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Boron neutron capture therapy of intracerebral rat gliosarcomas

(glioma/sulfhydryl borane dimer/radiotherapy)

D. D. JOEL*†, R. G. FAIRCHILD*, J. A. LAISSUE‡, S. K. SARAF*, J. A. KALEF-EZRA§, AND D. N. SLATKIN*

*Medical Department, Brookhaven National Laboratory, Upton, NY 11973; ‡Pathologisches Institut, Universität Bern, Bern, CH-3010, Switzerland; and §Medical School, University of Ioannina, Ioannina 45110, Greece

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ABSTRACT **The efficacy of boron neutron capture therapy (BNCT) for the treatment of intracerebrally implanted rat gliosarcomas was tested. Preferential accumulation of ^{10}B in tumors was achieved by continuous infusion of the sulfhydryl borane dimer, $Na_4{}^{10}B_{24}H_{22}S_2$, at a rate of 45–50 μg of ^{10}B per g of body weight per day from day 11 to day 14 after tumor initiation (day 0). This infusion schedule resulted in average blood ^{10}B concentrations of 35 μg/ml in a group of 12 gliosarcoma-bearing rats and 45 μg/ml in a group of 10 similar gliosarcoma-bearing rats treated by BNCT. Estimated tumor ^{10}B levels in these two groups were 26 and 34 μg/g, respectively. On day 14, boron-treated and non-boron-treated rats were exposed to 5.0 or 7.5 MW·min of radiation from the Brookhaven Medical Research Reactor that yielded thermal neutron fluences of ≈2.0 × 10^{12} or ≈3.0 × 10^{12} n/cm², respectively, in the tumors. Untreated rats had a median postinitiation survival time of 21 days. Reactor radiation alone increased median postinitiation survival time to 26 (5.0 MW·min) or 28 (7.5 MW·min) days. The 12 rats that received 5 MW·min of BNCT had a median postinitiation survival time of 60 days. Two of these animals survived >15 months. In the 7.5 MW·min group, the median survival time is not calculable since 6 of the 10 animals remain alive >10 months after BNCT. The estimated radiation doses to tumors in the two BNCT groups were 14.2 and 25.6 Gy equivalents, respectively. Similar gliosarcoma-bearing rats treated with 15.0 or 22.5 Gy of 250-kilovolt peak x-rays had median survival times of only 26 or 31 days, respectively, after tumor initiation.**

It is postulated that successful boron neutron capture therapy (BNCT) of human gliomas would require the preferential accumulation of ^{10}B in the tumor (1), low levels of ^{10}B in the blood and in the surrounding normal tissues, and the delivery of sufficiently high thermal neutron fluences at tumor sites (2). The initial clinical trials of BNCT of malignant brain tumors, conducted in the U.S.A. from 1951 through 1961, were disappointing, apparently because some of these conditions were not fulfilled (3).

The polyhedral sulfhydryl borane (monomer), $Na_2B_{12}H_{11}SH$, was first investigated in the 1960s for possible use in BNCT (4). Evidence in animal tumor models indicates that tumor uptake after administration of the sulfhydryl borane dimer ($Na_4B_{24}H_{22}S_2$) is about double the tumor uptake after administration of equal amounts of boron as monomer (5, 6). Furthermore, it was observed that the decrease in tumor boron concentration is much slower after infusion of dimer than of monomer (6). Studies in rats bearing transplanted cerebral gliosarcomas indicate that slow infusion of dimer at the rate of ≈50 μg of ^{10}B per g of body weight per day for 3 days consistently yields tumor boron concentrations >25 μg of ^{10}B per g with average concentrations in normal brain tissue <2 μg of ^{10}B per g. This degree of selective tumor boron uptake should provide an adequate therapeutic gain for BNCT. We used this infusion schedule to test the efficacy of BNCT in the treatment of transplanted intracerebral rat gliosarcomas.

