MINIREVIEW

Neutron-Capture Therapy of Brain Tumours: Neutron Sources, Neutron-Capture Drugs, Biological Tests and Clinical Perspectives in the Czech Republic

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Summary

The paper reviews neutron sources, chemical compounds and clinical perspectives of the boron neutron-capture therapy of brain tumours. Special attention is paid to the physical characteristics and biological effectiveness of the epithermal neutron beam constructed at the LVR-15 nuclear reactor at Řež near Prague.

The Principles of Boron Neutron-Capture Therapy

The ultimate goal of cancer radiotherapy is to achieve a degree of selectivity that would spare normal tissue and destroy malignant cells, namely those which cannot be eliminated by surgery. Neutron-Capture Therapy (NCT) is a new targeted radiation modality which brings together two components that have only small biological effects when kept separate. The first component is a stable isotope of boron (^{10}B), the second one is a beam of low energy neutrons which interact with the boron nucleus according to equation

$$^{10}B + n \longrightarrow {}^{7}Li\,(0.84\ MeV) + {}^{4}He\,(1.47\ MeV) + \gamma\,(0.48\ MeV)$$
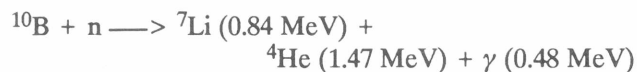
The released ^{7}Li atom and α-particle (^{4}He) have a total energy of 2.31 MeV which is several orders higher than that of the applied neutrons. In addition, the energy is deposited within the range of approximately 5 and 9 μm, i.e. at a distance corresponding to about one cell diameter. As a consequence, the biological effectiveness of this radiation is much higher than that of thermal neutrons. In principle, one boron-neutron interaction liberates enough energy to kill the cell in which the interaction is taking place. The short distance deposition of the released energy spares the surrounding boron-free tissue from radiation damage. The biological effects of alpha particles are less oxygen-dependent and can destroy hypoxic parts of a tumour more effectively than other types of radiation. The alpha particles cause DNA lesions repair (Kliegel 1980, Barth et al. 1992 etc.).

As it is evident, the therapeutic results of boron-NCT (BNCT) depend on the penetration of slow neutrons into the tissue and the selectivity of ^{10}B accumulation in tumour masses. Great effort is therefore concentrated on the improvement of thermal neutron beams, the development of ^{10}B containing molecules with high tumour cells affinity and further optimization of treatment-planning procedures.

