BNCT TRIALS IN CZECH REPUBLIC

J.Burian[1], M.Marek[1], S.Flibor[1], J.Rejchrt[1], L.Viererbl[1], H.Honova[2], L.Petruzelka[2], F.Tovarys[3], V.Dbaly[3], J.Honzatko[4], I.Tomandl[4], V.Mares[5], E.Buchar[6]

[1]Nuclear Research Institute Rez, plc , Czech Republic (CR)
[2]Dept. of Oncology, Faculty Hospital of Charles University, Prague, CR
[3]Department of Neurosurgery, Hospital Na Homolce, Prague, CR
[4]Nuclear Physics Institute, Academy of Science, CR, Rez, CR
[5]Institute of Physiology, Academy of Science, CR, Prague, CR
[6]Institute of Experimental Medicine, Academy of Science, CR, Prague, CR

ABSTRACT

The experiences from different part of project are presented. The BNCT facility at LVR-15 reactor of NRI consists of epithermal neutron beam and irradiation and control rooms equipped by appropriate devices. Internationally-recognized software NCTPlan is utilized for computational dosimetry and treatment planning. In the part of protocol for glioblastoma the following parameters are assessed: patient selection, sampling of tissues, BSH dosage, fractionation. At horizontal LVR channel a prompt gamma ray analysis (PGRA) system is operated for BNCT purposes. Boron content in human blood samples was analyzed, the results are presented. Some results are reported for clinical trials in the parts: patients, boron sampling and measurement, irradiation, follow-up. The possibility of progress in BNCT project is discussed.

Introduction

The Czech BNCT group of specialists from different scientific fields (physics, medicine, chemistry, radiobiology, pharmacology) decided as a first priority to initiate the glioma clinical trials at the LVR-15 reactor of NRI. The treatment protocol was prepared and approved by corresponding national authorities. The principal aim was to realize the Phase I trial with dose escalation to establish maximum tolerated dose by healthy tissue when irradiating with BSH drug. The activity has been concentrated also on experimental verifying of epithermal beam characteristics and on improvement of the parameters of the beam.

Epithermal beam

A beam of epithermal neutrons has been constructed at the LVR reactor using empty space of thermal column as described in [1]. The LVR-15 is a light water reactor with enriched fuel (36 %) and standard thermal power 10 MW. This, on commercial basis running reactor, is used for material testing experiments at water loops and rigs, for radio-pharmaceuticals production, irradiation of silicon crystals and for basic and applied research experiments at horizontal channels as well as for BNCT as a source of epithermal neutrons.
A principal disadvantage of our arrangement is a rather long distance between the core and irradiation point (about 4 m). Several assemblies have been experimentally tested with the aim to determine parameters both of the free beam and the beam with the phantom. The techniques used for measurement were described in [2]. Standard materials were used as aluminum and aluminum fluoride, lead and Ti and Li filters. Today free beam parameters are: Φ_{epi} = 7.13 x10^8 /cm^{2}s, Φ_{fast} = 6.1x10^7 /cm^{2}s, D_γ = 1.98 Gy/h. The configuration at LVR-15 rector is seen in Fig.1.
The BNCT facility used for irradiation at LVR consists of irradiation room that is equipped with appropriate devices as laser, TV camera, intercom, patient treatment table and control room where all information for communication with patient, monitoring and control of beam

are concentrated. The treatment table prepared for positioning with fixing mask in irradiation room is seen in Fig.2.

