dose deposited in normal tissue by gamma and fast neutron contamination of the neutron beam, as well as neutron capture in nitrogen, 14-N(n,p)14-C, hydrogen, 1-H(n,γ)2-H, and in boron present in blood and normal cells, limits the dose that can be delivered to tumor cells (Fairchild and Bond 1985). It is, therefore, imperative for the success of BNCT the doses delivered to normal tissues be accurately determined in order to optimize the irradiation geometry and to limit the volume of normal tissue exposed to thermal neutrons. These are the major objectives of BNCT treatment planning.

Materials and Methods

Between September 1994 and November 1997, thirty six glioblastoma multiforme patients were treated in phase I/II BNCT trials at the Brookhaven National Laboratory (Chanana et al., 1998, manuscript in preparation). In these trials an amino acid analog, boronophenylalanine (BPA) as a fructose complex (BPA-F; Yoshino et al. 1989), has been used as a boron delivery agent. BPA is transported across the blood brain barrier and tumor brain barrier and it preferentially accumulates in tumor cells. The second component of modern BNCT, epithermal neutrons, are produced by filtration of neutrons from the Brookhaven Medical Research Reactor (BMRR; Liu et al. 1994 and 1996).

A complete treatment planning system developed at the Idaho National Engineering and Environmental Laboratory is being used in clinical

DISTRIBUTION OF THIS DOCUMENT IS UNLIMITED

MASTER

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.

DISCLAIMER

Portions of this document may be illegible electronic image products. Images are produced from the best available original document.

BNCT trials at Brookhaven. This system provides means to create a three-dimensional model describing patient anatomy and regions of interest (Wessol and Wheeler 1993), calculate the complex radiation fields produced during the treatment (Wheeler and Nigg 1992), create dose-volume histograms, and coregister the isodose contours with MR or CT images (Nigg et al. 1997).

The treatment planning process involves: 1. Obtaining a contrast-enhanced MRI scan of the patient's head. Scans are carried out with fiducial markers located over the triangulation points, which are then used for patient positioning. 2. Reconstruction of a 3D model of the patient's head with defined anatomical regions of interest using a graphical environment provided by the treatment planning program. 3. Calculation of the neutron flux and secondary radiation distribution using a 3D Monte Carlo radiation transport program. 4. Estimation of the absorbed dose distribution assuming a brain/blood boron concentration ratio of 1:1 and a tumor/blood boron concentration ratio of 3.5:1. 5. Identification of an optimal treatment position and calculation of the time of neutron irradiation required to deliver the prescribed peak normal brain dose. 6. Post-treatment evaluation of the dose distribution using the actual irradiation time and the ^{10}B concentrations measured in the blood at the beginning, in the middle and at the end of the treatment. In order to minimize the radiation dose to the normal brain, while delivering the minimum protocol prescribed dose to the target volume, an appropriate configuration of neutron fields are applied.

The mixed radiation field produced during BNCT comprises radiations with different linear energy transfers (LETs) and different efficacies in biological systems. To express the total BNCT dose in a common unit, which would allow comparison of BNCT doses with the those of conventional photon irradiation, multiplicative factors: relative biological effectiveness (RBE) and compound-adjusted biological effectiveness (CBE) factor (Coderre et al. 1993) of the physical absorbed radiation doses from each high-LET components of the BNCT dose were used. BNCT doses are expressed in Gray-equivalent (Gy-Eq). The following biological effectiveness factors were employed: 1.0 for gamma, 3.2 for high-LET beam components, and 1.3 and 3.8 for boron neutron capture products in the normal brain and tumor tissue, respectively (Coderre et al. 1997).

Results

Figure 1A, shows isodose contours resulting from a treatment of one patient under the current protocol using a 12 cm collimator and a single field irradiation.