MATERIALS AND METHODS

Brain Tumor Model. The transplantable gliosarcoma (7) used in this study was originally induced in a Fisher 344 rat by weekly i.v. injections of *N*-nitrosomethylurea (8). Only scattered areas of the tumor have glial fibrillary acidic protein and S-100 protein antigens. However, pericellular reticulin fibrils are widespread in the tumor. Many tumor cells are strongly positive for the 57-kDa intermediate filament protein vimentin. Scattered foci of tumor cells are cytokeratin positive.

Intracerebral tumors were initiated in Fisher 344 rats (Taconic Farms) that weighed 200–220 g by inoculating 1.0 μl of culture medium containing 10^4 cultured gliosarcoma cells into the left frontal lobe at a point 4 mm lateral to the midline and 1 mm anterior to the coronal suture. A 27-gauge needle was fitted with a Teflon collar to ensure cell injection 4 to 5 mm beneath the skull. As in human gliosarcomas (9), this tumor does not produce blood-borne metastases but sometimes does seed ventricular or leptomeningeal surfaces. In preliminary studies, death ensued in 22 ± 4 (mean ± SD; n = 30) days from an expanding supratentorial tumor around the site of inoculation.

Preparation of Sulfhydryl Borane Dimer. The sulfhydryl borane dimer was prepared as described (10). Briefly, $Cs_2B_{12}H_{11}SH$ (Callery Chemical, Pittsburgh) was oxidized to $Cs_4B_{24}H_{22}S_2$ using *o*-iodosobenzoic acid and ion-exchanged to the sodium salt. Thin-layer chromatography with 3 M aqueous NH_4NO_3/acetonitrile (2:1) on DEAE-cellulose plates (Brinkmann) was used to assess purity (11). For animal infusion studies, aqueous solutions of the sulfhydryl borane were made isotonic to plasma by addition of sodium chloride and were sterilized bacteriologically by filtration through 0.22-μm-diameter pore filters. To minimize oxidation, aliquots of the continuously refrigerated $Na_4B_{24}H_{22}S_2$ solution were removed daily for infusion, which never began more than 2 days after the ion exchange.

Boron Analysis. Each tissue or blood sample was placed in a fused quartz test tube to which water was added to bring the net weight of the contents (H_2O + sample) to 1.00 ± 0.01 g. Boron concentrations of such aqueous samples were analyzed by prompt-γ spectrometry (12). Internal controls were samples of normal tissue to which an aqueous solution of ^{10}B-enriched boric acid (U.S. National Bureau of Standards) was added to bring the total net weight to 1.00 ± 0.01 g.

BNCT. Rats were anesthetized (120 mg of ketamine/20 mg of xylazine per kg of body weight) and prepared for intraperitoneal (i.p.) infusion using small-animal swivels and spring tethers (Harvard Apparatus), silicone tubing (i.d., 0.61 mm;

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Abbreviations: BNCT, boron neutron capture therapy; RBE, relative biological effectiveness; Gy-Eq, gray equivalent; kVp, kilovolt peak.

†To whom reprint requests should be addressed.

o.d., 1.15 mm; Dow), and syringe pumps (Rozel Scientific Instruments, Stamford, CT). After a 1- to 2-hr period of saline infusion, dimer was continuously infused for 72 hr in unanesthetized rats with little or no restriction of their movement within individual cages (48 × 26 × 20 cm). Similar schedules of i.p. and i.v. infusions of dimer in rats yield equivalent tissue boron concentrations (6).

Within 15 min after the termination of dimer infusion, rats were anesthetized and placed supine in a body-radiation shield (13) designed to reduce exposure to fast-neutron contamination (14) of the slow-neutron beam. The dorsum of the rat's head was abutted to the neutron collimator and positioned so that the intracranial tumor zone was centered in the 11.5-mm-diameter aperture (Fig. 1*A*). Reactor power was maintained at 1.25 ± 0.06 MW during a 4- or 6-min exposure, which corresponds to a 5.0- or a 7.5-MW·min reactor exposure, respectively.