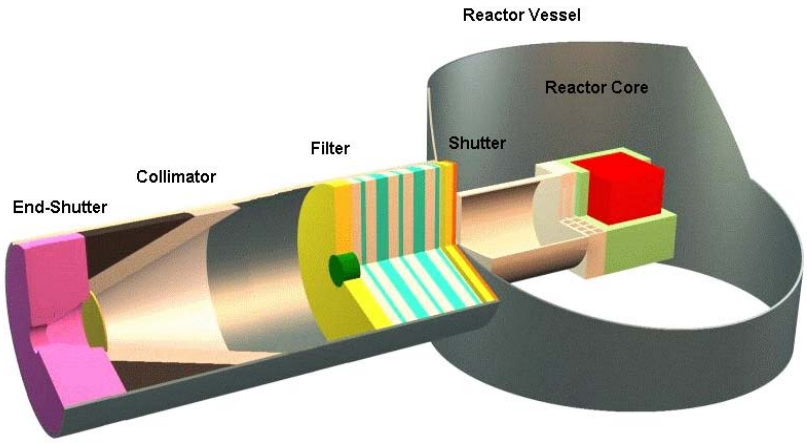

Fig.1. Configuration of epithermal beam at LVR-15 geometry

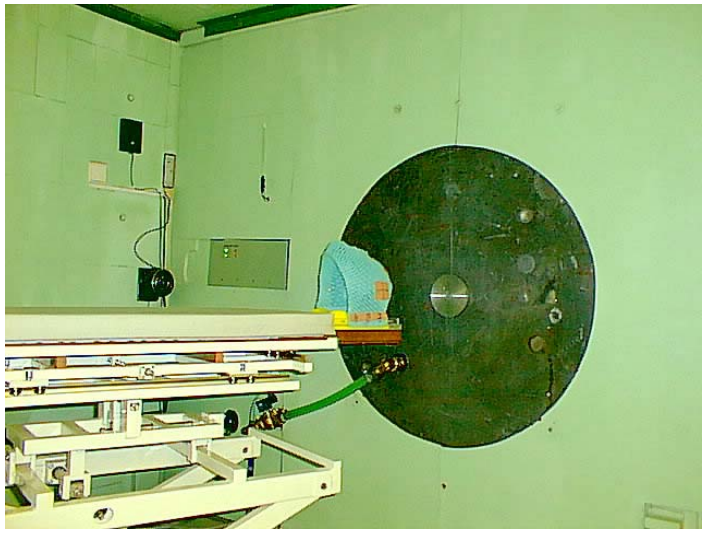

Fig.2. Irradiation room with the treatment table and fixing mask

Boron concentration measurement

The tissue samples are measured by the Inductively Coupled Plasma-Mass spectroscopy (ICP-MS), the samples of the blood and urine by the Prompt Gamma-Ray Analysis (PGRA) [3].A prompt γ-ray analysis (PGA) facility for determination of ^{10}B in biological samples was built inside the reactor hall. The 6-meter mirror neutron guide provides the neutron flux 2.8 10^6 n/ cm^2 s in the target position at the reactor power of 8 MW. It is possible to reach relative efficiency 25% for detection of characteristic 478 keV γ line HPGe. The device itself is shielded from a γ-ray and neutron background in reactor hall by a combined shielding made of Pb and Li_2CO_3. The experimental set-up makes it possible to measure 1.0 or 0.5ml liquid samples in teflon vials at the present time. The $^{10}B/H$ γ-ray signal ratio is used for determination of ^{10}B concentration.

The sensitivity of this facility is 4.9 counts within 478 keV Doppler broadened peak per 1 μg of ^{10}B. The facility was tested with water solutions of BSH and BPA as well as with blood solutions of BSH (see Fig.3). A good agreement was obtained between the values of ^{10}B concentration by the PGA method and the values from the ICP method.

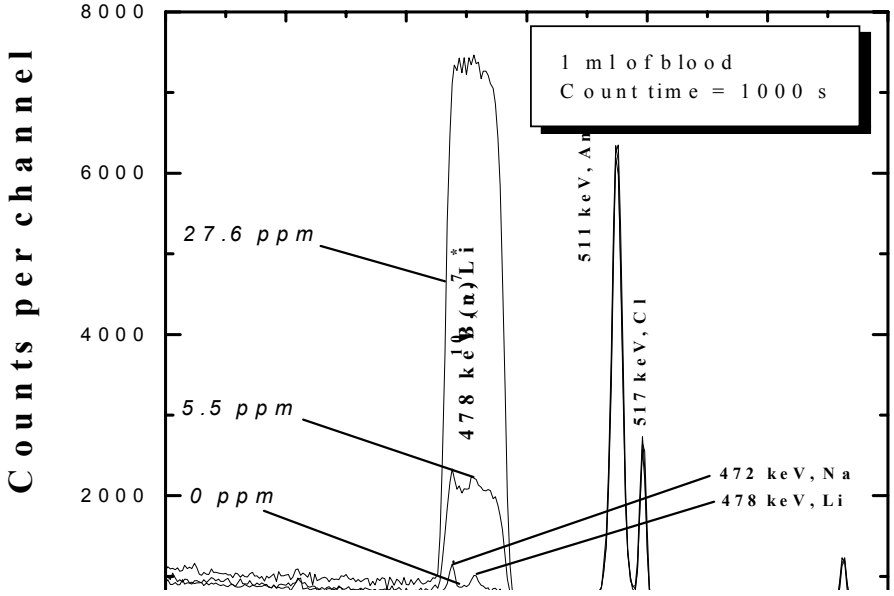

Fig.3. The spectra for boron concentration measurement in blood samples

Treatment planning

Perfect treatment planning is one of the most important part of the BNCT procedure. It was decided to accept the code NCTPlan - the internationally-recognized treatment planning software from Harvard-MIT [4]. CT and MR scans are acquired for identification of the tumor and healthy tissues. It serves as input to MCNP Monte Carlo transport calculations (with known source file and materials map). Individual parts of total dose (boron, fast neutrons, gamma rays, nitrogen) are calculated by the code. RBE-weighted isodoses for normal brain and the same for tumor are plotted as the output of the code.

