

I-1. PROJECT RESEARCHES

Project 6

M. Suzuki

Institute for Integrated Radiation and Nuclear Science, Kyoto University

Summary

This research projects consists of two clinical research programs on BNCT for malignancies other than malignant brain tumors or head and neck cancers. In P6-1, three patients were treated with BNCT. In P6-2, no patient was recruited in their study.

P6-1

We treated three patients with BNCT in this research program. The malignancies included malignant tissue soft tissue sarcoma, locally recurrent breast cancer and angiosarcoma. Since the patients treated with BNCT in this research problem are under-observation, no preliminary report is available.

P6-2

No patient was enrolled in this clinical research program. Yanagie et al. reported the case report on BNCT for multiple liver metastasis which was carried out previously. Details in this case report is referred to the P6-2 report. The large metastatic liver tumor was diminished, and the local pain derived from the tumor was improved.

Law on Clinical research (*rinsho kenkyu hou*)

New regulation on clinical research, Law on clinical Research (*rinsho kenkyu hou*), has come into effect since April in 2018. Clinical researches conducted by using Drugs and Medical Devices not approved under the Pharmaceutical and Medical Device LAW are categorized into Specified Clinical Research (*tokutei rinsho kenkyu*). Specified Clinical Research Plan should be reviewed by Certified Clinical Research Review Committee. Since BNCT is carried out using unapproved drug (boron compound) and research reactor, BNCT study is categorized into Specific Clinical Research. Six clinical researches on BNCT have been approved as Specific Clinical Research by Certified Clinical Research Review Committee established in medical institutes. Since BNCT studies on locally recurrent breast cancer and angiosarcoma have been approved as Specified Clinical Research, these studies will be carried out in 2019.

M. Suzuki¹, M. Iwamoto², J. Sugawara³, S. Moriwaki⁴, H. Tanizaki⁴, K. Yoshida⁵, S. Kawabata⁶, S. Miyatade⁷, S. Masunaga¹, Y. Kinashi¹, H. Tanaka¹, Y. Sakurai¹, N. Kondo¹, Y. Tamari¹, T. Fujimoto⁸, M. Fukahori⁹

¹ Institute for Integrated Radiation and Nuclear Science, Kyoto University

² Department of Breast and endocrine surgery, Osaka Medical College

³ Department of Ophthalmology, Osaka Medical College

⁴ Department of dermatology, Osaka Medical College

⁵ Department of Radiology Osaka Medical College

⁶ Department of Neurosurgery, Osaka Medical College,

⁷ Cancer center, Osaka Medical College

⁸ Department of Orthopedic Surgery, Hyogo Cancer Center

⁹ National Institutes for Quantum and Radiological Science and Technology

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 three patients with BNCT in this research program. The malignancies included malignant tissue soft tissue sarcoma, locally recurrent breast cancer and angiosarcoma. Since the patients treated with BNCT in this research problem are under-observation, no preliminary report is available.

In this report, we present the policy of prescribed neutron fluence adopted in the BNCT studies in this research problem.

Prescribed neutron fluence

Evaluation of irradiated dose is very complicated since irradiation filed in BNCT consists of multiple radiation components including $^{10}\text{B}(n,\alpha)^7\text{Li}$ radiation, high linear energy transfer (LET) proton radiation and γ -ray radiation. The physical dose (Gy) is calculated with an equation as follows,

Physical dose (Gy) = $\text{Dose}[^{10}\text{B}(n,\alpha)^7\text{Li}]^* + \text{Dose}[\gamma \text{ dose}] + \text{Dose}[^1\text{H}(n,n)^1\text{H}] + \text{Dose}[^{14}\text{N}(n,p)^{14}\text{C}]$

*: $\text{Dose}[^{10}\text{B}(n,\alpha)^7\text{Li}] = 7.43 \times 10^{-14} \times \text{B}_{\text{conc}} \times \Phi$

Φ : thermal neutron fluence

The equation for converting the physical dose (Gy) to the photon-equivalent dose (Gy-Eq) dose is as follows.

Photon-equivalent dose (Gy-Eq) = $\text{CBE} \times \text{Dose}[^{10}\text{B}(n,\alpha)^7\text{Li}]^* + \text{Dose}[\gamma \text{ dose}] + \text{RBE} \times \text{Dose}[^1\text{H}(n,n)^1\text{H}] + \text{RBE} \times \text{Dose}[^{14}\text{N}(n,p)^{14}\text{C}]$

*: $\text{Dose}[^{10}\text{B}(n,\alpha)^7\text{Li}] = 7.43 \times 10^{-14} \times \text{B}_{\text{conc}} \times \Phi$

CBE: compound biological effectiveness

RBE: relative biological effectiveness

In clinical studies of BNCT, the ^{10}B concentration in the blood sampled just before neutron irradiation has been used in deciding irradiation time according to the prescribed dose (Gy-Eq) for normal tissues.

As shown in the equation, the concentration of ^{10}B is necessary to calculate the dose. However, no method to measure ^{10}B concentration during irradiation is developed. Therefore, in evaluating the dose in BNCT, some uncertain is inevitable.

In the clinical pilot studies on BNCT for local recurrent breast cancer and angiosarcoma, we applied the idea of prescribed thermal neutron fluence. In the protocol of the studies, the prescribed thermal neutron fluence was determined as the value of $1.5 \times 10^{12} \text{ n/cm}^2$ at the skin of 10-cm diameter circle. Under the condition that ^{10}B concentration in the tumor cells are two times greater than normal cells, the tumor cells received the dose greater than approximately 20 Gy-Eq with keeping the dose for the skin within the tolerant dose.