Dosimetry. Thermal neutron fluences were measured by implanting 3-mm-long segments of gold wire (diameter, 0.25 mm) in the left frontal cerebrum of recently killed rats parallel to and at depths of 1.0–6.5 mm beneath the skull surface, and then exposing these rats to reactor radiations as shown in Fig. 1*A*. The positions of the wires were confirmed radiographically. At depths of 4–5 mm, which correspond to the location of an intracerebral gliosarcoma 14 days after tumor initiation, 5.0 MW·min exposures resulted in thermal neutron fluences of $\approx 2 \times 10^{12}$ cm^{-2}. Measurements in a Lucite rat phantom yielded similar results.

The fast (>10 keV) neutron and γ doses to the rat at the port were determined by using paired tissue-equivalent (TE) plastic chambers (Shonka A-150 plastic; Far West Technology, Goleta, CA) with TE gas (Rossi gas) and graphite chambers filled with CO_2 gas. The fast-neutron dose was calculated by subtracting the γ dose from the total dose. Thermoluminescent dosimeters (TLD-700; Harshaw Chemical, Solon, OH) were sometimes used instead of graphite chambers.

Experimental Design. Experimental groups are listed in Table 1. The BNCT groups received dimer infusion and either 5.0 MW·min (group Ia) or 7.5 MW·min (group IIa) reactor exposures. Two companion groups of rats received either 5.0 MW·min (group Ib) or 7.5 MW·min (group IIb) reactor exposures but no dimer infusion. Two control groups (groups Ic and IIc) were untreated and received neither dimer infusion nor reactor radiation. Another group (group III) of rats was infused with dimer but did not receive reactor radiation. Between days 11 and 14 after tumor initiation on day 0, groups Ia, IIa, and III were infused continuously with dimer for 72 hr. Groups Ia, IIa, Ib, and IIb were irradiated on day 14. At this time, the tumors were fully vascularized (7) and weighed 35–40 mg, which represents approximately the same fraction of the total brain weight as do the weights of most human malignant cerebral gliomas when they are first treated. In individual experiments, BNCT rats were accompanied by nearly equal numbers of untreated controls and non-boron-treated reactor-exposed rats, all of which had tumors initiated on the same day from the same cell suspension. Animals were weighed and observed daily. Rats were killed within 8 hr after they first exhibited periocular hemorrhage and neurologic signs of increased intracranial pressure associated with rapid loss of body weight, since experience showed that death would always occur 24–48 hr later. A small proportion of rats died suddenly without exhibiting any premonitory signs of disease. Necropsy of each rat confirmed that the observed neurological signs were attributable to a 200- to 350-mg brain tumor in the region of the inoculum, and not to a second brain tumor, to distant