Protocol

The Protocol specifying treatment of glioblastoma with BNCT at the LVR has been prepared in details.

Patient selection

Main inclusion (preoperative) criteria - age 40 – 60; Karnofski index ≥ 70; MRI (CT) diagnosed tumor, presumptive glioblastoma, unilateral, subcortical, subtotally resectable; informed consent. Inclusion (postoperative) criteria - histology of glioblastoma multiforme (G IV) resection of at least 70% of the tumor volume (MRI); Karnofski index ≥ 70. Exclusion criteria - any other malignant tumor; prior anticancer treatment for the present tumor; previous brain surgery (other than tumor biopsy); partial tumor resection; adverse reaction to BSH; severe disease of heart, lung, liver, kidney.

Sampling of tissues for boron analysis during surgery

Preoperative period is used for study of BSH pharmacokinetics, BSH is given to the patient 12 hours before operation, blood concentration is measured at regular intervals. Samples of skin, dura mater, normal brain and tumor tissue are taken at the time of operation and BSH concentration is measured.

Administered amount

The amount of BSH to be administered is directed by the fact that the better results in BNCT will be achieved with more boron present. At the LVR project BSH was administered at a amount 100 mg/ kg body weight, so far.

Fractionation

Considerable part of irradiation is provided by high LET radiation during BNCT treatment and the damage of healthy brain tissue is not practically repaired. Sparing of the tissue with fractionation is more effective for low LET component of radiation. Considering the fact that the irradiation time in LVR reactor is rather long and therefore the repairing of the healthy tissue could take place during irradiation, it has been decided to accomplish the treatment in one fraction in spite of the fact that long time irradiation is not comfortable for patient.

Continuation at the Phase II trial

The aim of Phase I trials is to establish the save dose for healthy brain tissue. There is a chance that patients may benefit from BNCT procedure even for the first steps of starting dose. The therapeutical effect is supposed not to be neglect for final steps. The Phase II investigating the effectiveness of this new treatment modality might go on in parallel to final dose steps, if no unacceptable frequency of serious adverse events are observed. The survival of patients will then be principal criterion in the Phase II.

Boron compound

The domestic supplier Katchem Ltd. produces BSH (as well as L-BPA). The quality of the product is in the agreement with Test of quality control asked in project.

Clinical trials

No progress was reached during year 2003. It was influenced by catastrophic flood in region of Prague and Rez (Vltava river) in 2002. Reactor LVR received new license for operation in May 2003, the continuation of BNCT trials (with new program of quality assurance) was approved by state authority in the half 2003. Maximum two patient are planned before the end of the year. Some results were reported on 10^{th} Essen Symposium [5].

Patients

Nine patients with the clinically diagnosed glioblastoma multiforme have been included in the study so far. 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.

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 different parts of the tumor.

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). The results are very individual, boron-10 concentration-time

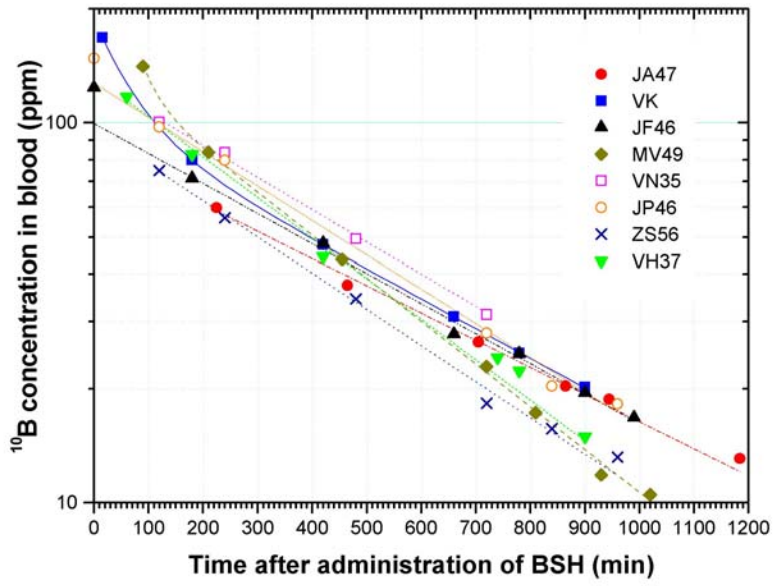

Figure 4. Blood ^{10}B concentration .

profile is seen in Figure 4. For BSH application the following ^{10}B concentration were received: Tumor 15 – 30 µg/g tissue, skin 7 - 15 µg/g, bone and brain healthy tissue 1µg/g approximately.

