Applied Radiation and Isotopes 88 (2014) 46–49

Contents lists available at ScienceDirect

Applied Radiation and Isotopes

journal homepage: www.elsevier.com/locate/apradiso

Glioblastoma, brain metastases and soft tissue sarcoma of extremities: Candidate tumors for BNCT☆

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HIGHLIGHTS

- BSH leads to high ^{10}B concentration ratios between sarcoma, muscle and brain as well as between glioblastoma and brain.
- The ^{10}B concentration in tumors is quite low as is the ^{10}B concentration ratio between tumors and blood.
- BPA-f leads to ^{10}B accumulation in tumors relative to blood and advantageous absolute ^{10}B concentrations in tumors.
- The ^{10}B concentration ratios between tumors and brain and sarcoma and muscle, are modest.
- The advantage of the sequential injection of both compounds is an enhanced intratumoral ^{10}B concentration.

ARTICLE INFO

Available online 28 November 2013

Keywords:
^{10}B biodistribution
BSH
BPA
Murine model
Soft tissue sarcoma
Glioblastoma multiforme

ABSTRACT

^{10}B-concentration ratios between human glioblastoma multiforme (U87MG), sarcoma (S3) and melanoma (MV3) xenografted in nu/nu mice and selected normal tissues were investigated to test for preferential ^{10}B-accumulation. Animals received BSH, BPA or both compounds sequentially. Mean ^{10}B-concentration ratios between tumor and normal tissues above 2 were found indicating therapeutic ratios. In addition to glioblastoma, brain metastases and soft tissue sarcoma appear to be promising targets for future BNCT research.

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1. Introduction

Boron Neutron Capture Therapy (BNCT) is a targeted form of radiotherapy, which uses the ability of the non-radioactive isotope ^{10}B to capture thermal neutrons with high probability leading to the nuclear reaction $^{10}B(n,\alpha,\gamma)^{7}Li$. The resulting He-4 and Li-7 ions have both high linear energy transfer (LET) properties and a high relative biological effectiveness. As the range of these particles in tissue is limited to 10–14 μm, the $^{10}B(n,\alpha,\gamma)^{7}Li$ reaction offers the potential for a highly selective destruction of tumor cells (Wittig et al., 2008a). The selectivity however depends on the biological targeting of a ^{10}B-carrier molecule.

Two compounds used clinically have proven to have some therapeutic potential in selected tumor entities (Kageji et al., 2011; Kankaanranta et al., 2011; Kawabata et al., 2009; Wittig et al., 2009a, 2008b): sodium mercaptoundecahydro-*closo*-dodecaborate (BSH) and para-boronophenylalanine (BPA). The purpose of this study was to evaluate the uptake of BSH and BPA in glioblastoma multiforme and spindle cell sarcomas in a murine model in order to identify tumor entities, which preferentially take up one or both compounds and to substantiate current clinical trial strategies.

2. Material and methods

2.1. Boron compounds

BSH and BPA were purchased from Katchem Ltd. (Rez, Czech Republic). Quality controls of compounds and preparation of injection-solutions were performed according to standard operating procedures established for clinical trials of the EORTC (Wittig et al., 2009a). BSH ($Na_2{}^{10}B_{12}H_{11}SH$) was dissolved in distilled water (infusion grade). Sterile 0.9% NaCl solution was added to obtain the required concentrations. BPA ($C_9H_{12}{}^{10}BNO_4$) was injected as fructose complex (BPA-f) for reasons of solubility (Wittig et al., 2009a).

☆The work was financially supported by the European Commission contract QLK3-CT-1999-01067

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http://dx.doi.org/10.1016/j.apradiso.2013.11.038

2.2. Animals

Male nude mice (HsdCpb:NMRI-*nu/nu*) were used, which were bred at the Central Animal Laboratory of the University Duisburg-Essen under controlled pathogen-free (CPF) conditions. Animals had unlimited access to water and a high calorific nude mouse diet (12 ZH 10, Altromin, Germany). Experiments were started in 6–9 week-old animals. The experiments were authorized by the regulatory authority under No. TSG 683-02.

2.3. Anesthesia and transplantation

Human glioblastoma multiforme (U87MG) and human sarcoma (S3) were investigated. For tumor transplantation mice were anesthetized by intraperitoneal injection of Xylazine and Ketamine (1 ml Ketamine 10%+0.25 ml Xylazine 2%+Aqua inj. ad 5 ml). Tumor chunks with a diameter of 2–3 mm were transplanted subcutaneously at the chest wall and wounds closed for 5 days with clips (Wittig et al., 2009c).

2.4. Injection of compounds and tissue extraction

Both drugs were applied intraperitoneally, BSH at a dose of 200 mg/kg b.w. (113.18 mg ^{10}B/kg b.w.), BPA-f at a dose of 700 mg/kg b.w. (33.36 mg ^{10}B/kg). Dosing was twice as high as compared to the therapeutic EORTC studies (Sauerwein, 1996; Wittig, 2003). One group of animals received either BSH or BPA-f, a third group received both drugs sequentially. Tissue and blood samples were collected 1.5 h after BPA-f injection and 2.5 h after BSH injection. For tissue extraction, animals were deeply anesthetized. Blood samples were taken by intracardial cannulation. Samples of tumor and normal tissues were extracted, weighed and kept in airtight containers at −20 °C until analysis (Wittig et al., 2009c).