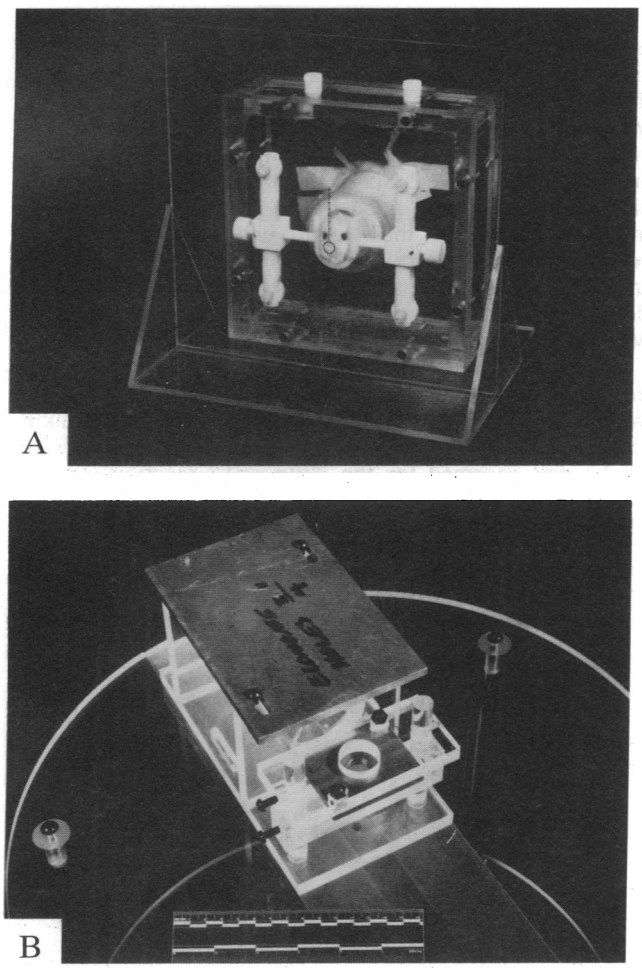

FIG. 1. (*A*) Anesthetized rat held supine in the body radiation shield of the beam-modification assembly. The gantry-supported head is photographed through a Lucite plate, a surrogate for the neutron collimator, to depict the orientation of the rat head at the therapy aperture. The positions of the 11.5-mm circular aperture and of several horizontal fiducial lines at the reactor port are marked on the Lucite plate. This permits accurate adjustment of the rat's head prior to placement at the reactor port. (*B*) Holder for x-irradiation therapy of rats bearing intracerebral gliomas. The lead plates are 11 mm thick. A 1.4-cm-diameter aperture in the head plate was positioned directly over the tumor area. The circular Plexiglas table was rotated slowly around the center of the aperture. The dose rate was 3.75 Gy/min; 250 kilovolt peak (kVp); 30 mA; 0.5-mm Cu plus 1.0-mm Al filtration.

Table 1. Summary of treatment conditions for each experimental group of rats

Experimental group	No. of animals	Total amount of ^{10}B infused, μg of ^{10}B per g of body weight (mean ± SD)	Reactor radiation, MW·min
Ia	12	130 ± 9	5.0
Ib	15	—	5.0
Ic	12	—	—
IIa	10	144 ± 9	7.5
IIb	13	—	7.5
IIc	12	—	—
III	8	149 ± 11	—

^{10}B, as ^{10}B-enriched sulfhydryl borane dimer, was continuously infused i.p. for 72 hr beginning on day 11 after tumor implantation (day 0). Reactor power was 1.25 MW while rats were exposed for 4 min (5.0 MW·min) or 6 min (7.5 MW·min). This corresponds to a thermal neutron fluence of $\approx 2.0 \times 10^{12}$ cm^{-2} (groups Ia and Ib) or $\approx 3.0 \times 10^{12}$ cm^{-2} (groups IIa and IIb) near the center of the tumor on the day of irradiation.

metastases or to spread via the cerebrospinal fluid to ventricular or meningeal tissue of the brain or spinal cord.

X-Ray Therapy. Similar gliosarcomas were treated by photon irradiation 14 days after tumor initiation, using a 250-kilovolt peak (kVp) General Electric Maxitron 250 x-ray generator. Rats were anesthetized and placed prone in a holder shielded by 11-mm-thick lead (Fig. 1*B*). The head shield contained a 1.4-cm-diameter aperture centered over the tumor. The 22-cm distance from the anode to the head surface resulted in an average dose rate of ≈3.75 Gy/min (250 kVp, 30 mA, 0.5-mm Cu and 1.0-mm Al filtration) as measured with a Victoreen ionization chamber and confirmed with LiF thermoluminescent dosimeters (TLD-100; Harshaw Chemical) placed on rats after euthanasia. The holder was slowly rotated in a horizontal plane around the center of the aperture during irradiation. One group of rats received 15.0 Gy (surface) in 4 min to correspond to the 5.0 MW·min, BNCT-treated rats. A second group received 22.5 Gy (surface) in 6 min to correspond to the 7.5 MW·min BNCT-treated animals. A third group was untreated and was observed concurrently.

RESULTS

BNCT. Rats tolerated the 3-day i.p. infusion of dimer; however, they all lost weight (mean, 15%) due in part to the cannulation/tethering procedure and in part to dimer hepatotoxicity (15).

