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The radiobiological principles of boron neutron capture therapy: A critical review

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ABSTRACT

The radiobiology of the dose components in a BNCT exposure is examined. The effect of exposure time in determining the biological effectiveness of γ-rays, due to the repair of sublethal damage, has been largely overlooked in the application of BNCT. Recoil protons from fast neutrons vary in their relative biological effectiveness (RBE) as a function of energy and tissue endpoint. Thus the energy spectrum of a beam will influence the RBE of this dose component. Protons from the neutron capture reaction in nitrogen have not been studied but in practice protons from nitrogen capture have been combined with the recoil proton contribution into a total proton dose. The relative biological effectiveness of the products of the neutron capture reaction in boron is derived from two factors, the RBE of the short range particles and the bio-distribution of boron, referred to collectively as the compound biological effectiveness factor. Caution is needed in the application of these factors for different normal tissues and tumors.

1. Introduction

The initial treatment of patients with glioblastoma, in the early 1950s, at Brookhaven National Laboratory, were carried out using thermal neutrons and borax as the boron carrier (Farr et al., 1954). These patient treatments were undertaken after an extremely limited number of preclinical animal studies. Moreover, the understanding of the increased biological effectiveness of particle irradiation relative to X- or γ-rays was in its infancy at that time. Although never published, a small study was carried out on dogs (Calvo, personal communication) to assess the safety of the proposed clinical irradiation protocol. Four animals were exposed to thermal neutrons after the administration of borax and they remained fit and well after 48 h. Thus the treatment was judged to be safe.

While such an approach would be considered insufficient in the present era, it should be recognized that none of the present concepts underlying the radiobiological basis of radiotherapy were established at that time and even conventional radiotherapy had developed largely on the basis of anecdotal evidence from observations on patients. Thus, the early attempts at boron neutron capture therapy (BNCT) were understandably limited in terms of the ability to estimate and predict responses from such a complex, mixed field of irradiation.

A greater understanding of the increased biological effectiveness of particle radiation, relative to X- or γ-rays, has come from studies related to the application of fast neutron radiotherapy (Field, 1976). However, yet again, the initial clinical attempts at fast neutron therapy were compromised by a lack of radiobiological knowledge. The early investigators were well aware that fast neutrons were biologically more effective than X-rays and animal experiments were undertaken to determine the relative biological effectiveness (RBE), the ratio of absorbed doses from the novel experimental radiation and X-rays required to produce the same biological effect. However, patients were still seriously overdosed in the initial clinical study (Stone, 1948). Only later did it become evident that this was because the initial experiments were carried out using large single doses and that the low RBE values obtained were then applied to patients treated with fractionated irradiation doses. It was not recognized initially that RBE increased with decreasing dose/fraction and depended on the tissue and endpoint observed (Fowler, 1982).

While relevant and extensive preclinical studies are now often the norm and should indeed be mandatory, the problems of the past should serve as a pointer to the future use of BNCT, particularly for new applications. Failure to take full account of our current understanding of radiobiological principles, or the application of inappropriate weighting factors to new applications, could result in

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clinical under- or over-dosage of patients and significantly delay the full clinical application of this potentially useful radiotherapy modality. The various radiobiological issues involved in the safe application of BNCT are discussed in greater detail elsewhere (Hopewell et al., in press).

2. Basic radiobiological considerations

BNCT is a mixed field irradiation. The principal dose components, in addition to the α-particles and ^{7}Li ions resulting from the boron capture reaction:

$$^{10}B + {}^{1}n = {}^{7}Li + {}^{4}He\ (\alpha) + 2.79\,MeV$$

include γ-rays (d_γ), both incident within the neutron beam and induced by the neutron capture reaction in hydrogen:

$$^{1}H + {}^{1}n = {}^{2}H + \gamma + 2.2\,MeV$$

plus protons, either as recoil protons (d_n) from fast neutron interactions, largely with hydrogen, or from neutron capture (d_N) by nitrogen in tissue:

$$^{14}N + {}^{1}n = {}^{14}C + {}^{1}p + 580\,keV$$

These various absorbed dose components, contributing to the total radiation dose, are usually assumed to act independently of each other in patient treatment planning. Thus the total photon-equivalent dose (D_w) is given by the equation:

$$D_w = (d_\gamma \times DRF) + (d_n \times RBE_n) + (d_N \times RBE_N) + (^{10}B \times CBE)$$

where DRF is the dose reduction factor for γ-rays, which varies with dose-rate; RBE_n is the relative RBE of fast neutrons, which depends on neutron energy, RBE_N the equivalent value for protons from the nitrogen capture reaction and CBE the compound biological effectiveness factor, which is derived from two factors: the RBE of α-particles and ^{7}Li ions and the micro-distribution of ^{10}B in a particular tissue. Due to the short range of these particles in tissue, 9 and 5 μm, respectively, the biological effect depends critically on both the gross and microscopic distributions of boron in tissues.

