PR11 Clinical Research on Explorations into New Application of BNCT

M. Suzuki

Research Reactor Institute, Kyoto University

Summary

This research projects consists of three clinical research programs on BNCT for malignancies other than malignant brain tumors or head and neck cancers. In P11-1, three patients were treated with BNCT. In P11-2, no patient was recruited in their study. In P11-3, no patient was recruited in their study. Yanagie (Principal investigator of P11.3) et al. reported basic study on BNCT for hepatocellular carcinoma (HCC) using a pig.

P11-1

In P11-1 clinical research study, three patients including two malignant soft tissue tumors and one malignant plural mesothelioma (MPM) were treated with BNCT. BNCTs for two malignant soft tissue tumors, clear cell sarcoma and synovial sarcoma, were the first attempts in the world. BNCT for MPM was carried out to alleviate the symptom such as stiffness of neck or back from huge tumors of MPM.

Summary of the BNCT procedure and dose-distribution in the BNCT for MPM was reported in the report of P11-1.

Details of the case reports of three cases will be reported after proving the consequence of BNCTs.

P11-3

Yanagie et al. reported a preclinical study on feasibility of intra-arterial injection of ^{10}BSH entrapped water-in-oil-in-water (WOW) emulsion using pig. They performed intra-arterial injection according to the injection data that maximum dose 0.8mL/kg was injected for rabbit experiments, equivalent maximum dose for pig is possible to be injected 8mL/body. Transient hypotension at a 2mL infusion of WOW emulsion was happened in this experiment, but it was improved. The constitution drugs of this emulsion are safety, because ^{10}BSH is used in a clinic of BNCT, and the lipiodol and the surfactant HCO40 are authorized from the Ministry of Health.

The abnormal changes in the liver, the kidney, the heart, the pancreas were not found in the histopathologic examination one week after intra-arterial injection of ^{10}BSH entrapped WOW emulsion.

PR11-1 Clinical Research on Explorations into New Application of BNCT

M. Suzuki, S. Masunaga, Y. Kinashi, H. Tanaka, Y. Sakurai, N. Kondo, Y. Tamari, T. Fujimoto[1], E. Shibata[2] and T. Kijima[2]

Research Reactor Institute, Kyoto University

[1]Department of Orthopedic Surgery, Hyogo Cancer Center

[2]Division of Respiratory Medicine, Department of Internal Medicine, Hyogo College of Medicine

Introduction

Boron neutron capture therapy (BNCT) has been applied mainly for the treatment of locally recurrent malignant brain tumors or head and neck cancers in the irradiated region using neutron beams from the research reactor. In some BNCT clinical trials, the survival data or tumor response were suggested to be better compared those by other clinical studies. Collaborative project to develop an accelerator-based (AB)-BNCT system between Sumitomo Heavy Industrial and Kyoto University succeeded to construct available cyclotron-based AB-BNCT system.

Clinical trials using the AB-BNCT system are currently in progress. The targets of the ongoing clinical trials are two malignancies as follows: recurrent malignant gliomas and head and neck cancers. In a few years, the system and boron-containing drug is expected to get medical device approval and pharmaceutical approval from national agency. Since the AB-BNCT system installed in the hospital is available to more patients suffering from malignant tumors compared with those by the BNCT using research reactor. However, in a few years before getting medical device approval and pharmaceutical approval, patients with malignant tumors other than malignant gliomas and head and neck cancers will be treated with research reactor-based BNCT. When the AB-BNCT system will be applicable to many clinical trials to search for new application of BNCT in the hospitals, experience of BNCT for new malignancies will be helpful for the new clinical AB-BNCT trials.

We treated two patients wit malignant tissue soft tissue sarcoma and one patient with malignant pleural mesothelioma (MPM) in this research program. In this report, we present summary of the BNCT for malignant pleural mesothelioma.

BNCT for malignant pleural mesothelioma

A 64 year-old man with MPM had received a number of chemotherapy cycles. His main symptom was stiffness of the neck and back. The large MPM tumors refractory to the chemotherapy located mainly between the dorsal and lateral skin of the thorax and the pleura rather than between the pleura and the lung parenchyma. He referred to our center for further treatment of MPM with BNCT. Since the tumor was so large that the epithermal neutron beam using the maximum-sized collimator could not encompass all the volume of the tumor, the BNCT was carried out in order to alleviate the symptom.

