Report on the First Patient Group of the Phase I BNCT Trial at the LVR-15 Reactor

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Summary

The phase I study of the Protocol approved by State Institute for Drug Control and State Office for Nuclear Safety of the Czech Republic has been used to define the limiting toxicity of the BNCT procedure. The group of 9 patients received BSH and underwent surgery, 5 patients were treated using BSH at the epithermal neutron facility of LVR-15 reactor in NRI Rez.

Introduction

Clinical trials of Neutron Capture Therapy were initiated in some European countries including Czech Republic [1]. An epithermal neutron beam was constructed at the LVR-15 nuclear reactor at Řez near Prague [2,3]. A toxicity study of BSH on animal models and its pharmacokinetics were carried out [4]. For determination of ^{10}B content in biological samples the Inductively Coupled Plasma-Mass spectroscopy (ICP-MS) and the Prompt Gamma-Ray Analysis on LVR-15 reactor (PGRA) were adopted [5]. Biological efficiency of the epithermal neutron beam has been verified by an animal model [6,7]. In this report the pilot data of the clinical phase I study are presented.

Material and Methods

1. Patients. Nine patients with the clinically diagnosed glioblastoma multiforme have been included in the study lasting from September 2000 to March 2002 (Table 1). The group consists of 4 women (average age 53.3 years) and 5 men (average age 58.4 years). In 7 patients, a subtotal resection of tumor was carried out. In remaining 2 patients a partial decompression of tumor cyst and a radical operation were carried out. Two patients have had different histology (gliosarcoma and oligoastrocytoma). In the remaining 7 patients the diagnosis of glioblastoma multiforme WHO grade IV was confirmed by both intraoperative and final histology. Five patients of this group were finally indicated for BNCT. Two patients were excluded from the BNCT irradiation because of not sufficient boron-10 accumulation in tumor or worsened neurological performance status.
2. BSH administration and sampling of the blood and tissues. Nine patients with a clinical diagnosis of glioblastoma multiforme received i.v. infusion of BSH in saline solution (100 mg BSH/kg b.w., 55mg of ^{10}B/kg b.w., Katchem Ltd.Rez) within 1 h. Blood samples were taken at 0, 2, 4, 8, 12, 14 and 16 h after the BSH administration; the urine was currently collected. The tissues sampled during the operation (starting cca 12 h after BSH infusion) included the skin, muscle and the bone of the head, galea aponeurotica, dura mater, cerebrospinal fluid (CFS) and tumor and non-tumor brain tissue. The brain samples were taken from 6 different parts of the tumor (20-30 mg each). After mechanical cleaning of the blood clots, the samples were briefly rinsed by a few drops of saline, frozen and stored in dry ice. (Haselberger et al., Glioma treatment at Petten with BNCT, personal communication, 1999).
3. Boron-10 measurements. The tissue samples were measured by the Inductively Coupled Plasma-Mass spectroscopy (ICP-MS), the samples of the blood and urine by the Prompt Gamma-Ray Analysis (PGRA) [5].
4. Irradiation. The patients were treated by the epithermal neutron facility of LVR-15 reactor in NRI Rez Reactor. Code MacNCTPLAN was used for treatment planning [8]. Individual parts of total dose (boron, fast neutrons, gamma rays, nitrogen) were calculated by MCNP Monte Carlo code. The maximum dose of 14.2 GyEq have been reached in a defined part of healthy tissue.
5. Clinical criteria followed after BNCT . All patients have been followed-up clinically and by MRI every 2-3 months.

Results and Discussion

1. Boron distribution. Boron-10 concentration in the blood and the tissue samples are given in Table 1. With respect to a tri-exponential decay of boron values in the blood the main attention was paid to the middle half-time $T_{1/2}$ as the most suitable interval for determination of the beginning of irradiation. These half-lives ranged from 4.4 h to 7.3 h (Table 1). In two cases (VK49 and MV49) two-exponential decay function was used to improve fitting of a boron concentration-time profile (Figure 1).

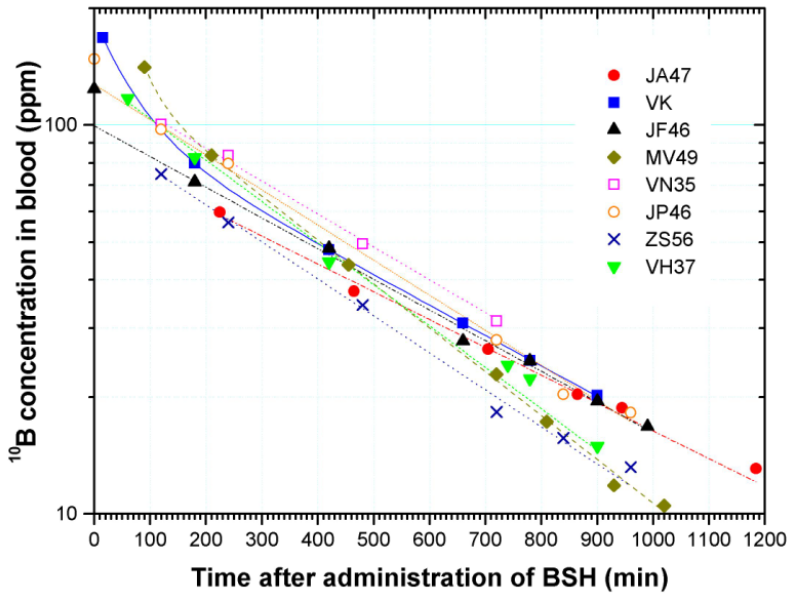

Figure 1. Blood ^{10}B concentration .

