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Theory and Design

Opportunities for Using an Accelerator-Based Epithermal Neutron Source for Boron Neutron Capture Therapy

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Specific design features and main characteristics of a compact accelerator-based epithermal neutron source for boron neutron capture therapy are described. High quality of the neutron flux generated by the accelerator-based source has been experimentally confirmed. The opportunities for medical use of the accelerator-based epithermal neutron source in oncological centers for boron neutron capture therapy are assessed.

Introduction

Selective accumulation of ^{10}B in cancer cells followed by epithermal neutron irradiation leads to specific elimination of tumor cells without affecting surrounding healthy cells [1]. To carry out boron neutron capture therapy (BNCT), neutrons in a restricted energy range of 0.5 to 30 keV (near the upper limit of the epithermal range) with a high flux density (10^9 $cm^{-2}·s^{-1}$) are used [2].

Further development of neutron capture therapy requires a multi-field approach and collaboration of specialists from different fields, including physicists, biologists, and medical doctors. Development of BNCT techniques using accelerator-based neutron sources is presently at the research stage. The goal of the research is to confirm the therapeutic effect of neutron flux and to prepare the ground for clinical trials. Until recently, specialized or reequiped nuclear reactors were the only neutron sources used for BNCT. Hundreds of patients all over the world have undergone successful BNCT of various oncological diseases. Clinical trials using nuclear reactors have shown that BNCT can be used to treat brain tumors [3], including glioblastomas [4], and tumors of soft tissues, parenchymatous organs, and skin [5].

The experience with reactors for obtaining epithermal neutrons revealed a number of problems. First, it is rather difficult to attain the beam parameters making it fit for clinical use. Second, maintaining the reactor operation in the safe mode requires considerable resources. Besides, the majority of reactors are located outside hospitals, which makes it more difficult to use them for clinical trials. That is why equipping hospitals with complete sets of devices required for BNCT is very important. In addition, accelerator-based neutron sources are consid-

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erably more available and less expensive than neutron sources based on nuclear reactors.

The use of accelerators makes it rather easy to generate neutron beams fit for BNCT due to the possibility of rapidly and effecttively modifying the neutron spectrum and flux by changing the energy and current of the charged particle beam and by replacing the target [6]. Since 1990s, a variety of designs for accelerator-based neutron sources have been proposed for BNCT. However, the majority of these designs have not been implemented, mainly because of the difficulties involved in solving the problems.

A neutron source for BNCT based on a novel type of accelerator – tandem accelerator with vacuum insulation and lithium target – has been developed at the Budker Institute of Nuclear Physics of the Siberian Branch of the Russian Academy of Sciences [7]. The developed neutron source provides generation of a stationary proton beam (energy, 2 MeV; current, up to 5 mA) [8] and a neutron beam. The device has successfully undergone preclinical trials in vitro and vivo [9, 10]. The obtained data have shown the generated neutron beam to be safe and effective for treatment of malignant tumors.

Materials and Methods

Cell lines. To study the effect of the neutron beam on cell viability in humans and animals, experimental studies were performed in cell lines conventionally used to study the effect of X-ray irradiation. Human glioblastoma cell line T98G, Chinese hamster ovary cells CHO-K1, and Chinese hamster lung fibroblasts V-79 were obtained from the Institute of Cytology, Russian Academy of Sciences (St. Petersburg). The cells were cultivated in Iscove's modified Dulbecco's medium (IMDM) (SIGMA 17633 with L-glutamine and 25 mH HEPES, without soidum bicarbonate) supplemented with 10% fetal bovine serum (Thermo scientific HyClone SV30160.03, HyClone UK Ltd.) and maintained at 37°C in the atmosphere of 5% CO_2.

L-p-boronophenylalanine (BPA, Katchem Ltd., Czech Republic) was used for targeted boron delivery by cell incubation in a growth medium with BPA at a concentration of 40 ppm boron-10 for 24 h. After incubation, the cells were washed with buffer solution, trypsinized with 0.05 % trypsin-EDTA (Nacalai Tesque, Inc., Kyoto, Japan), and placed into 2-mL plastic vials containing medium identical to that in which the cells had been originally incubated (with the initial concentration of ^{10}B). The vials were placed into a plexiglass phantom under the lithium target at a distance of 3 cm from the phantom surface. Cells irradiated without boron were used as controls.

Epithermal neutron irradiation. The samples were exposed to epithermal neutrons for 1-2 h with the following accelerator settings: 2 MeV proton energy, 1.5-2 mA proton current; total neutron flux passing through the samples was $3.6 \cdot 10^{11}$, $7.2 \cdot 10^{11}$, or $10.8 \cdot 10^{11}$ cm^{-2}.

Colony-forming assay. The viability of cells after exposure to epithermal neutrons was evaluated using colony-forming assay [9]. After irradiation, the cells were counted, diluted, and seeded into round plastic dishes 6 cm in diameter. 1-2 weeks later, the dishes were rinsed with buffer solution, fixed with glutaraldehyde, stained with crystal violet, and dried. Colonies containing 50 or more cells were counted in each sample. The obtained data was presented as mean ± standard deviation (SD). The statistical significance of difference from the control was evaluated using one-way analysis of variance (ANOVA).