The BNCT for the large MPM tumors mainly located between the dorsal and lateral skin of the thorax and the pleura was performed with an epithermal neutron beam using a 24 x 24 cm square collimator. The irradiation time, 20 minutes, was determined according to the dose constraint for the skin. Dose constraint was set to 9.0 Gy-Eq as a maximum dose for the skin. The dose delivered to the tumors ranged from 0.1 to 58 Gy-eq. Since approximately one third of the whole tumor volume existed out of the collimator, the tumor volume greater than 50 % of the tumor received less than 20 Gy-eq. However, the tumor volume greater than 1,500 cm3 was irradiated with the dose greater than 20 Gy-eq. The maximum dose delivered to the liver, left lung and spinal cord was 4.6 Gy-eq, 7.5 Gy-eq and 1.9 Gy-eq, respectively. The mean left lung dose was 2.8 Gy-eq. For two month after BNCT, no acute adverse event greater than grade 3was experienced. At two months after BNCT, a grade 2 lymphopenia developed. The computed tomography (CT) examined at one month after BNCT, the tumor size remained stable in size.

No sever acute adverse event was observed in the treatment of large MPM tumor with BNCT.

PR11-2 Pilot Study of Single Dose Toxicity Evaluation of ^{10}BSH Entrapped WOW Emulsion on Intraarterial Delivery in Pig for Neutron Capture Therapy to Hepatocellular Carcinoma

H. Yanagie[1,2,3], M. Fujihara[4], Y. Sakurai[1,3], K. Mouri[1,3], Y. Morishita[5], M. Yanagawa[6], Y. Nonaka[7], Y. Ohno[8], S. Maruyama[8], K. Oyama[8], K. Seguchi[9], Y. Sakurai[10], H. Tanaka[10], M. Suzuki[10], S. Masunaga[10], K. Ono[10], S. Higashi[9], M. Ono[3,11], J. Nakajima[3,12], M. Eriguchi[8] and H. Takahashi[2,3]

[1]Niigata University of Pharmacy and Applied Life Sciences, [2]Dept of Nuclear Engineering & Management, Graduate School of Engineering, The University of Tokyo, [3]Cooperative Unit of Medicine & Engineering, The University of Tokyo Hospital, [4]SPG Techno Ltd. Co., [5]Dept of Human & Molecular Pathology, Graduate School of Medicine, The University of Tokyo, [6]Obihiro University of Agriculture & Veterinary Medicine, [7]Keiai-kai Hoyo Hospital, [8]Dept of Surgery, Shin-Yamanote Hospital, [9]Kojin-kai Medical City East Hospital, [10]Research Reactor Institute, Kyoto University, [11]Dept of Cardiac Surgery, The University of Tokyo Hospital, [12]Dept of Thoracic Surgery, The University of Tokyo Hospital, JAPAN

INTRODUCTION: The principle of cancer cell destruction in boron neutron capture therapy (BNCT) is due to the nuclear reaction between ^{10}B and thermal neutrons to release al-pha-particles (^{4}He) and lithium-7 ions (^{7}Li) after delivery of ^{10}B atoms to cancer cells selectively. The ^{4}He kills cells in the range of 10 μm from the site of ^{4}He generation.

Higashi et al prepared a long term inseparable Water-in-oil-in-water (WOW) emulsion by the double emulsification technique to be used in arterial injection therapy to treat patients with hepatocellular carcinoma (HCC) [1, 2].

WOW emulsion could deliver high concentration of 10Boron compounds to cancer tissues, so we applied this delivery system to BNCT. We performed preclinical BNCT study for VX-2 rabbit tumour model using 10BSH-entrapped WOW [3], and also proceeded clinical BNCT study for HCC using this WOW system [4].

