Eur J Cancer, Vol. 26, No. 8, pp. 912–914, 1990.
Printed in Great Britain

0277–5379/90 $3.00 + 0.00
Pergamon Press plc

Feature Articles

New Developments in Neutron Capture Therapy

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INTRODUCTION

DURING THE past two decades, there has been renewed interest in neutron capture therapy, due mainly to the development of improved delivery systems for suitable nuclides and to improvements in neutron beam quality [1–3]. The most attractive stable radionuclide for neutron capture therapy is boron-10 (^{10}B), which has a large microscopic cross-section for thermal neutron capture. When thermal neutrons are captured by ^{10}B, the isotope becomes unstable and generates short-range, high Linear Energy Transfer (LET) particles. The nuclear reaction is:

$$^{10}_{5}B + n_{th} \rightarrow \begin{cases} ^{7}_{3}Li\ (1.01\ MeV) + ^{4}_{2}He\ (1.78\ MeV)\ (6.3\%) \\ ^{7}_{3}Li\ (0.85\ MeV) + ^{4}_{2}He\ (1.47\ MeV)\ (93.7\%) \\ \quad \rightarrow \gamma\ (0.48\ MeV) \end{cases}$$

The ^{7}Li atom and the ^{4}He nucleus have a maximum range in tissue of approximately 5 and 9 μm, respectively. Thus, in 93.7% of the disintegrations, a total energy of 2.31 MeV is deposited within the range of one cell diameter.

The other main nuclear reactions occurring with low energy neutrons in tissue are:

$$^{1}H + n \rightarrow {}^{2}H + \gamma\ (2.22\ MeV)$$

and

$$^{14}N + n \rightarrow {}^{14}C + p\ (0.63\ MeV)$$

Neutron capture therapy is clinically attractive only with a sufficiently high thermal neutron fluence in the target volume and if sufficiently high ^{10}B concentrations are obtained in the tumour, with low concentrations in the surrounding normal tissues.

RADIATION SOURCES

Nuclear reactors are the most suitable sources for obtaining an intense thermal neutron beam. Previously, thermal columns have often been used, consisting mainly of heavy water or graphite. Such beams are 'pure', but have limited penetration capacity (a half-value layer of about 2 cm). Almost all clinical experience has been gained with thermal neutron beams.

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Attention has been focused on developing epithermal neutron beams, either nearly monoenergetic [4] or with an energy spectrum ranging from a few electron volts to tens of kiloelectron volts [5]. The advantage of an epithermal neutron beam is that in tissue the neutrons first need to be moderated to thermal neutrons before being captured by ^{10}B. As a result, the thermal neutrons are generated at a certain depth, with a peak fluence typically at 2–3 cm from the surface. Furthermore, the decrease of the thermal neutron fluence beyond the peak as a function of depth is considerably less in an epithermal beam than in a thermal neutron beam. For instance, over 7 cm, the thermal neutron fluence of an epithermal neutron beam reduces by a factor of 2–3 compared with 6–12 for a thermal neutron beam. Therefore the average energy of an 'optimal' epithermal neutron beam should be in the range of 2 to 8 keV. Increasing the average energy further would not improve the beam quality because it increases the fast neutron component, thereby also increasing the production of recoil protons from the $^{1}H(n,p)$ reaction. Further optimization in homogeneity of the thermal neutron fluence within the target volume can be obtained by the use of, for instance, multiple beam portals.

Various combinations of filter materials have been tested to moderate the energy spectrum of the primary fast or epithermal neutron beam [3, 4]. In general, the choice of a particular group of filter elements is based on the beam quality at the core end of a particular reactor, aiming at reducing the fast neutron fluence and in-core gamma rays as much as possible while still maintaining an acceptable epithermal neutron fluence at the treatment position. In Europe, only a few potential neutron sources are available. At the high-flux reactor in Petten in the Netherlands, a combination of aluminum, sulphur, liquid argon, cadmium and titanium has been chosen as the filter system. According to Monte Carlo calculations, this should give at the treatment position a neutron beam of an average energy of 7–8 keV, with about 11% of neutrons of more than 10 keV, a total neutron flux of 2×10^{9} neutrons per cm^2 per s and a gamma component with a dose rate of about 60 cGy per hour (P. Watkins, Joint Research Centre, Petten NL, 1990). These values compare favourably with, for instance, those of the Brookhaven medical research reactor beam, where a combination of aluminium oxide, heavy water and bismuth is used as filter materials.