3. Radiobiological properties of γ-rays

The radiobiological effects of low-LET X- or γ-rays have been extensively investigated as they are the predominant radiation used in radiation therapy. The radiobiological property of most significance for BNCT is the variation in the biological effectiveness of the low-LET radiation, as a function of dose-rate. This effect is due to the repair of sublethal radiation damage during the time of exposure. For prolonged exposures to low dose-rate γ-rays, the effectiveness is decreased compared to γ-rays delivered at a dose-rate of 1 Gy/min or more. This is clearly illustrated by examining the effects of different dose-rates on the clonogenic survival of cells *in vitro* (Bedford and Mitchell, 1973). The γ-ray dose-rates for the present generation of clinically used epithermal neutron beams are in the range 0.16–0.086 Gy/min, a range where these γ-rays would be less biologically effective than those delivered at approximately 1 Gy/min; i.e. they would have a DRF of <1.0.

The radiation response of CNS, along with many other tissues, has been shown to depend on dose-rate (e.g. Pop et al., 2000). Moreover, based on the kinetics of repair of sublethal damage, models have now been developed to allow the calculation of equivalent X- or γ-rays doses for different exposure times and for fractionated irradiation with incomplete repair intervals (Millar and Hopewell, 2007). For dose-rates <0.1 Gy/min, comparable to existing epithermal neutron beams, the DRF (relative to a high dose-rate of 1.8 Gy/min) is <0.7 as illustrated in the examples in Table 1. The dose-rate effect for γ-rays was not taken into account in the initial studies in many centers, including Petten and BMRR. Only when overall exposure times are short (<10 min), as in some biological studies with thermal neutron beams (Morris et al., 1994a, 1994b), can the effects of repair of sublethal damage be considered sufficiently small to be ignored.

Table 1
Variation in γ-ray characteristics of three epithermal neutron beams used clinically for BNCT.

Beam	FiR1[a]	HFR	BMRR
γ-rays (%)[b]	80.0	66.8	73.0
Dose-rate (Gy/min)	0.076	0.035	0.017
DRF	0.6	0.5	0.45
	–	(1.0)[c]	(1.0)[c]

[a] Center location: Helsinki, Petten and Brookhaven, respectively.
[b] γ-rays contribution to the total absorbed dose.
[c] DRF values assumed by the centers involved.

4. Radiobiological properties of fast neutrons

Studies on the relative biological effectiveness of fast neutrons have been carried out in relation to neutron therapy. Neutron facilities for therapy vary in the energy spectrum of the neutrons produced. The implications of this have been compared using a range of *in vitro* and *in vivo* assays. The most extensive set of comparative studies have used the mouse intestinal crypt assay (Gueulette et al., 1996). These studies showed up to a 50% difference in biological effectiveness when other neutron beams were compared to a relatively high average energy reference beam. The higher the mean energy of the neutron beam, the lower the RBE.

In vitro studies, using V79 cells, with relatively mono-energetic neutron sources, have shown a defined relationship between neutron energy and RBE (Hall et al., 1975). For damage assessed at the doses required to reduce the surviving fraction to 37%, neutrons with an energy of 0.3–0.4 MeV appeared to be the most biologically effective with a RBE of ~6.0. As the energy of the neutrons was increased the RBE value decreased, appearing to reach a minimum value of 1.7 for neutron energies in the range 5–15 MeV. For neutron energies <0.3 MeV the RBE also declined, being less than 4.0 for 0.1 MeV neutrons. In a study with 24 keV neutrons, from a filtered reactor beam, the trend continued for the same endpoint (Morgan et al., 1988).