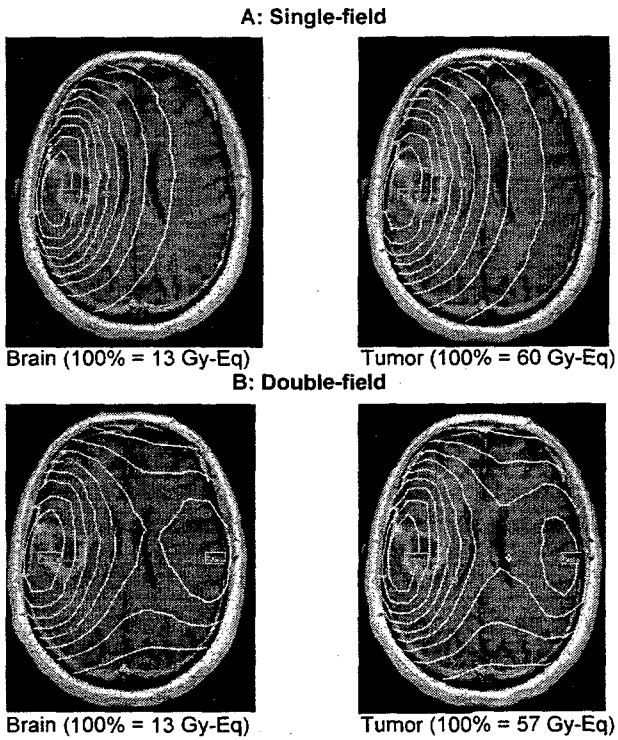

Figure 1. Isodose contours for normal brain (left panels) and tumor (right panels) resulting from treatment plans employing single- (A) or double-field (B) irradiations. The isodoses (at 10% interval) are superimposed on transaxial sections of MRI scans of head. The tumor volume is defined as the contrast enhancing volume.

Patients treated under the current single-field protocol received peak and average nominal brain doses ranging, respectively, from 12 to 14 Gy-Eq and from 3 to 4 Gy-Eq. The minimum doses delivered to tumor and target (tumor volume enclosed in a 2 cm shell) volumes were in the range 20 - 55 and 18 - 29 Gy-Eq, respectively. Note the rather steep gradient for both tumor and normal brain due to the rapid attenuation of thermal neutrons in tissue. In the previous protocols (Coderre et al. 1997),

patients treated at 2 MW with 8 cm collimator employing single field received peak and average nominal normal brain doses ranging from 9 to 12 Gy-Eq and from 2 to 3 Gy-Eq, respectively. The minimum tumor volume and target volume doses ranged from 20 to 37 Gy-Eq, and from 8 to 17 Gy-Eq, respectively.

Because of the rapid attenuation of the thermal neutrons in tissue and the limitations imposed by the radiation tolerance of the normal brain, two-field irradiation is employed for patients with relatively deep tumors. Figure 1B shows isodose contours resulting from treatment of such a patient. A 12 cm collimator and double field irradiation were used. In this example, 70% of the irradiation was delivered from the ipsilateral side and 30% was given from the contralateral side to minimize the radiation dose to the normal brain in the contralateral hemisphere. The patients treated under the current protocol with double-fields received higher average brain doses ranging from 4 to 5.5 Gy-Eq. The minimum doses delivered to tumor and target volume were in the range 18 - 41 and 15 - 29 Gy-Eq, respectively.

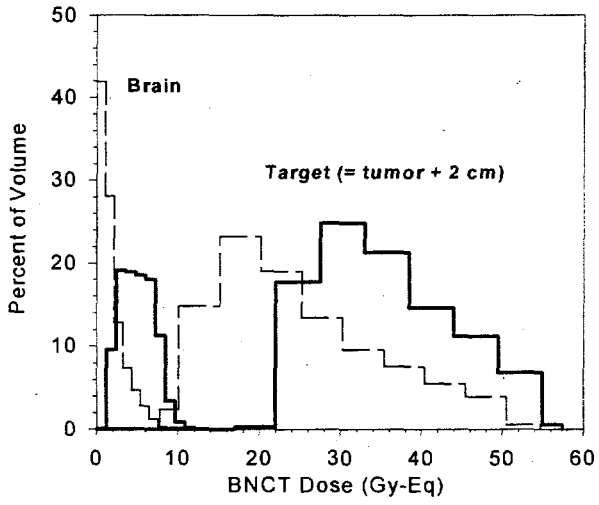

Figure 2. Dose volume histograms for the brain and target volumes resulting from treatment plans employing single- (dashed, thin line) or double-field (solid, thick line) irradiations.

Figure 2 shows the dose-volume histograms for brain and target volumes resulting from single-field BNCT (dashed lines) or double-field BNCT (solid lines). In this example, double-fields BNCT significantly increases the target volume dose, while the average brain dose, although higher, is still within the limits of 7.5 Gy-Eq prescribed by the protocol. It is noteworthy, that even the lowest doses delivered to the tumor cells within the target volume are higher than any dose delivered to the normal brain.

Discussion

BNCT is a promising modality for selective irradiation of tumor tissue. Due to the large cross section of boron for thermal neutron capture reaction and short range of products of this reaction, the radiation dose depends predominantly on the concentration of boron in the tissues exposed to thermal neutrons. The tumor cells containing relatively high concentrations of boron receive much higher radiation doses than the surrounding normal brain tissue. Unlike the conventional radiotherapy, the selectivity of BNCT is based on the biological characteristics of the tissue leading to selective accumulation of boron rather than the geometry of irradiation. This feature is especially useful for treatment of GBM, in which tumor cells are known to infiltrate normal brain away from the main tumor.