Neutron Sources

At present, nuclear reactors serve exclusively as sources of neutrons for BNCT. Thermal neutron beams with energies around 0.025 eV and beams of higher-energy epithermal neutrons (1–10 000 eV) are most often used. Due to the high radiation capture during the passage of thermal neutrons, their energy is rapidly attenuated in the irradiated tissues. As a consequence, it is difficult to obtain sufficient fluxes of thermal neutrons in inner parts of large tumours. Beams of epithermal neutrons with higher energy can be produced by using a filter or moderator as a spectrum shifter which slows the fast neutrons to an intermediate energy range. Epithermal neutrons are still relatively non-destructive and provide better penetration than thermal neutrons. Moreover, they produce thermal neutrons in the tissue because of its moderating effects. As a consequence, such a beam of neutrons peaks the thermal neutrons deep in the irradiated tissue. The number of reactors suitable for BNCT all over the world is, however, limited and their therapeutic use requires building of additional hospital facilities close to the reactor. In the future, introduction of alternative sources of neutrons, such as hospital-based nuclear reactor-independent accelerators may make BNCT more accessible and safer (Allen and Beynon 1995). At present, the main centres with NCT operated reactors are at the Brookhaven National Laboratories, Upton, N.Y.,(epithermal neutron beam with a flux of 1.8 x 10^9 cm^{-2} s^{-1}), Massachusetts Institute of Technology, Cambridge, Mass., USA (epithermal neutron flux 2 x 10^8 cm^{-2} s^{-1}), Joint Research Center at Petten, the Netherlands (epithermal neutron flux 3.3 x 10^8 cm^{-2} s^{-1}). In Japan, thermal neutron beams (10^9 neutrons cm^{-2} s^{-1}) are used at the Kyoto University, Kyoto and Japan Atomic Energy Research Institute in Tokai-Ibaraki.
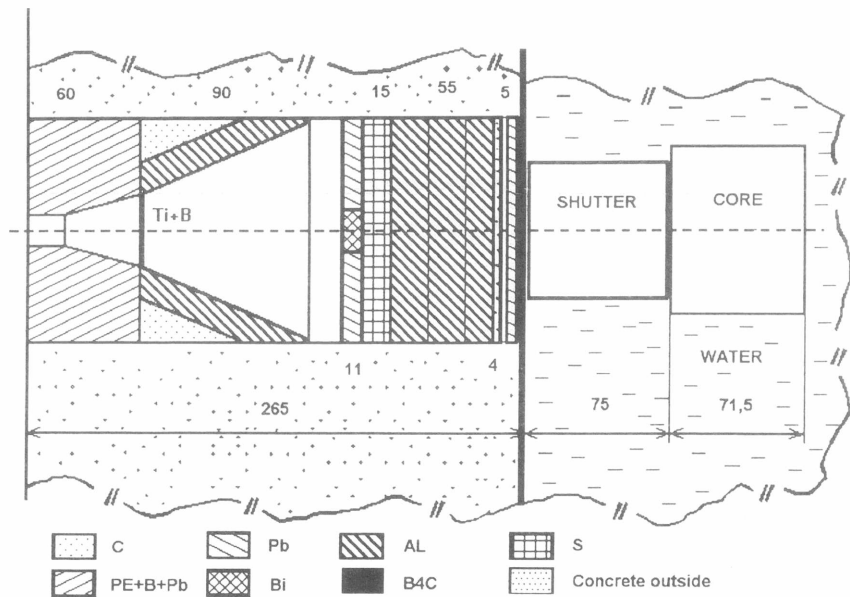

Fig. 1. *Configuration of epithermal neutron beam in LVR-15 reactor.*
Core: source of the fast neutrons. Shutter: inner tank filled with water. The block of filters in front of the shutter consists of 0.5 cm B4C, 5 cm Pb, 4 cm C, 55 cm Al and 11 cm Pb. The conical collimator (90 cm) is made of Al+C and 1 cm of Ti+B. The outer shutter is made polyethylene (PE), B and C and a thin layer of Ti+B (60 cm). The place of irradiation of a patient is at the mouth of the outer shutter (*).

A beam of epithermal neutrons has also been constructed at the LVR-15 reactor of Nuclear Research Institute in Řež near Prague for the treatment of brain glioblastomas. In this case, it was necessary to overcome technical problems caused by the long distance (4 m) between the core of the reactor and the irradiation point. As is shown in Fig. 1, the beam was obtained by moderating and filtrating

neutrons by cylindrical blocks of graphite, aluminum, sulphur and titanium, with a thickness of 5, 55, 15 and 1 cm, respectively. The outer diameter of the beam is 11.5 cm which is adjusted by a final shutter. A graphite collimator is placed between the shutter and block of filters. The beam parameters in the "shorter" filter modification without the graphite layer are given in Table 1. They were obtained by semiconductor Si-Li and solid state nuclear track detectors, fission chambers, silicon diodes, thermoluminescence detectors and scintillation spectrometer for gamma radiation. The neutron spectrum was evaluated by Bonner spheres, a scintillation spectrometer, a proportional hydrogen spectrometer and activation monitors (Burian *et al.* 1993, Marek and Burian 1994). The input spectrum was calculated by the discrete ordinates transport code (DORT) using the SAILOR-DLC76 cross section library. As is shown in Table 1, at 2.5 cm from the outer aperture (reactor power 10 MW) the flux of epithermal neutrons is 1.07×10^8 cm^{-2} s^{-1}. The flux is approximately 2.5 times lower at a distance of 20 cm.