5. Radiobiological properties of protons from the nitrogen capture reaction

The protons produced as a consequence of the thermal neutron/nitrogen capture reaction have a low energy of 580 keV and thus have very high-LET characteristics. There are no ways of directly determining the RBE of this energy of protons from a mixed field irradiation involving either thermal or epithermal irradiations and hence, for practical reasons, the nitrogen capture dose is frequently included with the fast neutron dose, as a combined beam high-LET dose.

Only a limited number of studies have been undertaken using mono-energetic protons of similar energies (e.g. Belli et al., 1989). Those studies, like those with fast neutrons, were carried out using V79 cells. For protons of decreasing energy (increasing LET) from 7.4 to 1.16 MeV, the RBE, for a surviving fraction of 37%,

increased from a little over 1.0 up to a maximum value of ~3.0. For protons with an even lower energies of 0.84 and 0.73 MeV, the RBE declined progressively from the maximum value. The RBE value, based on a surviving fraction of 37% of 1.8, appeared to be lower than might have been anticipated from the fast neutron studies (Hopewell et al., in press). This observation raises doubts about the assumption that the biological weighting factor used for recoil protons should be the same as that for protons from the nitrogen capture reaction, the common assumption in BNCT treatment planning.

6. Implications for the weighting of dose for epithermal neutron beams

It has already been mentioned that although a lower DRF of 0.45 has been estimated to be appropriate for CNS for use with the epithermal neutron beam at the BMRR and elsewhere, a value of 1.0 was actually used (Table 1). In a separate analysis (Benczik et al., 2003) the dose-related incidence of a number of endpoints, after epithermal neutron irradiation of dog brain on the FiR1 beam, was converted into photon-equivalent doses based on the weighting factors derived from studies on dogs and used clinically for the epithermal neutron beam at the BMRR, namely 1.0 for low-LET γ-ray component and 3.2 for the high-LET component of the beam (Gavin et al., 1997). The use of the BMRR weighting factors for the FiR1 beam consistently produced an over-estimate of the equivalent photon dose received when compared with the actual data for dogs irradiated with 6 MV X-rays. The magnitude of the over-estimate of the photon-equivalent dose using the BMRR weighting factors for the FiR1 beam was 12%. In an alternative approach, the kinetics of repair of sublethal damage for CNS tissue have been used to calculate equivalent X-ray doses for the different experiments that were carried out to establish weighting factors for the FiR1 and BMRR epithermal neutron beams (Hopewell et al., in press). Based on the endpoint of multiple contrast-enhancing lesions in the brain of dogs, the weighting factors for the FiR1 beam were 0.78 for the low-LET γ-ray component and 3.3 for the high-LET component of that beam. The comparable values for the epithermal neutron beam at the BMRR, for a slightly more severe endpoint—lethal necrosis in the dog brain, were 0.73 for the low-LET γ-ray component and 4.1 for the high-LET component of that beam, values close to alternative weighting factors initially suggested for application to the BMMR beam (Gavin et al., 1997) but not adopted for clinical use. These data illustrate the inherent dangers of applying weighting factors derived in one epithermal neutron beam to another neutron beam, no matter how similar the two beams may appear from the point of view of the absorbed dose components.

7. Radiobiological properties of boron capture agents

The amino acid, p-boronophenylalanine (BPA), and the sulfhydryl borane (BSH) were two of the compounds extensively evaluated. Compound development continues to be an active area of BNCT research. However, given the degree of characterization required, it would take several years for any new compound to enter a clinical trial. At this time, BPA and BSH are the only two boron compounds in use for clinical BNCT.

Experimentally derived CBE factors are very tissue specific and can also be related to the boron compound administration protocol and thus must always be used with caution in any clinical treatment protocol. The bio-distribution profile of a given boron delivery agent needs to be as thoroughly characterized as possible in the relevant animal models and in patients. In particular, the vascular/nonvascular ^{10}B partition ratio in the animal model used to derive the CBE factor must be similar to the ratio in patients at the time of irradiation for a specified type of tumor or normal tissue. It cannot be emphasized enough that comparability of ^{10}B bio-distributions is a prerequisite to translate an animal model-derived CBE factor to the clinical situation. Equally, the determination of a relevant CBE factor, for any new application of BNCT, should be a mandatory part of any development program. For a more detailed discussion of this important aspect of radiobiological research see Hopewell et al. (in press).