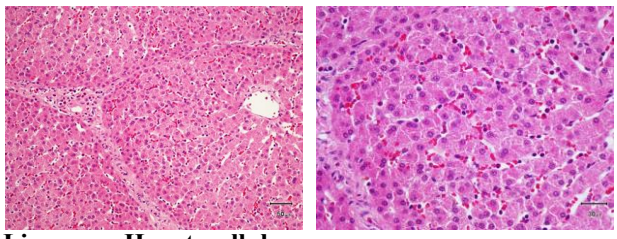
In this study, we prepared ^{10}BSH-entrapped WOW, and evaluated the toxicity by checking histopathological findings after intra-hepatic injection of ^{10}BSH entrapped WOW emulsion in healthy rabbits.

EXPERIMENTS: As a part of the pilot safety evaluation of ^{10}BSH-entrapped WOW emulsion(175mg ^{10}BSH/mL), the test article was dosed once by hepatic arterial administration to one female healthy pig at 0.05mL/kg to investigate its toxicity. The investigated items included clinical observation, measurement of body weights and food consumption, blood chemistry, and histopathological findings.

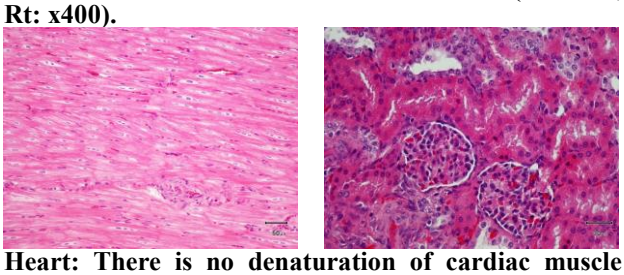
RESULTS: We performed intra-arterial injected ^{10}BSH entrapped WOW emulsion. According to the injection data that maximum dose 0.8mL/kg was injected for rabbit experiments, equivqlent maximum dose for pig is possible to be injected 8mL/body. Transient hypotension at a 2mL infusion of WOW emulsion was happened in this experiment, but it was improved. The constitution drugs of this emulsion are safety, because ^{10}BSH is used in a clinic of BNCT, and the lipiodol and the surfactant HCO40 are authorized from the Ministry of Health.

The abnormal change in the liver, the kidney, the heart, the pancreas were not found in the histologic examination one week after intra-arterial injection of ^{10}BSH entrapped WOW emulsion.

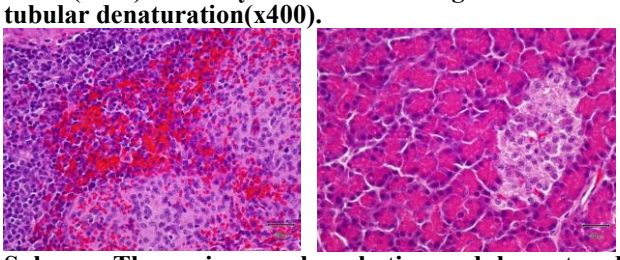
In the next experiments, we hope to increase a dose in quantity of WOW emulsion with an anti-histamine drug or steroid administration to prevent shock or hypotension before hepatic arterial infusion. We hope to refer these results of toxicity examinations to the clinical studies of BNCT to hepatocellular carcinoma with intra-arterial boron delivery using WOW emulsion.



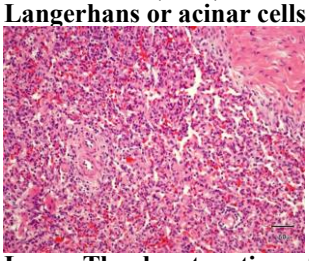
Liver: Hepatocellular denaturation and the destruction are absent (Lt: x200, Rt: x400).



Heart: There is no denaturation of cardiac muscle cells (x400). Kidney: There is no glomerulus or tubular denaturation(x400).



Spleen: There is no lymphatic nodule-centered denaturation(x400). Pancreas: There is no islet of Langerhans or acinar cells denaturation(x400).



Lung: The denaturation of pulmonary epithelial cells is absent(x200).

REFERENCES:

[1] S Higashi *et al.*, Cancer, **75** (1995)1245–1254.
[2] I. Kushima *et al.*, Eur J Radiol., **69** (2009)114-9.
[3] H Yanagie *et al.*, Br J Radiol. (2017) [Epub ahead of print] doi:10.1259/bjr.20170004.
[4] H Yanagie *et al.*, Appl Radiat Isot., **88** (2014)32-7.

29P11-3