Rats in the BNCT groups Ia and IIa were initially the same in total number as those in the reactor-irradiation-only groups Ib and IIb. Three rats in group Ia died within hours after reactor exposure without recovering from anesthesia. Increased sensitivity to anesthetics in dimer-treated rats may be associated with altered liver function, as was observed with hexobarbital anesthesia in mice pretreated with monomer (16). Three animals from group IIa, not included in the analysis, developed bilateral hind-limb paralysis and were killed 35–40 days after tumor implantation. At necropsy, tumors were observed at the base of the cerebellum and in the caudal spinal canal but not in the cerebrum. These findings, which were not evident in other experiments, are attributable to rare, accidental seeding of tumor cells in the lateral ventricle at the time of tumor initiation, with subsequent translocation to distal sites via the cerebrospinal fluid. Increased life-span from effective control of the cerebral tumor by BNCT may have provided additional time for the growth of distal tumors to cause paralysis, which was never observed in experiments in which rats bore untreated or ineffectively treated cerebral tumors.

The survival of rats (Fig. 2) in group III was essentially the same as that of untreated controls. All rats in group III died or were killed between days 21 and 24 after tumor initiation. The 26-day median survival of non-boron-treated rats that received 5.0 MW·min of reactor radiation was longer than the 21-day median survival of control rats, with only 90% probability. Although the median survival of non-boron-treated rats that received 7.5 MW·min (28 days) was numerically higher than that of non-boron-treated rats that received 5.0 MW·min (26 days), this difference was not statistically significant.

The median survival (60 days) of rats in the BNCT group Ia (5.0 MW·min) was significantly longer ($P < 0.01$) than either control rats or rats receiving reaction radiation only. Of the 12 animals in this group, 2 are alive 15 months after treatment. When the reactor radiation exposure was increased to 7.5 MW·min (group Ib), a further increase in survival was observed. Six of the 10 animals so treated are alive and generally in good health 11 months after tumor initiation. Thus, the median survival time of this group remains unknown. Between 10 and 15 months after BNCT treatment, the 2 long-term survivors in the 5.0 MW·min group developed cataracts in the left eye, while all 6 rats in the 7.5 MW·min group developed cataracts in both eyes.

Dosimetry. The calculated radiation doses in Gy and Gy equivalents (Gy-Eq) to the tumor and other critical tissues within the field of exposure are listed in Table 2. In making these calculations, a relative biological effectiveness (RBE) of 2.3 was assumed for the $^{10}B(n,\alpha)^{7}Li$ reaction (18) and RBEs of 2.0 each were assumed for fast neutrons and for charged particles from the $^{14}N(n,p)^{14}C$ reaction. With a 5.0