H. Yanagie^{1,2,3}, Y. Nonaka⁴, S. Maruyama⁵, R. Hatae⁵, K. Oyama⁵, M. Eriguchi⁵, Y. Sakurai⁶, H. Tanaka⁶, N. Kondo⁶, T. Kinashi⁶, M. Suzuki⁶, S. Masunaga⁶, K. Ono⁷, S. Higashi⁸, K. Seguchi⁸, I. Ikushima⁹, M. Nashimoto³, T. Sugihara³, H. Terada³, and H. Takahashi^{1,2}

¹Dept of Nuclear Engineering & Management, School of Engineering, Univ of Tokyo, Tokyo, ²Cooperative Unit of Medicine & Engineering, Univ of Tokyo Hospital, Tokyo, ³Niigata Univ of Pharmacy & Applied Life Sciences, Niigata, ⁴Dept. of Surgery, Keiai-kai Hoyo Hospital, Iwate, ⁵Shin-Yamanote Hospital, Japan Anti-Tuberculosis Association, Tokyo, ⁶Kyoto Univ Institute for Integrated Radiation & Nuclear Science, Osaka, ⁷Kansai BNCT Medical Center, Osaka Medical College, Osaka, ⁸Depat. of Surgery, Kojin-kai Medicalcity East Hospital, Miyazaki, ⁹Dept. of Radiology, Miyakonojo Metropolitan Hospital, Miyazaki, JAPAN

INTRODUCTION: We had experienced the boron neutron capture therapy (BNCT) to cancers in gastrointestinal regions. Our cases treated by BNCT were 1 case of cervical metastatic gastric cancer (Partial Remission), 2 cases of recurrent rectal cancers (Stable Disease), and 1 case of hepatic metastatic sigmoidal colon cancer (Locally Stable Disease).

In this study, we performed the literature consideration of combination therapies to the case of hepatic metastatic sigmoidal colon cancer.

EXPERIMENTS: The 38y.o. male patient with sigmoidal colon cancer & multiple hepatic metastasis had been performed sigmoidectomy, intra-arterial chemotherapies (CDDP), and molecular targeted therapy (XELOX+ Cmab, XELOX+Pmab, IRIS+Pmab). But the tumour volume of hepatic metastasis was increased, and then the local pain caused tumour swelling was occurred. In order to decrease the chief complaint by the tumour swelling, we performed the BNCT on January 2012. The procedure points were (1) target lesion: S4 hepatic metastatic lesion (Figure 1), (2) ¹⁰BPA 400mg/kg drip infusion, (3) Tumour dose: 30>Gy-Eq/5cm, Normal Liver dose: <4.9Gy-Eq, (4) Tumour/Blood ration of ¹⁸F-¹⁰BPA PET: 2.6.

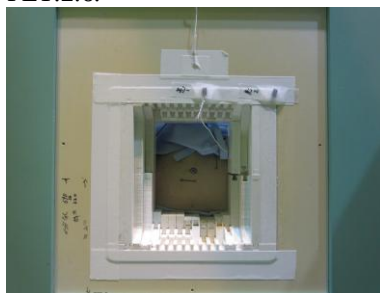


Figure1:
Irradiation
positioning of
BNCT.

RESULTS & DISCUSSION: As shown in Figure 2, Maximum Tumour dose will be 31Gy-Eq, Mean Tumour dose was 20Gy-Eq, Maximum Normal Liver dose was 17Gy-Eq, Mean Liver dose was 3Gy-Eq in 43 minutes BNCT.

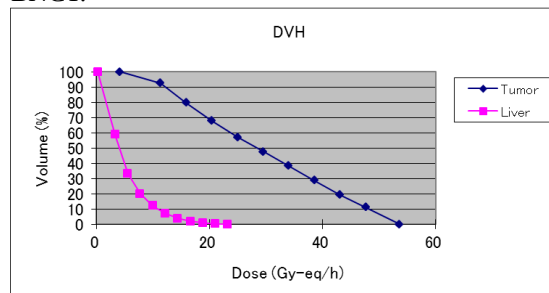
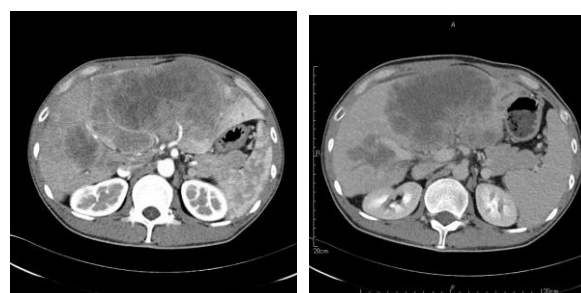


Figure 2: Calculation of Tumour/ Normal Liver Dos.



Before BNCT
(2011.11.25)

Post 3 months BNCT
(2012.04.20)

Figure 3: Tumour growth was suppressed, and the local pain caused tumour swelling was markedly diminished.

The tumour volume was diminished and the chief complaint of patient was improved. The tumour volume in hepatic metastasis was regulated in 3 months by single irradiation of BNCT locally.

We had one experienced case of intra-arterial injection of immunostimulating substance, OK432 (Picibanil) to the multiple large metastasis of colon cancer patient after operation, and systemic & intra-arterial (IA) chemotherapies. Our case was decrease of tumour volume and recover the QOL of patient. So, we hope to apply the combination therapies with BNCT and Intra-Arterial Immunotherapy in the next step.

Recently, immunotherapies become attractive combination therapies to cancer. Immune checkpoint blockade, Dendritic Cell Therapy, CTL/NK Cell Therapy, OK432-IA will be considered in the consideration of indications to liver cancer in near future.

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