I-1. PROJECT RESEARCHES

Project 2

PR2

The effect of BNCT on normal tissues

M. Suzuki

Institute for Integrated Radiation and Nuclear Science, Kyoto University

Clinical trials of BNCT for head and neck cancer began at two medical institutes in 2020 as approved medical treatments. Several clinical trials of BNCT with accelerator BNCT are currently underway for new indications including malignant melanoma, angiosarcoma, malignant brain tumors, and breast cancer. In all clinical trials, the prescribed dose is the dose to normal tissues or organs. In conventional radiotherapy, on the other hand, the prescribed dose is the dose to the malignant tumors, and the dose to normal tissues is used as a dose limit. The reason for this is that real-time measurement of boron concentration in the tumors during irradiation is not realized. Therefore, the dose to critical normal organs in the irradiation field is used as the prescription dose, and the dose to normal tissues is estimated based on the boron concentration in the blood sampled from the patient just before irradiation.

The therapeutic efficacy of BNCT for malignant tumors depends on the accumulation of the boron drug in the tumor or tumor cells at the high boron concentration. Normal tissues, on the other hand, when considering the adverse effects of BNCT on them, those will differ depending on which of the multiple components (parenchymal cells, blood vessels, nonparenchymal cells, etc.) taken up the boron compound selectively. Borocaptate sodium (BSH), which has been used clinically, and boronophenylalanine (BPA), which is currently used in daily practice, have been studied with respect to their local distribution in normal tissues, but not enough research has been conducted. In addition, many new boron agents are currently being developed. To try the new boron drugs in first-in-human clinical studies, the prerequisites is the investigation of the BNCT effects on normal tissues. More BNCT researchers are expected to have interest in the research on BNCT for normal tissues and struggle with this research thema.

In this research project, two research projects were included in this year. One research was not performed. Details of one project are referred to the progress report.

P2-1. Evaluation of the Anticancer Effects and Side Effects of BNCT in a Mouse Model

In previous study, the anti-tumor effect of Boron Neutron Capture Therapy (BNCT) for a mouse model of pelvic recurrence of Colorectal cancer (CRC) was elucidated. In this study, the late ad-verse effect of BNCT on pelvic organs.

PR2-1

Evaluation of the Anticancer Effects and Side Effects of BNCT in a Mouse Model

S. Hagihara[1], J. Arima [1], K. Taniguchi[1,2], Y. Inomata[1], A. Miyamoto[1], M. Suzuki[3], and Sang-Woong Lee [1]

[1] Department of General and Gastroenterological Surgery, Osaka Medical and Pharmaceutical College, Osaka, Japan
[2] Translational Research Program, Osaka Medical and Pharmaceutical College, Osaka, Japan
[3] Department of Particle Radiation Oncology, Research Reactor Institu te, Kyoto University, Kumatori, Osaka, Japan.

INTRODUCTION: Previously, we reported the anti-tumor effect of Boron Neutron Capture Therapy (BNCT) for a mouse model of pelvic recurrence of Colorectal cancer (CRC). On the other hand, we could not fully evaluate side effects in terms of immune response or the later complications, because we examined the effectiveness of BNCT in the nude mouse model only a month after treatment. This study investi-gates early and late effect of pelvic BNCT.

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EXPERIMENTS: We used Boronophenylalanine (BPA) as a boron compound. Also, we used seven-week-old female BALB/c mouse. Firstly, we established a mouse model of pelvic recurrence of CRC using Colon-26-Luc cells concentrated to 1.0×10^5/100μL in 0.1ml of PBS. We injected BPA intraperitoneally at 3h before irradiation. Animals were divided into three groups; the cold control (no treatment, no neutron irradiation), hot control (neutron irradiation only), and BNCT (intraperitoneal BPA administration and neutron irradiation) groups. Also, we conducted an irradiation experiment using BALB/c mice without tumor implantation to investigate the long-term effects on pelvic organs.

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RESULTS: Our results are the first to show that BPA-mediated BNCT prolonged the survival of experimental in BALB/c mice with pelvic tumors. (**Fig.1)** There were the significant differences of body weight among three groups after BNCT (**Fig.2)** However, all mice did not have symptoms such as diarrhea and survived for 189 days. Based on the result, BNCT for the pelvis was considered to be safely feasible.

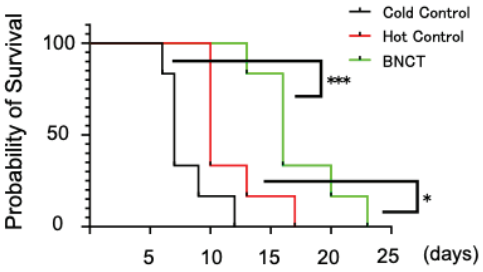

Fig.1 The survival was significantly prolonged in BNCT group.
N=6 in each group. Error bar: means±SD

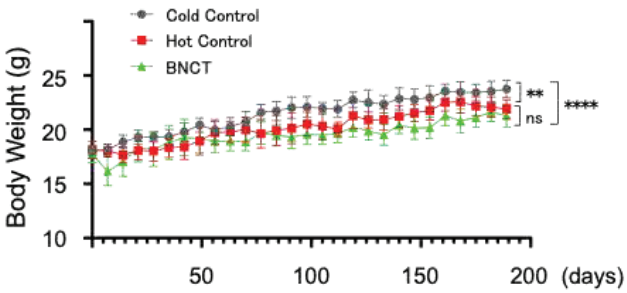

Fig.2 Body weight was reduced in BNCT group.
N=7 in cold group, N=6 in hot control and BNCT group, Error bar: means±SD

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REFERENCES:

[1] Jun Arima *et al.*, Biomed. Pharmacother. **154** (2022) 113632, (doi) 10.1016/j.biopha.2022.113632.