Table 1. Characteristics of the BNCT epithermal neutron beam at the LVR-15 reactor (10 MW power)

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Total neutron flux	1.47×10^8 cm^{-2} s^{-1}
Thermal neutron flux (<0.414 eV)	2.43×10^7 cm^{-2} s^{-1}
Epithermal neutron flux (0.414 eV to 10 keV)	1.07×10^8 cm^{-2} s^{-1}
Fast neutron flux (>10 keV)	1.57×10^7 cm^{-2} s^{-1}
Ratio of fast to epithermal flux	0.15
Ratio of fast to total flux	0.11
"Average" neutron energy	13.3 keV
Fast neutron dose rate	0.5 Gy/h
Fast neutron dose per epithermal neutron	1.3×10^{-12} Gy.cm^2
Incident gamma dose rate	2.25 Gy/h
Incident gamma dose per epithermal neutron	7.3×10^{-12} Gy.cm^2
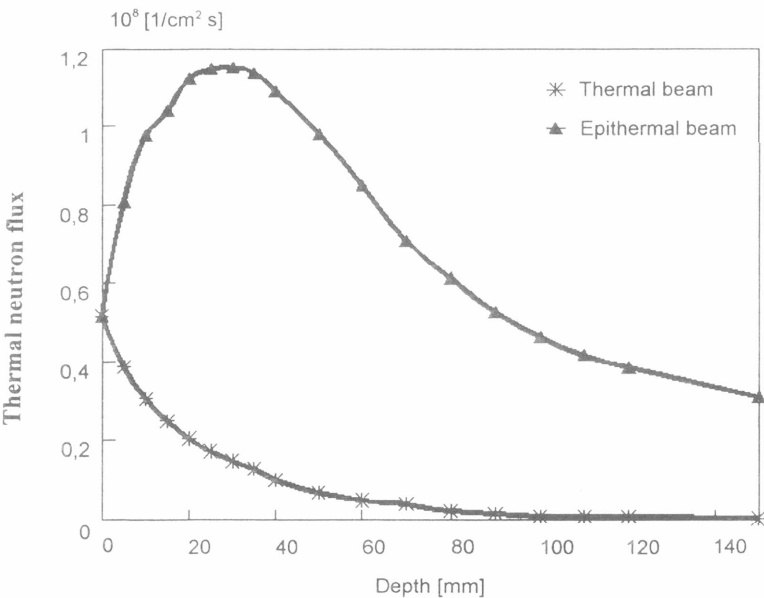
Fig. 2. *Distribution of thermal neutrons in the human head phantom.*

The thermal neutron flux inside the tissue depends on the beam-patient geometry and the average energy of epithermal neutrons. Distribution of the thermal neutron inside the head of a human water-filled phantom with artificial skeleton and plexiglass cover (Si semiconductor detector with a natural Li radiator were built in the head, Marek 1995) is presented in Figure 2. For monitoring of the irradiation conditions during a treatment session, the physical on-line dosimetry data for both neutrons and gamma rays are collected by a CAMAC PC-linked system. A further increase in neutron fluxes is expected to be

achieved by remodelling of filters and core reconfiguration in the near future.

Biological monitoring of the effects of the described beam of neutrons was performed on the brain of one-week-old rats using an additional polyethylene moderation block (25 mm). It was shown that in animals irradiated in the presence of sodium borocaptate (150 μg BSH in 3 μl saline injected intracranially, [10]B unenriched compound, Plešek et al. 1985) dead cells appeared in the dividing and early postmitotic populations of the cerebellum and of the forebrain periventricular layer. The damage was much more extensive than in the intact or saline-injected animals i.e. it significantly exceeded the effects of unavoidable background radiation represented by fast neutrons and γ-rays originating from the neutron-capture reaction on tissue elements, namely hydrogen. Compared to dividing cells, the lethal damage of postmitotic cells in BSH-injected animals was more extensive and present only in animals irradiated with the highest doses (Mareš et al. 1997). Significant reduction of growth followed by cell death was also found in C6 glioma cells in cultures irradiated with 3.06×10^8 thermal neutrons $cm^{-2} s^{-1}$ for 30 min in the presence of 100 μg BSH/ml (Mareš et al. 1992b)