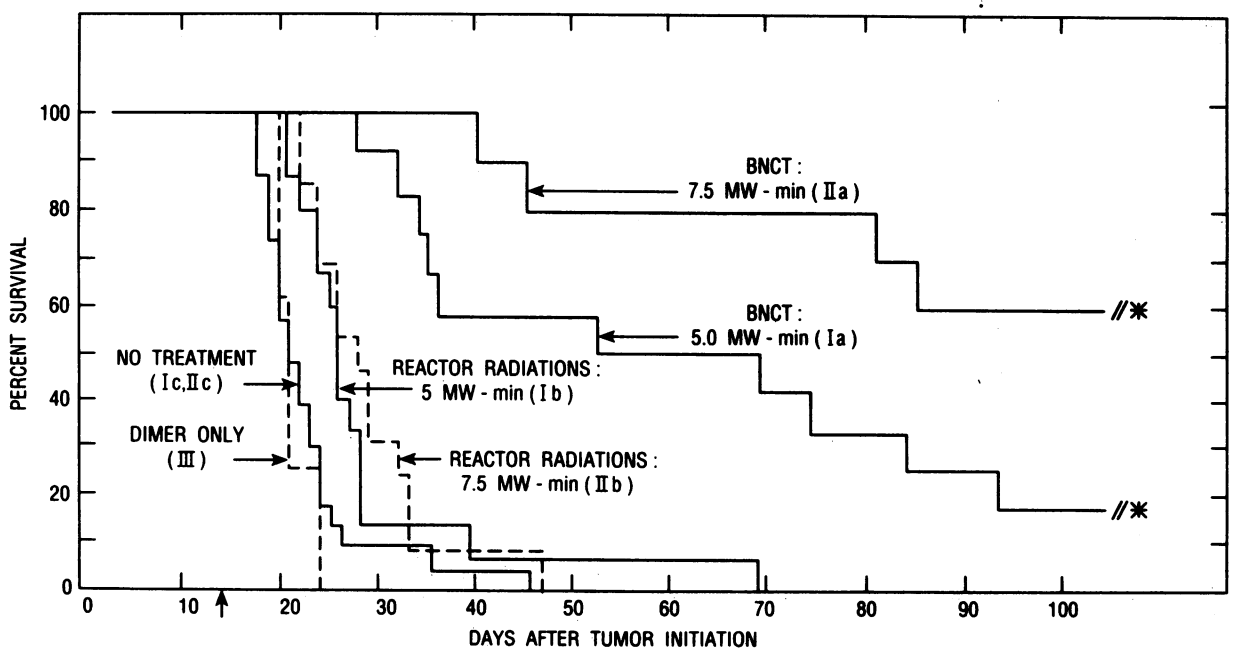

FIG. 2. Effect of BNCT as compared to no treatment, reactor radiation only, and dimer only, on the survival of rats bearing intracerebral gliosarcomas. Intraperitoneal infusion of sulfhydryl borane dimer (≈50 μg of ^{10}B per g of body weight per day for 3 days) preceded reactor irradiation. Experimental group numbers listed in Table 1 are in parentheses. Reactor exposure was on day 14 after tumor initiation (arrow). *, Survival >10 months.

Table 2. Radiation doses to critical tissues during BNCT of rat brain tumors

Tissue	Radiation dose			
	5.0 MW·min		7.5 MW·min	
	Gy	Gy-Eq	Gy	Gy-Eq
Blood	8.2	17.6	14.8	32.2
Brain tumor	6.7	14.2	12.0	25.6
Capillary endothelium	4.4	8.8	7.6	15.2
Brain parenchyma	2.5	4.6	3.8	6.9

The Gy-Eq dose is defined here as the sum of the physical doses in Gy of each radiation component multiplied by the RBE of that component. The term RBE-dose may also be used to describe Gy × RBE. In making these calculations, a RBE of 2.3 was assumed for the $^{10}B(n,\alpha)^7Li$ reaction and RBEs of 2.0 each were assumed for fast neutrons and for charged particles from the $^{14}N(n,p)^{14}C$ reaction. The average (±SD) blood ^{10}B concentrations, as measured by prompt γ spectrometry of blood specimens, were 34.9 ± 5.5 μg/ml in the 5.0 MW·min group and 44.9 ± 8.9 μg/ml in the 7.5 MW·min group. ^{10}B concentrations of brain tumors for the two BNCT groups were estimated to be 26.2 and 33.7 μg/g, respectively, based on previous studies, which indicated that, with the infusion regimen used in this study, the average tumor concentration was 75% of the blood concentration (6). Radiation doses to normal brain capillary endothelial cells were estimated to be the sum of one-third of the blood dose plus two-thirds of the dose to the brain parenchyma (17), assuming that $(B_{24}H_{22}S_2)^{4-}$ does not cross the normal blood–brain barrier in appreciable amounts (5). The average ^{10}B concentration in brain parenchymal tissue of rats receiving these dimer infusion schedules was found to be only 1.4 ± 1.0 μg of ^{10}B per g (n = 24).

MW·min reactor irradiation exposure, the thermal neutron fluence at the tumor depth, as measured *in situ* with cadmium correction of gold wire activation, was 1.95 × 10^{12} n/cm^2, which corresponds to a dose of 0.39 Gy-Eq per μg of ^{10}B per g in tissue. The dose of radiation resulting from the $^{14}N(n,p)^{14}C$ reaction in tissues during the 5 MW·min exposure was calculated to be 0.76 Gy-Eq, assuming a tissue nitrogen concentration of 2.6% (wt/wt). Fast neutron and γ-radiation dose equivalents, measured in air, were 2.70 and 0.55 Gy-Eq per 5.0 MW·min reactor irradiation, respectively. Intrinsic γ radiation from the $^1H(n,\gamma)^2H$ reaction with body hydrogen was negligible. Tumor doses were proportionately (50%) greater for the 7.5 MW·min exposures than for the 5.0 MW·min exposures. Body (abdominal) doses from fast neutrons and γ photons, measured 7 cm from the 11.5-mm neutron port, were 1.7 and 2.6 Gy-Eq, respectively.

