I. Project Research

Project 4

PR4 Clinical research on explorations into new application of BNCT

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An accelerator-based boron neutron capture therapy (BNCT) system and boronophenylalanine (BPA)-based new drug were approved by the Ministry of Health, Labour and Welfare of Japan for the treatment of locally unresectable recurrent or unresectable advanced head and neck cancer on March 2020. Since BNCT will be carried out at the medical institute, the accessibility of BNCT will improve dramatically and much greater patients will be treated with accelerator-BNCT compared with reactor-BNCT.

In 2019, under the Low on Clinical research* (rinsho kenkyu hou), clinical researches on BNCT for local recurrent breast cancer and angiosarcoma have been approved.

***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.

In this research projects, two researches are included.

P4-1: We treated one patient suffering from angiosarcoma of the face in this research program. Since the patient treated with BNCT in this research problem are under-observation, no detailed report is available.

P4-2: No patient was enrolled in this clinical research program. Yanagie et al. reported a preclinical study on syringe-shaped medical device attached with Shirasu porous glass (SPG) membrane to the preparation of ^{10}BSH-entrapped WOW emulsion for clinical use. Details in this case report is referred to the P4-2 report.

PR4-1

Clinical research on explorations into new application of BNCT

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An accelerator-based boron neutron capture therapy (BNCT) system and boronophenylalanine (BPA)-based new drug were approved by the Ministry of Health, Labour and Welfare of Japan for the treatment of locally unresectable recurrent or unresectable advanced head and neck cancer on March 2020. Since BNCT will be carried out at the medical institute, the accessibility of BNCT will improve dramatically and much greater patients will be treated with accelerator-BNCT compared with reactor-BNCT. One of the drawbacks of BNCT is that thermal neutrons necessary for tumor control cannot be delivered to the deep portion of the tumor which is located at > 6 cm in depth from the skin surface.

For BNCT to be recognized as effective treatment modality for malignant tumor, expanding indication of BNCT is very important.

We treated one patient suffering from angiosarcoma of the face in this research program. Since the patient treated with BNCT in this research problem are under-observation, no detailed report is available.

PR4-2 Preparation of Boron entrapped WOW emulsion by Mixing Medical Device for Boron Neutron Capture Therapy to Hepatocellular Carcinoma

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INTRODUCTION: Hepatocellular carcinoma (HCC) is one of the difficult cancers to cure with conventional treatment. Higashi et al prepared a long term inseparable Water-in-oil-in-water(WOW) emulsion for use in arterial injection therapy to treat patients with HCC by the double emulcificating technique[1]. Suzuki et al. had reported the tumor growth suppression by BNCT using boron compound with IPSO administered intra-arterially[2]. We performed preclinical BNCT study using ^{10}BSH entrapped WOW [3], and had experienced clinical BNCT study for HCC using this system[4].

In this study, we developed syringe-shaped medical device attached with Shirasu porous glass (SPG) membrane to the preparation of ^{10}BSH-entrapped WOW emulsion for clinical use, and evaluated the boron encapsulating activity to measure the ^{10}B concentrations of WOW emulsion by using ICP-Mas.

EXPERIMENTS: We developed the syringe-shaped medical device by attaching to SPG Millipore membrane. ^{10}BSH (262.5 mg) was dissolved in 1.5 ml of a 5% glucose solution, which was first filtered through an SPG controlled pore glass membrane and then emulsified in 1.5 ml IPSO containing surfactant to form the water-in-oil emulsion (WO). The WO emulsion was then emulsified again with an aqueous phase containing 3 ml saline solution and surfactant through a second SPG controlled pore glass membrane using this medical device. The ^{10}B concentration in WOW vesicles was determined by ICP-AES of Jyuntendo University.

RESULTS: By using this device, we were able to produce the WOW emulsion of the same size even after changing the persons who perform the experiment more than ten times. About 7300 ppm ^{10}B concentrations were recognized in the ^{10}BSH-WOW emulsion as same as Day 0 and Day 1 after preparation using Mixing medical device (Table 1).

In the conventional preparation of WOW emulsion, the procedure takes about 6 hours. By using this device, we were able to prepare the WOW emulsion with the single peak of 100 μm in about 30 minutes.

Since WOW emulsion can deliver high amounts of ^{10}B to tumor as the first targeting delivery to tumor. We hope to develop the second targeting delivery to cancer cells with the increase of mechanism by endocytosis, fusion, etc.

Table 1. ^{10}B concentration in ^{10}BSH-entrapped WOW emulsion prepared with Mixing medical device

	^{10}B	^{11}B	^{10}B	^{11}B
^{10}BSH-WOW	**DAY0**		**DAY1**	
1	**6626.3**	**N.D.**	**7586.3**	**N.D.**
2	**7333.0**	**N.D.**	**7360.8**	**N.D.**
3	**7213.0**	**N.D.**	**6663.2**	**N.D.**
4	**7829.6**	**N.D.**	**7510.5**	**N.D.**
5	**7726.0**	**N.D.**	**7813.6**	**N.D.**
Mean	**7345.6**		**7386.9**	
S.D.	**478.0**		**436.3**	
Lactose-WOW	**DAY0**		**DAY1**	
1	**0.07**	**0.19**	**0.02**	**0.25**
2	**0.04**	**0.2**	**0.11**	**0.45**
3	**0.05**	**0.18**	**0.07**	**0.32**
4	**0.05**	**0.29**	**0.08**	**0.34**
5	**0.05**	**0.20**	**0.08**	**0.32**
Mean	**0.05**	**0.21**	**0.07**	**0.33**
S.D.	**0.01**	**0.04**	**0.03**	**0.07**

The original ^{10}B concentration (ppm) in WOW emulsion was determined using ICP-AES at Juntendo University.

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[1] S Higashi S *et al.*, Cancer, **75**(1995):1245–1254.
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