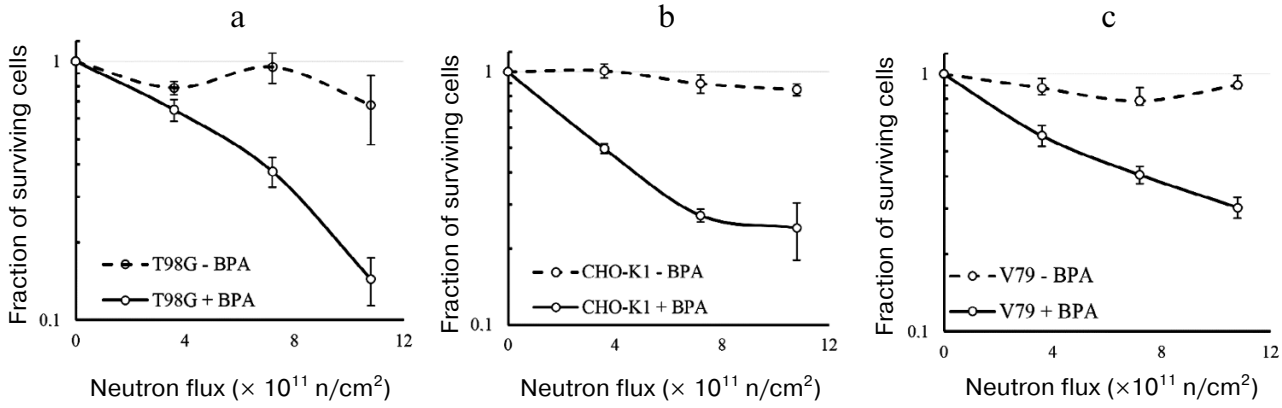

Fig. 1. Fraction of surviving T98G (a), CHO-K1 (b), and V-79 (c) cells after incubation in the medium with 40 ppm BPA (in terms of ^{10}B) or in the absence of BPA with further exposure to an epithermal neutron beam (mean ± SD).

Animal experiments. Animal experiments were approved by the Ethics Committee of the Novosibirsk State University. To evaluate the effect of a neutron beam on a living organism, immunodeficient SCID line mice were used. The radiosensitivity of different organs and the survival rate were studied as functions of the neutron radiation dose and the presence/absence of boron. Sodium borocaptate (Katchem Ltd., Czech Republic) was used for targeted delivery of boron; it was administered intraperitoneally at a dose of 200 mg/kg. The mice were placed in a special container made of lithium polyethylene sheets. The mice were positioned radially, heads towards the center of the container. The container was designed in such a way as to make the absorbed dose rate under a hole in the container twice as high as under polyethylene; this made it possible to reduce the level of irradiation of the body parts which should not be irradiated. The animals were irradiated with neutron beams with various time durations. The total irradiation dose did not exceed 5.7 Gy-Eq in mice administered with borocaptate and 2.0 Gy-Eq in irradiated controls [10]. After exposure, the animals were kept in the SPF vivarium of the Institute of Cytology and Genetics of the Siberian Branch of the Russian Academy of Sciences, under controlled conditions. The observation period lasted one month. During this period, the state of health of the mice was checked daily. In particular, changes in the state of the skin, activity, and behavior were evaluated. To evaluate the effect of different radiation doses on the organs of experimental animals, morphological study of tissues of various organs (kidney, liver, brain, heart, spleen) fixed with formaldehyde was performed.

Results and Discussion

The accelerator-based epithermal neutron source for BNCT considerably enhances the range of experimental studies. Investigation of neutron beam influence on T98-G, CHO-K1, and V-79 cells shows reduction of the viability of cells incubated with boronophenylalanine. The viability decreased with increasing radiation dose (Fig. 1).

The experiments also show that the radiation has almost no effect on cells without boron, because in the absence of the "boron" dose the integral dose considerable decreases. The increase in the dose received by cells as the result of neutron capture by boron led to a statistically significant ($P < 0.05$) decrease in the survival rate of cells irradiated with boron compared to that of control cells (i.e., cells irradiated in the absence of boron). Our previous studies had shown that BNCT also had an expressed effect on the reproductive capacity of U251 human glioma cells [9].

A month after irradiation, there was no lethality or any external symptoms of pathology found in the laboratory animals. Morphological studies showed that neutron irradiation had a minimal effect on kidney and liver tissues in terms of variable hydropic degeneration and on spleen cells in the form of decrease in the number of white pulp follicles. No structural changes in brain tissues were revealed, despite the fact that the brain received the highest radiation dose. Thus, it was shown that the therapeutic doses of epithermal neutrons generated using the accelerator had no effect on the viability of laboratory animals and did not lead to considerable damage to vital organs.

Conclusion

The compact neutron source for BNCT developed at the Budker Institute of Nuclear Physics of the Siberian Branch of the Russian Academy of Sciences makes it possible to avoid the necessity of filtration, biological shielding, and elimination of damage inflicted by fast neutrons and other types of concomitant radiation. The proton beam current of 5 mA obtained using the accelerator-based neutron source is sufficient to generate the epithermal neutron flux of the required density and meets all requirements for use in neutron capture therapy. The in vitro and in vivo studies have shown the obtained neutron beam to be safe and effective for treatment of malignant tumors. The specialized neutron source for BNCT forms the basis for clinical studies, because it provides, for the first time, the possibility of sufficiently homogeneous generation of accelerated epithermal neutrons. The developed neutron source is unique; it has been designed to solve highly relevant problems of BNCT. It remains necessary to perform the complete set of clinical trials on the device. The compact accelerator-based source of epithermal neutrons for BNCT can be used as an island medical system or installed in a multi-special hospital. It allows the safety of BNCT to be improved, increasing the safety of this therapeutic technique, whose implementation still poses a number of problems.

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