X-Ray Therapy. To assess the photon-radiation sensitivity of this tumor, two groups of rats with 14-day intracerebral tumors were exposed to 15.0 Gy (n = 10) or 22.5 Gy (n = 16) (Fig. 3). The median survival of 15.0-Gy-exposed rats was 26 days. One of these 10 animals is alive 10 months after treatment. Rats exposed to 22.5 Gy had a median survival time of 31 days. Four of the 16 animals in this group are alive and in apparent good health 10 months after treatment.

DISCUSSION

To our knowledge, there has not been another report of systematic control of a rapidly lethal experimental brain tumor by using BNCT. Clendenon *et al.* (19) reported some statistically significant extension of life in rats treated with BNCT at the Brookhaven Medical Research Reactor using monomer as the boron transport agent, but there were no long-term survivors.

Although the monomer is used in Japan for BNCT of malignant brain tumors, we have been unable to obtain sustained, therapeutic ^{10}B levels in rat gliosarcoma tumors with this compound. In contrast, tumor ^{10}B concentrations exceeding 25 μg/g are readily achieved with slow infusion of dimer. Furthermore, after the termination of dimer infusion, tumor boron levels decrease so slowly that therapeutic concentrations can be maintained during the time of reactor irradiation. If it were necessary to artificially reduce the blood boron concentration by plasmapheresis, tumor boron levels should be virtually unaffected (6).

Estimated tumor boron concentrations at the time of reactor irradiations were 26.2 μg of ^{10}B per g in the group of rats receiving 5.0 MW·min and 33.7 μg of ^{10}B per g in the 7.5 MW·min group. Assuming a RBE of 2.3 for the $^{10}B(n,\alpha)^7Li$ reaction (18), the tumor radiation doses for the two BNCT groups were calculated to be 14.2 and 25.6 Gy-Eq, respectively. About 75% of the total effective dose to the tumor was from the $^{10}B(n,\alpha)^7Li$ reaction. In these two experimental