Irradiation

The patients were treated by the epithermal neutron facility according to results of code NCTPlan. Total dose and its individual parts (boron, fast neutrons, gamma rays, nitrogen) were low, so far, see Fig 5. The maximum dose of 14.2 GyEq have been reached in a defined part of healthy tissue.

Clinical criteria followed after BNCT

All patients have been followed-up clinically and by MRI every 2-3 months according to Protocol.

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.

Progress

The principal progress is awaited if a new substance with high biological effectiveness will be synthesized. For next year it is supposed in our project to continue in clinical trials with mixture of present boron agents BSH+BPA. It was not decided so far to what types of diseases the protocols will be oriented (glioblastoma, melanoma brain metastases, primary melanoma).

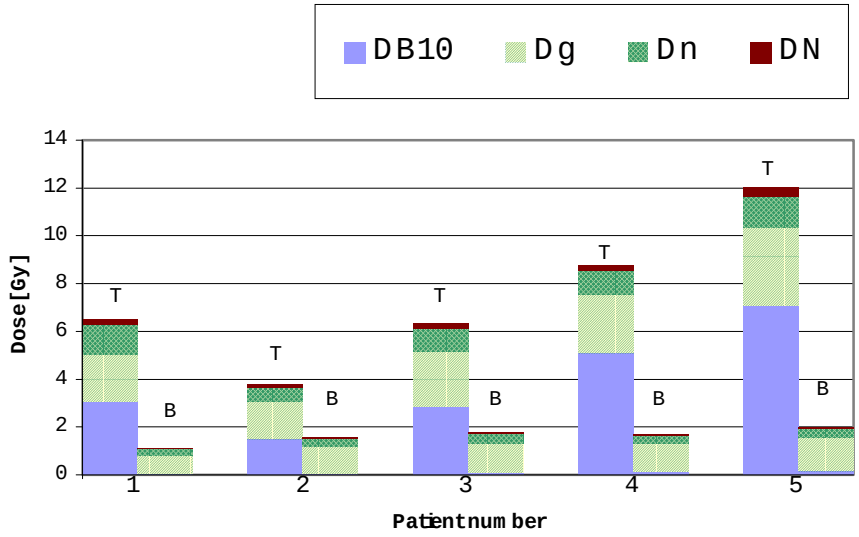

Figure 5. Median absorbed dose in the target volume(T) and in the whole brain(B)

Acknowledgements

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References

[1]. BURIAN J.,MAREK M.,RATAJ J.,PROKES K.,NOVY F.,TOVARYS F.,DBALY V., HONZATKO J.,TOMANDL I.,KRIZ.: The BNCT project in the Czech Republic before the start of clinical treatment**,** 8th Int. Symposium on NCT for Cancer, La Jolla, USA, September 1998

[2] M.Marek, L.Viererbl, S.Flibor, J.Burian, J.Rejchrt: Validation of epithermal neutron beam at LVR-15, 9th Int. Symposium on NCT for Cancer, Osaka, Japan, October 2000

[3] J.Honzatko, I.Tomandl: Boron Concentration Measurement System for the Czech BNCT Project, Proc. 10th Int. Symposium on Capture Gamma-Ray Spectroscopy and Related Topics, Santa Fe, 30.8-3.9.1999.(Wender S.,ed.), AIP 529, Melville, New York, 2000

[4] S.J.Gonzales, G.A.Santa Cruz, W.S.Kiger, J.T.Goorley, M.R.Palmer, P.M.Busse, R.G.Zamenhof: NCTPlan, the New PC Version of MacNCTPlan – Improvement and Verification of a BNCT Treatment Planning Systém, 10th Int. Symposium on NCT for Cancer, Essen, Germany, September 2002

[5] J.BURIAN, M.MAREK, J.RATAJ, S.FLIBOR, J.REJCHRT, L.VIERERBL, F.SUS, H.HONOVA, L.PETRUZELKA, K.PROKES, F.TOVARYS, V.DBALY, V.BENES, P.KOZLER, J.HONZATKO, I.TOMANDL, V.MARES, J.MAREK, M.SYRUCEK: Report on the First Patient Group of the Phase I BNCT Trial at the LVR-15 Reactor, „Research and Development in Neutron Capture Therapy“ (Sauerwein, Moss, Wittig editors) Proceedings of 10th Int. Congress on NCT for Cancer, Essen, Germany, September 2002,