Other potential sources of epithermal neutrons are linear accelerators. Two approaches are being pursued. One uses a low energy, high current proton beam bombarding a lithium-7 target [6]. The other makes use of a high energy proton beam on a tungsten, lead or copper target [7]. Both approaches generate useful epithermal neutron beams, at least in their design phase.

Radionuclides such as californium-252 are also potentially useful alternatives as epithermal neutron sources. The neutron energy is similar to that of fission neutrons. This radionuclide has, however, a short half-life and would therefore be expensive for neutron capture therapy [8].

BORON COMPOUNDS

To deliver a tumoricidal dose, intratumoral boron concentrations of 20–30 μg/g are required. At present, two boron compounds are used clinically. The first is ^{10}B enriched $Na_2B_{12}H_{11}SH$ (BSH), a polyhedral borane with selective accumulation in gliomas [9]. The second is *p*-dihydroxyborylphenylalanine (BPA), a tyrosine analogue and a melanin precursor [10].

For BSH, tumour/blood boron concentration ratios above unity have been observed in small experimental animals, but only several hours after administration [4, 11, 12]. Interestingly, higher intratumoral boron concentrations were observed after infusion of the dimer, BSSB, than of the monomer [12, 13]. In large animals, on the other hand, tumour/blood ratios of only about 0.5 were found at various times after BSH administration. Concentrations in normal brain were invariably low, since the compound does not easily pass the blood–brain barrier. On the other hand, high boron concentrations, similar to those in tumours, were observed in some critical tissues such as the retina, pituitary gland and oral mucosa (S.L. Kraft, Washington State University, Pullman WA, 1989). Furthermore, in small animals, considerable heterogeneity in boron distribution was found in most animal tumours, presumably due to a variation in vascularity and vessel wall permeability [11, 14].

52 tumour samples from 24 patients have been analysed by a Japanese group after intra-arterial administration of 30–80 mg ^{10}B/kg [9]. In 30 specimens from 15 patients, the tumour/blood ratio was above unity, 2.1 (S.D. 1.0) at 14 (±3) h after BSH infusion. The average tumour concentration of ^{10}B was about 30 μg/g, with a large standard deviation, however. In 22 biopsy samples from 9 patients, the tumour/blood ratio was less than unity, 0.7 (0.3) at 15 (3) h after administration. In these cases, the average tumour concentration of ^{10}B was approximately 15 μg/g [9]. No toxicity has been observed from BSH doses at this level by these investigators in more than 100 patients with various intracranial tumours (H. Hatanaka, Teiko University, Tokyo, 1990).

The biochemical basis for increased concentrations of BSH in gliomas in relation to the blood compartment and normal brain is unknown, but the presence of a sulphydryl group appears to be essential [15]. It has therefore been speculated that the formation of disulphide moieties with various plasma proteins is important. Selective accretion of such boronated proteins in neoplastic cells has been demonstrated [15].

BPA is an amino acid analogue that is incorporated in melanomas [16] as well as in other tumours [17]. Tumour/blood or tumour/normal tissue ratios of 3–15 have been found in experimental animals, with intratumoral concentrations of ^{10}B up to 30 μg/g [10, 16, 17]. No acute toxicity was observed after single doses of 3000 mg/kg, whereas repeated high doses (1500 mg daily for 28 days) caused some haemolysis and a slight increase in urine ketone levels [18]. BPA has recently been approved by the U.S. Food and Drug Administration for clinical application.

Other boron compounds are still in the preclinical or developmental stage. These include boronated porphyrins [19] and phthalocyanines (W. Tjarks and D. Gabel, University of Bremen, F.R.G., 1990), which, for unknown reasons, accumulate in various tumour types. Also, boron-containing pyrimidines, which are incorporated into DNA, are under investigation [15], as well as thioureas [20] and promazines [15], which are incoporated into melanin. For the porphyrins, a major problem remains the low hydrophilicity, whereas for the pyrimidines, the low fraction of pyrimidine replacement by its boronated counterpart is the limiting factor, which also applies to melanogenesis-seeking compounds.

Efforts are also being made to boronate tumour-associated monoclonal antibodies. For cell surface antigens, 10^9 ^{10}B atoms per cell are required to obtain sufficient absorbed dose in the cell nucleus from the $^{10}B(n,\alpha)^7Li$ reaction. With approximately 10^6 antigenic sites per cell, about one thousand ^{10}B atoms should therefore be linked to a monoclonal antibody. Various investigators have been able to bind small boron cages to polymers [21] or to synthesize boron-containing polypeptides [15]. Both methods have certain limitations, but some groups have been successful in binding sufficient boron atoms to monoclonal antibodies without reducing immunospecificity [22, 23]. Effectiveness *in vivo* for neutron capture therapy remains to be established.