2.5. Measurements with prompt gamma ray spectroscopy

Tissue and blood samples were processed for ^{10}B-concentration measurements by prompt gamma ray spectroscopy at the High Flux Reactor HFR Petten. Before each series of measurements, the system was calibrated using standard samples (Nievaart et al., 2009; Wittig et al., 2008c). The minimal number of animals per data point was 4.

2.6. Criteria of evaluation

Based on previous experience, criteria were defined to judge whether a compound should be further investigated in a selected tumor entity: low toxicity, sufficiently high intratumoral ^{10}B concentration ($>$15–20 ppm (Barth et al., 2012)), a ^{10}B-concentration ratio between tumor and normal tissues of at least $>$2–3, a ^{10}B-concentration ratio between tumor and blood of least $>$0.6 in the case of BSH and $>$1.5 in the case of BPA and low normal tissue uptake (Sauerwein, 2002; Wittig et al., 2009b).

3. Results

None of the animals showed any signs of toxicity after intraperitoneal injection of either BSH or BPA-f or both compounds. Animals received both compounds in a volume of 1 ml to avoid any toxicity caused by fluid accumulation.

In both tumor entities the absolute ^{10}B concentration was $>$13 ppm after injection of BSH, $>$19 ppm after BPA-f injection and $>$34 ppm after injection of both compounds. The sequential injection of both compounds led to a near additive affect.

Mean ^{10}B-concentration ratios between tumor and normal tissues are summarized in Table 1a and b. After BSH-injection, the ^{10}B-concentration ratio between both neoplastic tissues and brain was very high. The highest ratio was observed between glioblastoma and brain. Likewise, after injection of BPA, the ^{10}B-concentration ratio between both tumors and brain was well above 3 but ratios were lower as compared to the ratios after BSH injection. Sequential injection of both compounds did not improve the ratio between tumors and brain but ratios were all $>$3. The ^{10}B-concentration ratio between sarcoma and muscle was highest after BSH injection but considerably lower after BPA-injection or application of both compounds. The ratio between sarcoma and brain was also highest after BSH-injection, intermediate after co-application of both compounds and lowest after BPA injection. The ^{10}B-concentration ratio was $>$3 for both compounds and the combination, respectively.

^{10}B concentrations in liver and kidneys were assessed to estimate the potential risk of normal tissue toxicity associated with BNCT. ^{10}B-concentration ratios below 1.0 between the tumors and the kidney regardless of the compound infused are caused by high ^{10}B concentrations in the kidneys as compounds are known to be eliminated via the renal pathway. The ^{10}B-concentration ratios between both tumors and the liver were low after BSH injection and injection of both compounds. Surprisingly, after BPA injection the ratio was 4.2 between glioblastoma and liver, however this is of no potential clinical relevance.

The ^{10}B-concentration ratio between tumor and blood was $>$0.6 after BSH-injection and $>$2 after BPA injection for both tumor entities. Co-application of BSH and BPA did neither improve the ^{10}B-concentration ratios between tumors and normal tissues nor the ratio between tumors and blood.

Table 1a
Mean ^{10}B concentration ratios ($\pm$ 1 SD) between glioblastoma multiforme (U87MG) and normal tissues 2.5 h after injection of BSH (200 mg/kg b.w.) or 1.5 h after injection of BPA (700 mg/kg b.w.) or both compounds sequentially.

	BSH	BPA	BSH+BPA
Glioblastoma/blood	0.7 ± 0.1 n=8	2.0 ± 0.6 n=10	0.9 ± 0.2 n=10
Glioblastoma/brain	15.9 ± 9.6 n=5	6.5 ± 3.8 n=8	5.4 ± 1.3 n=4
Glioblastoma/muscle	9.6 ± 4.5 n=4	4.8 ± 7.5 n=9	2.7 ± 0.8 n=6
Glioblastoma/liver	0.8 ± 0.7 n=8	4.2 ± 6.1 n=9	0.9 ± 0.1 n=6
Glioblastoma/kidney	0.4 ± 0.1 n=6	± 1.1 n=10	0.8 ± 0.7 n=6

Table 1b
Mean ^{10}B concentration ratios ($\pm$1 SD) between human sarcoma (S3) and normal tissues 2.5 h after injection of BSH (200 mg/kg b.w.) or 1.5 h after injection of BPA (700 mg/kg b.w.) or both compounds sequentially.

	BSH	BPA	BSH+BPA
Sarcoma/blood	1.0 ± 0.8 n=9	1.6 ± 0.6 n=10	1.1 ± 0.5 n=8
Sarcoma/brain	8.4 ± 6.8 n=6	3.2 ± 1.3 n=10	3.7 ± 0.7 n=7
Sarcoma/muscle	7.2 ± 3.2 n=6	1.7 ± 0.9 n=9	2.2 ± 0.7 n=7
Sarcoma/liver	0.7 ± 0.3 n=8	1.4 ± 0.5 n=10	1.2 ± 0.6 n=7
Sarcoma/kidney	0.5 ± 0.3 n=8	0.6 ± 0.3 n=11	0.6 ± 0.1 n=7

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