Following a two-hour intravenous infusion of BPA-F, the average concentration of boron in the normal brain ranges from 75% to 100% of that in the blood (Coderre et al., 1997). Recent studies in our laboratory have shown that corresponding microscopic concentration of boron in human glioblastoma multiforme cells is 3 to 4 times higher than that in the blood (Coderre et al. 1998). Tumor to blood and brain to blood ratios of, respectively, 3.5 and 1.0 were used for calculations of the nominal doses reported in this work. This difference, combined with CBE factors obtained for the boron neutron capture reaction from pre-clinical radiobiological studies (Coderre et al. 1993, Morris et al. 1994), resulted in a therapeutic ratios from 4.5 at the locations coincident with maximum flux of thermal neutrons (approximately at 2 cm) to < 1.0 at locations where thermal neutron flux was low. We have proposed a beam modification, which will increase the thermal neutron flux at depth by a factor of ≈ 7 and, thereby, improve the therapeutic ratios for deep tumors.

It is noteworthy that BNCT doses to normal brain to date under the dose escalation protocols are considerably lower than the prescribed doses that are permitted under the current protocol. In the next protocol, we intend escalation of the BNCT radiation dose to the normal brain in order to increase the tumor and target volume doses.

This research was supported in part by the U.S. Department of Energy under Contract DE-AC02-76CH00016.

References

Barth, R.F.;Adams, D.M.; Soloway, A.; Hbrugger, R.M. Borom neutron capture therapy of brain tumors: past history, current status, and future potential. Cancer Invest. 14:534-550; 1996.

Byrne, J.; Neutrons, nuclei and matter. An exploration of the physics of slow neutrons. Philadelphia, PA: Institute of Physics Publishing; 1995.

Coderre J.A.; Chanana, A.D.; Joel, D.D.; Elowitz, E.H.; Micca, P.L.; Nawrocky, M.M.; Chadha, M.; Gebbers, J.-O.; Shady, M.; Peress, N.S.; Slatkin, D.N.; Biodistribution of boronophenylalanine in patients with glioblastoma multifirme: boron concentration correlates with tumor celularity. Rad. Res. 1998, in press.

Coderre J.A.; Elowitz E.H.; Chadha, M.; Bergland, R.; Capala, J.; Joel, D.D; Liu, H.B.; Slatkin, D.N.; Chanana, A.D. Boron nautron capture therapy for glioblastoma multiforme using *p*-borophenyloalanine and epithermal neutrons: Trial design and early clinical results. J. Neuro-Oncol. 33:141-152; 1997.

Coderre, J. A.; Makar, M. S.; Micca, P. L.; Nawrocky, M. M.; Liu, H. B.; Joel, D. D.; Slatkin, D. N.; Amols, H. I.; Derivations of relative biological effectiveness for the high-LET radiations produced during boron neutron capture irradiations of the 9L rat gliosarcoma *in vitro* and *in vivo*. Int. J. Radiat. Oncol. Biol. Phys. 27:1121-1129; 1993.

Fairchild, R.G. and Bond, V.P. Current status of 10-B neutron capture therapy: enhacement of tumor dose via beam filtration and dose rate, and the effects of these paramenters on minimum boron content: a theoretical evaluation. Int. J. Radiat. Oncol. Biol.Phys. 11:831-840; 1985.

Liu, H.B.; Greenberg, D.D.; Capala, J; Wheeler, F.J. An improved neutron collimator for brain tumor irradiations in clinical boron neutreon capture therapy. Med. Phys. 23:2051-2060; 1996.

Liu, H.B.,; Brugger, R.M.; Greenberg, D.D.; Rorer, D.C.; Hu, J.-P.; Hauptman, H.M. Enhancement of the epithermal neutron beam used for boron neutron capture therapy. Int. J. Radiat. Oncol. Biol.Phys. 28:1149-1156; 1994.

Morris, G.M.; Coderre, J.A.; Hopwell, J.W.; Micca, P,L.; Nawrocky, M.M.; Liu, H.B.; Bywaters, T. Response of the central nervous system to boron neutron capture irradiation: evaluation using rat spinal cord model. Radiotherapy and Oncologu 32:249-255;1994.

Nigg, D.W.; Wheeler, F.J.; Wessol, D.E.; Capala, J.; Chadha M. Computational dosimetry and treatment planning for boron neutron capture therapy. J. Neuro-Oncol. 33:93-104; 1997.

Wessol, D.E.; Wheeler, F.J. Creating and using a type of free-form geometry in Monte carlo particle transport. Nucl. Science and Engineering. 113:314-323; 1993.
Wheeler, F.J.; Nigg, D. W. Three-dimentional radiation dose distribution analysis for boron neutron capture therapy.Nucl. Science and Engineering. 110:16-31; 1992.
Yoshino, K.; Suzuki, A.; Mori, Y.; Kakihana, H.; Honda, C.; Mishima, Y.; Kobayashi, T.; Kanda, K. Improvement of solubility of *p*-borophenylialanine by complex formation with monosaccharides. Strahlentherapie und Oncologie. 165:127-129; 1989.