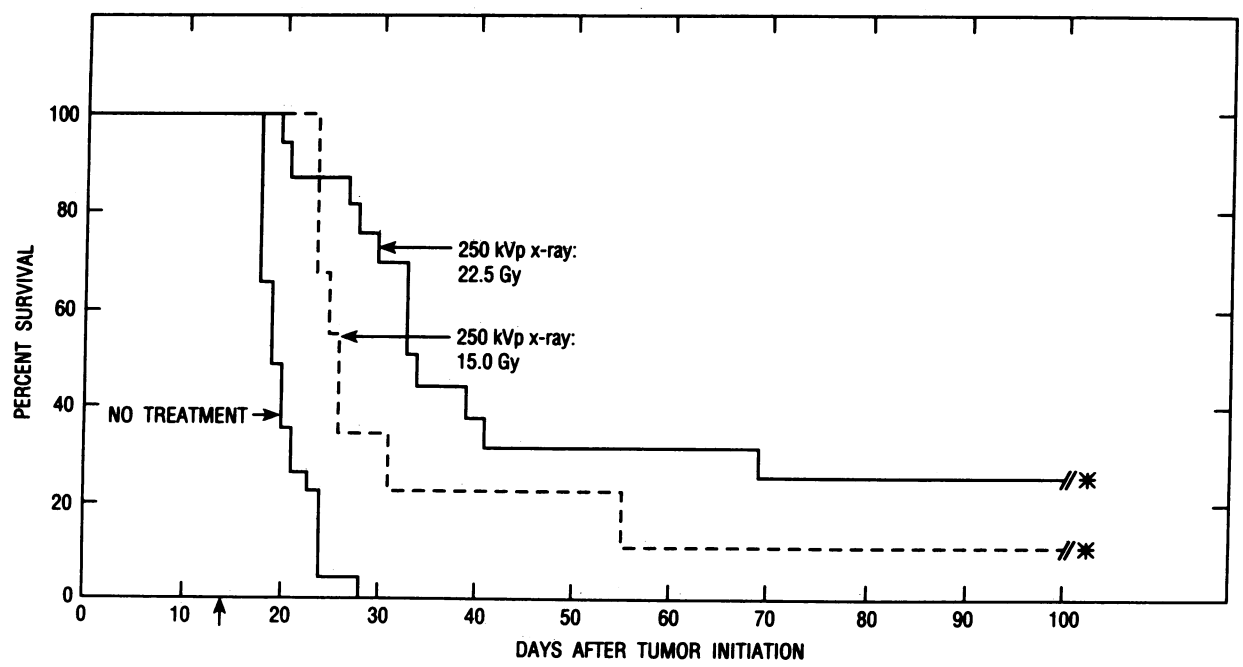

FIG. 3. Effect of x-irradiation on the survival of rats bearing the intracerebral gliosarcomas. Irradiation was given on day 14 after tumor initiation (day 0; arrow). *, Survival >10 months.

groups, the total radiation doses to normal brain tissue were 4.6 and 6.9 Gy-Eq, yielding unprecedented tumor-to-brain therapeutic gains of >3:1.

The use of 2.3 as the RBE of the $^{10}B(n,\alpha)^7Li$ reaction is based in part on studies by Gabel *et al.* (18) *in vitro* and by Slatkin *et al.* (17) *in vivo*. This value for RBE was also accepted at the Massachusetts Institute of Technology Workshop on neutron beam design for BNCT (13) for calculating the contribution to the radiation dose equivalent from the neutron–^{10}B reaction. The doses presented here are based on an average distribution of ^{10}B throughout the tumor. Clearly, the effectiveness of BNCT will vary with the microdistribution of ^{10}B within the tumor. Whether most of the boron is extracellular, bound to the cell membrane, in the cytoplasm, or in the nucleus of tumor cells is an important dosimetric consideration. At present, however, the cellular and subcellular localization of ^{10}B after infusion of the sulfhydryl boranes has not been ascertained. Moreover, the contribution of BNCT-induced injury to vascular endothelium in the control of tumor growth remains to be clarified.

Six of the 10 BNCT-treated animals in the 7.5 MW·min group are alive 10 months after tumor initiation, which suggests that the 50% tumor control dose may be ≈25 Gy. This is reasonably consistent with a long-term survival of 4 of the 16 rats treated with 22.5-Gy x-rays. Using the same tumor model, Barker *et al.* (20) reported long-term survival in only 1 of 20 rats treated with 20-Gy x-irradiation to the whole head. Although an x-irradiation dose of 20–25 Gy may be effective in controlling a small fraction of tumors, it is possible that rats receiving these doses may develop delayed radiation-induced brain damage several months after treatment (21). Calvo *et al.* (22) reported that 39 and 52 weeks after local irradiation of the rat brain, the doses of x-rays associated with a 50% incidence of necrosis were 23.45 ± 0.49 and 20.89 ± 0.91 Gy, respectively. Over a dose range of 15–20 Gy of x-rays, vascular lesions have been reported in rats after a latent period of up to ≈2 years (23). In contrast, with BNCT it was possible to deliver doses of radiation that controlled or eliminated a large fraction of tumors while keeping radiation doses to brain parenchyma and to normal capillary endothelium below 7 and 16 Gy-Eq, respectively, which are doses that should cause little or no detectable brain damage in the rat.

Damage to brain endothelium may present particular problems if reactor exposures take place when blood boron levels are high. Since some BNCT-treated rats may develop late-delayed brain lesions, surviving rats will be observed throughout their life-span. Potential problems from radiation damage to endothelium can, if necessary, be alleviated by lowering the blood boron concentration with plasmapheresis. When dimer is used as the capture agent, tumor boron levels are essentially unaffected by this procedure (6). The question of how the lowered blood boron levels may influence the overall effectiveness of BNCT for gliomas is, however, unresolved.

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