The average value of $T_{1/2}$ = 5.7±0.9 h is similar to that obtained earlier by others. The urinary excretion of the boron varied from 64% up to 74% of the total administered dose within one and half day after the BSH infusion (group of 4 patients).

The boron-10 content in the compact tissue samples are given in Table 1. Large variation in the uptake of boron-10 in the individual patients and parts of tumor were found. Substantially lower boron-10 concentrations were measured in normal brain tissue. An average ratio of the ^{10}B concentration in the tumor and the normal brain tissue was 7:1 (Table 1). The tumor to ^{10}B blood concentration ratio, T/B, at the 12 h post-infusion interval ranged from 0.13 to 0.66 (Table 1).

Table 1.
The Boron-10 concentration in the patient´s blood and tissue samples

Patient code	Sex	$T_{1/2}$ (h)	Tumor max. (μg/g)	Tumor mean (μg/g)	T/B ratio (12h)	Normal brain (μg/g)	Skin (μg/g)	Muscle (μg/g)	Bone (μg/g)	Dura mater (μg/g)
JA47	M	7.3	22.8	14.4±5.3	0.57	1.0	10.8	-	2.3	8.7
EK40	F	7.3	5.0	4.1±0.6	0.13	0.4	9.9	-	1.4	10.5
VK49	M	6.4	23.1	9.5±6.2	0.34	1.0	13.9	-	0.5	11.9
JF46	M	6.4	4.7	3.2±1.2	0.16	4.0	10.1	1.7	0.8	10.5
MV49	F	4.4	8.4	6.2±1.5	0.27	1.0	5.7	-	1.5	10.9
VN35	M	5.9	21.1	16.4±4.3	0.52	-	16.2	10.7	2.6	16.5
JP46	F	5.6	31.8	18.5±7.0	0.66	1.9	14.4	7.4	3.4	21.8
ZS56	F	5.3	15.0	9.3±4.8	0.51	1.0	7.9	11.1	1.0	8.7
VH37	M	4.7	6.6	5.1±1.2	0.22	0.6	7.3	7.5	0.6	11.9

Irradiated patients are labeled by bold and those in which glioblastoma multiforme was not confirmed histologically are in italics
The Boron-10 concentration in galea for patients JA47 and VK49 is 22.2 μg/g and 18.9 μg/g and in CFS 0.5 μg/g and 2.9 μg/g, respectively.

2. Irradiation. Tumors localized in superficial part of temporal or occipital lobe were irradiated from 30 to 40 min at the reactor power from 8 to 9 MW. The peak dose in the healthy brain, predominantly influenced by fast neutron dose and gamma dose, did not exceed 14.2 Gy-Eq. The structure of the dose, expressed as the median absorbed dose in the target volume and whole brain dose is shown in Fig. 2.
3. Clinical observations. No clinical deterioration of patients or laboratory data were observed during and after infusion of BSH including normal kidney and liver functions . Immediately after the irradiation acute reaction in two patients in terms of nausea, vomiting or a grade II skin reaction in the irradiated area appeared within 3 weeks after the irradiation. One patient died in the first week after irradiation due to pulmonary embolism. In the remaining 4 irradiated patients signs of tumor growth progression appeared 2.5 to 6 months after irradiation. In 3 of them further subtotal resection of the tumor was carried out; in one re-operated patient radiation necrosis was diagnosed histologically in the MRI presumed tumor location.

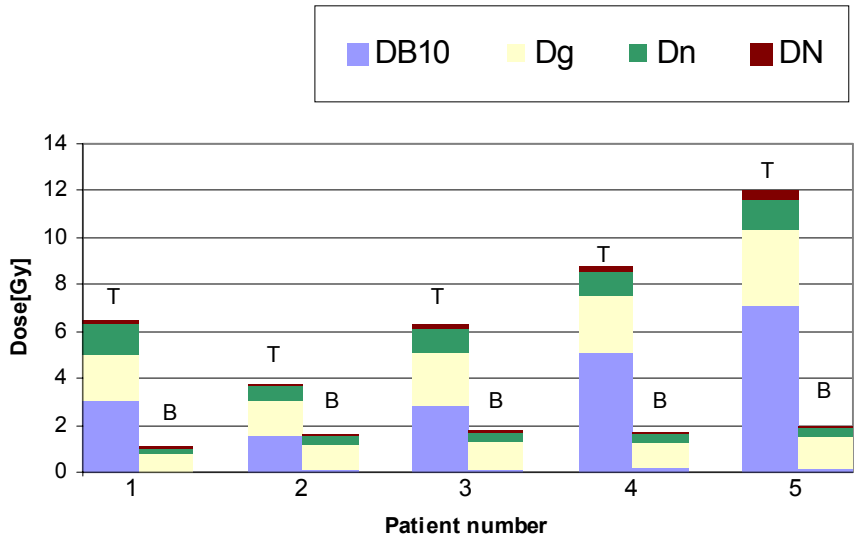

Figure 2. Median absorbed dose in the target volume(T) and in the whole brain(B)

Conclusions

The study showed relatively good tolerance of the BNCT performed under the above described conditions. Considering that the level of used radiation doses to target volume in Phase I study was low so far and the number of patients was not high enough, evaluation of the efficacy of BNCT under the above described conditions awaits further study.

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