8. Potential interaction between high- and low-LET radiations

As indicated previously, it is presently assumed that the different components of the mixed field irradiation used in BNCT act totally independently. In the calculation of weighting factors for the high-LET component of the total dose, assumptions are made about which DRF to use for the γ-ray contribution to the total dose based on experience from conventional radiotherapy. However, only a relatively small increase in the biological effectiveness of γ-rays, due to what appears to be an enhanced biological effectiveness of the low-LET radiation component when given in combination with a high-LET radiation (McNally et al., 1988), relative to γ-rays alone, would significantly reduce the apparent RBE/CBE of the high-LET components of this mixed beam irradiation, since assumptions about the DRF used for γ-rays will have an impact on the RBE/CBE values. While of considerable importance, this potential interaction between high- and low-LET radiations has not been extensively studied. The only study that has been undertaken is the sequential irradiation of V79 cells with fixed doses of α-particles prior to exposure to high dose-rate X-rays (McNally et al., 1988). A recent re-evaluation of these data has been performed (Hopewell et al., in press). The RBE of X-rays, combined with 2.5 Gy of α-particles was ≥ 1.15, compared with X-rays given alone. This requires more extensive investigation.

References

Bedford, J.S., Mitchell, J.B., 1973. Dose-rate effects in synchronous mammalian cells in culture. Radiat. Res. 54, 316–327.

Belli, M., et al., 1989. RBE–LET relationship for the survival of V79 cells irradiated with low energy protons. Int. J. Radiat. Biol. 55, 93–104.

Benczik, J., et al., 2003. Evaluation of the relative biological effectiveness of a clinical epithermal neutron beam using dog brain. Radiat. Res. 159, 199–209.

Farr, L.E., et al., 1954. Neutron capture therapy with boron in the treatment of glioblastoma multi-forme. Am. J. Roentgenol. Radium Ther. Nucl. Med. 71, 279–293.

Field, S.B., 1976. An historical survey of radio-biology and radiotherapy with fast neutrons. Curr. Top. Radiat. Res. Q 11, 1–86.

Fowler, J.F., 1982. Workshop summary. Int. J. Radiat. Oncol. Biol. Phys. 8, 2207–2210.

Gavin, P., et al., 1997. A review: CNS effects and normal tissue tolerance in dogs. J. Neuro-Oncol. 33, 71–80.

Gueulette, J., et al., 1996. RBE variation between fast neutron beams as a function of energy. Inter-comparison involving 7 neutron therapy facilities. Bull. Cancer Radiother. 83 (Suppl.), 55s–63s.

Hall, E.J., et al., 1975. RBE as a function of neutron energy. I. Experimental observations. Radiat. Res. 64, 245–255.

Hopewell, J.W., et al., Boron neutron capture therapy: application of radiobiological principles. In: Sauerwein, W., et al. (Eds.), Textbook of Neutron Capture Therapy. Springer, in press.

McNally, N.J., et al., 1988. Interaction between X-ray and α-particle damage in V79 cells. Int. J. Radiat. Biol. 53, 917–920.

Millar, W.T., Hopewell, J.W., 2007. Effects of very low dose-rate $^{90}Sr/^{90}Y$ exposure on the acute moist desquamation response of pigskin: comparison based on predictions from dose fractionation studies at high dose-rate with incomplete repair. Radiother. Oncol. 83, 187–195.

Morgan, G.R., et al., 1988. The radiobiology of 24 keV neutrons: measurement of the relative biological effect free-in-air, survival and cytogenetic analysis of the biological effect at various depths in a polyethylene phantom and modification of the depth–dose profile by boron 10 for V79 Chinese hamster and HeLa cells. Br. J. Radiol. 61, 1127–1135.

Morris, G.M., et al., 1994a. Response of rat skin to boron neutron capture therapy with p-boronophenylalanine or borocaptate sodium. Radiother. Oncol. 32, 144–153.
Morris, G.M., et al., 1994b. Response of the central nervous system to boron neutron capture irradiation: evaluation using rat spinal cord model. Radiother. Oncol. 32, 249–255.
Pop, L.A., et al., 2000. Radiation tolerance of rat spinal cord to pulsed dose rate (PDR-) brachytherapy: the impact of differences in temporal dose distribution. Radiother. Oncol. 55, 301–315.
Stone, R.S., 1948. Neutron therapy and specific ionization. Am. J. Roentgenol. Radium Ther. 59, 771–785.