Boron Neutron-Capture Compounds

The first compounds developed for BNCT concerned brain tumours. Studies on animals showed, however, that these molecules were either toxic or had low selectivity for tumour cells. As a consequence, the first results obtained in the U.S.A. in 1959–1961 were not satisfactory. The main drawback was the great radiation damage of normal cells, namely the vascular endothelium of the brain. More promising results were obtained by $Na_2B_{12}H_{11}SH$ (sodium borocaptate, BSH) used for BNCT of brain tumours by Hatanaka at Teikyo University in Japan (Hatanaka 1991, Hatanaka et al. 1992, Hatanaka and Nagawa 1994). His results have stimulated new interest in this method in the U.S.A. and Europe. Besides BSH, a wide scale of other boron containing molecules has been synthesized. This includes a boronated p-boronophenylalanine-fructose complex (p-BPA, Mishima et al. 1989), low density lipoproteins, tumor specific antibodies, porphyrin derivatives, growth factor receptors, polyamines, nucleosides, oligophosphates etc. (Barth et al. 1992, (Barth 1996, Ceberg et al. 1995a,b and others). Up to now, most clinical experience has been collected for BSH and the p-BPA-fructose complex.

The BSH is a hydrophilic molecule which does not pass easily across the haematoencephalic barrier (Hasselsberger et al. 1994, Stragliotto and Fankhauser 1995). A lower efficacy of the barrier in the tumour is therefore considered to be the primary reason for enrichment of tumour cells with [10]B and, vice versa, to be responsible for its low content in the surrounding

normal brain tissue (Hatanaka 1991, Hatanaka et al. 1992, Hatanaka and Nagawa 1994). Pharmacokinetic studies of BSH, performed in over 200 tumour bearing patients, confirmed the therapeutically suitable tumour vs. blood and normal brain tissue distributions of [10]B (Moss and Gabel 1995, Ceberg et al. 1995a,b, Gabel 1996, Horn et al. 1996a,b). An even better blood-to-brain tumour [10]B ratio was reported for the BPA-fructose complex which is also used for targeting skin melanomas (Coderre et al. 1994, 1996a,b). Because of the highly demanding synthesis and strategic control of [10]B distribution, the commercial availability of BSH has until recently been limited. At present, the drug can be purchased as a chemical compound from several producers (e.g. Centronic Ltd., New Addington, England and Katchem Ltd., Prague, Czech Republic) but not as a pharmacotherapeutic species for direct medical use. The drug has relatively low toxicity in experimental animals and man (Kliegel 1980, Hatanaka 1991, Hatanaka et al. 1992, Hatanaka and Nagawa 1994, Hasselsberger et al. 1994, Stragliotto and Fankhauser 1995, Horn et al. 1996a, etc.). Good tolerance of BSH was also shown in cell cultures, namely those growing at a slow rate. In addition, some lines of glioma cells in culture appeared to be more active in the uptake of this drug than normal glial or other tumour cells (Mareš et al. 1992a, Mareš et al. 1996). The drug is rapidly excreted from the organism by the kidneys. In our recent study carried out on 10 patients with glioblastomas, the drug disappeared from the blood with half-times of 0.85–3.65 h and 22.2–111.8 h in 7 patients. In three patients the initial decline was faster (17–37 min) while the final decline occurred after 415 h, i.e. it was much slower (Horn et al. 1996a). Similarly, the cells preloaded with BSH in culture lost about 75 % of [10]B in 2 h. About 10–20 % of [10]B was, however, still present in the cells at 96 h (Mareš et al. 1992b). The therapeutically optimal tumour-to-blood ratio (>1.5) appeared at the time less than 12 h (Horn et al. 1996a). In spite of the low toxicity, administration of BSH in higher or repeated doses is accompanied by some side effects. These include, for instance, transitional changes in renal blood flow, the morphology of kidney tubules in small laboratory animals (Janků et al. 1993, Horn et al. 1996b) and excitation of the motor and cardiovascular systems (Kliegel 1980, La Hann et al. 1996). The adverse acute effects of BSH, as well as of some other more toxic polyborates, are attributed to the inhibition of enzymes using pyridoxal 5-phosphate as the cofactor (Kliegel 1980). This group of enzymes includes aminotransferases, decarboxylases and monoamine-oxidases which take part in the metabolism of many biologically active molecules, especially biogenic amines. Recent in vitro studies on isolated mitochondria showed that BSH can also inhibit the activity of other enzymes, namely mitochondrial ATPase, cytochromoxidase, glycerophosphate