Another potentially attractive route of delivering ^{10}B complexes is by incorporation into low-density lipoproteins (LDL). The cholesterol esters in the core of a spherical LDL particle can be readily replaced by stable carborane esters or alkyl carboranes, giving about 0.20–0.89 μg B per μg protein [24]. These LDL particles have a high affinity for specific cell surface receptors. Cancer cells have up to a 20 fold higher uptake capacity of LDL than normal cells [25]. In this way, boronated complexes might be carried selectively inside tumour cells.

OTHER NUCLIDES

Gadolinium-157 (^{157}Gd) has a microscopic thermal neutron cross-section that is approximately 66 times that of ^{10}B. The gamma rays released from the $^{157}Gd(n,\gamma)$ reaction have a maximum energy of 7.9 MeV. More interestingly, after thermal neutron capture, ^{158}Gd disintegrates by internal conversion with the production of Auger and Coster–Kronig electrons (about 0.8 conversion electrons per neutron capture event) [26]. Due to the short range of these high LET electrons, efforts are being directed towards incorporating ^{157}Gd into DNA, for instance, by coupling to plasmids [27].

CLINICAL EXPERIENCE

The first clinical trials on brain tumours, done between 1951 and 1961 at the Brookhaven National Laboratory and at the Massachusetts Institute of Technology were unsuccessful because compounds such as $Na_2B_{10}O_{16}$, $C_7H_7B_{10}O_4$ and $Na_2B_{10}H_{10}$ did not accumulate selectively in the tumour. Because of high boron concentrations in the blood, excessive radiation doses in the superficial brain layers caused severe vascular damage with secondary brain tissue necrosis [28].

With BSH, more than 100 patients with brain tumours have been treated since 1968 by Hatanaka and colleagues [9]. 4 weeks after surgery, 30–80 mg ^{10}B/kg was administered via the carotid or vertebral artery in a 1–2 h infusion, followed 16 h later by craniotomy and thermal neutron irradiation to a total neutron fluence of 2.5×10^{12} neutrons per cm^2. Actuarial 5 and 10 year survival for the 38 cases with primary high-grade astrocytomas was 19% and 10%, respectively. Patients with smaller tumours within 6 cm from skin surface fared even better [29]. Few radiation-induced complications were encountered

by these investigators. 1 of 7 long-term survivors developed radiation myelitis and brain necrosis in the peritumoral area.

Various other research groups are designing pilot studies with BSH and epithermal neutron irradiation for glioma patients. In Japan, the first patient with melanoma has been treated with BPA and thermal neutron irradiation [30]. It is obvious that for such a complex treatment modality, optimum interaction between the various research disciplines is necessary. Within Europe, such collaboration has been organized within a 'concerted action' from the Medical and Health Research Programme of the European Communities.

EUROPEAN COLLABORATION GROUP

In July 1989, the European Collaboration on Boron Neutron Capture Therapy was set up to bring together researchers from various specialties to coordinate research within Western Europe. At present, 25 groups from 11 countries collaborate in this action, which is financially supported by the Commission of the European Communities.

This European Collaboration has two major scientific goals. The first is to construct a medical epithermal neutron beam facility at the high flux reactor in Petten for starting clinical pilot studies with BSH and BPA in glioma and melanoma patients, respectively. These clinical studies will be preceded by physical experiments including beam characterisation, dosimetrical calculations, measurements and treatment planning, and radiobiological experiments with small and large animals. The pharmacokinetics of the boron compounds and their biodistribution in various organs will be investigated in animals and in patients for increasing drug doses, with analytical methods such as prompt gamma-ray spectroscopy, inductively coupled plasma-atomic emission spectroscopy and quantitative neutron capture radiography [2]. In addition, the tolerance and efficacy of increasing radiation exposures for a given drug schedule will be investigated.

The second goal is to promote more basic scientific research into neutron capture therapy. It includes the development of new boron compounds, investigating the mechanisms of their cellular uptake and subcellular biodistribution, and developing alternative radiation sources for producing epithermal neutrons. These research activities will hopefully provide a scientifically sound basis for a broader application of neutron capture therapy in the future.

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