dehydrogenase and membrane Na^+,K^+-ATPase (Drahota *et al.* 1994). The inhibition of mitochondrial ATPase appeared to be of the competitive type. This suggests a possibility of diminishing and/or avoiding these side effects by increasing the supply of ATP at the time of BSH administration.

Clinical Applications and New Perspectives

In the pioneering work of Hiroshi Hatanaka carried out on brain tumours, the main mass tumor was first excised and this was later followed by thermal neutrons irradiation combined with an intra-arterial infusion of sodium borocaptate (Hatanaka 1991, Hatanaka *et al.* 1992, Hatanaka and Nagawa 1994). The encouraging results, however, raised a number of doubts. First, there was no proper control of radiation injury to the healthy brain tissue. Second, indication criteria for tumours suitable for BNCT were not properly established. The principal problem was also the poor penetration of slow neutrons into deeper parts of the tumour. For improvement, saturation of the brain with heavy water, opening of the haematoencephalic barrier by osmotic or enzymatic interventions, different dose application schemes, etc. were introduced. By the end of last year, 191 patients with different types of brain gliomas and 23 patients with skin cancer were treated by BNCT in Japan. In the glioma group of patients treated by a standard radiation procedure, the 5-year survival rate was less than 3 % while in the BNCT group of patients, whose tumours were within the range of neutron penetration, 58 % of subjects survived for five years (Hatanaka *et al.* 1991, Hatanaka *et al.* 1992, Hatanaka and Nagawa 1994, Kanda 1996). The median survival of the glioblastoma multiforme bearing patients treated with BNCT was 640 days. This is 2 to 3 times longer than reported for patients treated with other therapeutic procedures (Scott *et al.* 1995). The most encouraging result was that 6 out of 12 BNCT treated patients lived for more than 10 years (Nakagawa *et al.* 1996). At the Brookhaven Medical Research Laboratories, Long Island, U.S.A (BMR Reactor with epithermal neutrons), 13 patients with glioblastoma multiforme were treated with epithermal neutrons and the BPA-

fructose complex since September 1994. The median survival was 13.5 months. It is, however, important that in two patients treated with the highest radiation doses (17.2 Gy-Eq) no recurrence of tumour has appeared by September 1996 (Coderre *et al.* 1996a, Elowitz *et al.* 1996). On the basis of these results, a new phase I/II study protocol was activated on May 1996 (Chanana − personal communication). BNCT treatment of the metastatic subcutaneous melanoma with epithermal neutrons and p-BPA were started at the Massachusetts Institute of Technology and the New England Medical Center, Boston, Mass. (Massachusetts Institute of Technology Reactor, Cambridge, Mass., U.S.A). Two of the four subjects manifested clear regression of those parts of the tumour which were included in the radiation field (Busse *et al.* 1996). Attempts for the implementation of BNCT are also under progress in other countries and institutions. An interdisciplinary research team which includes 40 research centres from 16 countries has been assembled in Europe by Detlef Gabel, University of Bremen, Germany. The treatment facility with epithermal neutrons was realized at the High Flux Reactor of the Joint Research Center in Petten, the Netherlands. The treatment of patients with glioblastomas is supposed to start after overcoming the last administrative and legal obstacles caused by the multinational character of the project (Sauerwein 1996). The 7th Biannual Meeting of the International Society for BNCT held in Zurich (1996) showed that the physical and biological BNCT programs have also been started in Finland, Switzerland, Thailand, Latin America, Slovenia, Australia, Hungary and other countries. It may be concluded that, in spite of the persisting problems in the proper targeting of tumour cells, as well as of the relatively high price of the initial clinical trials, BNCT is a promising and fast expanding new tool for therapy of some forms of cancer, namely brain glioblastomas and skin melanomas.

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