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Pilot clinical study of boron neutron capture therapy for recurrent hepatic cancer involving the intra-arterial injection of a ^{10}BSH-containing WOW emulsion

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HIGHLIGHTS

- We started the pilot clinical study of BNCT to recurrence hepatic cancer.
- The tumor size was remained stable during 3 months after BNCT(SD).
- No adverse effect as a result of BNCT was observed during follow-up period.
- ^{10}B-containing WOW emulsion can be applied as a novel intra-arterial boron carrier for BNCT for HCC.

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ABSTRACT

A 63-year-old man with multiple HCC in his left liver lobe was enrolled as the first patient in a pilot study of boron neutron capture therapy (BNCT) involving the selective intra-arterial infusion of a ^{10}BSH-containing water-in-oil-in-water emulsion (^{10}BSH-WOW). The size of the tumorous region remained stable during the 3 months after the BNCT. No adverse effects of the BNCT were observed. The present results show that ^{10}BSH-WOW can be used as novel intra-arterial boron carriers during BNCT for HCC.

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1. Introduction

The cytotoxic effects of boron neutron capture therapy (BNCT) are due to a nuclear reaction between ^{10}B atoms and thermal neutrons. The α particles and ^{7}Li ions that arise from the above-mentioned capture reaction damage any cell structures located within a path length of about 10 μm. So, it is very important to develop selective boron delivery systems for effective BNCT (Yanagie, 1997, 2006, 2008). We would like to use BNCT to treat radioresistant tumors, such as locally advanced or locally recurrent breast cancer, hepatocellular carcinoma (HCC), metastatic liver tumors, and lung cancer (Yanagië et al., 2008, 2011).

Most HCC are considered to be incurable, and there are few treatment options for prolonging survival. Iodized poppy-seed oil (IPSO) is selectively deposited in HCC cells. Suzuki et al. (2000, 2004, 2007) reported that the intra-arterial administration of a boron compound mixed with IPSO is technically a form of chemo-embolization, which has been widely used in the treatment of liver tumors. They also reported the clinical results of the first patient with multiple HCC to be treated with BNCT. Higashi et al. (1995) prepared a long-term inseparable water-in-oil-in-water emulsion (WOW) containing 8–60 mg of epirubicin for use in arterial injection therapy for patients with HCC. The WOW was prepared using a membrane emulsification technique involving a controlled pore glass membrane. Emulsification using a fine-pore glass membrane with pores of a defined size (i.e., a controlled-pore glass membrane) is a new technique for preparing lipid microdroplets of equal size (monodispersed) containing fine aqueous microdroplets, which can be used to produce WOW emulsions.

Here, we present a new protocol for BNCT for HCC, which could be an option for patients who cannot be treated with conventional therapies. In this study, we developed a boron compound-containing WOW emulsion and evaluated its toxicity to the human body as well as the efficiency of tumor growth suppression by BNCT involving the intra-arterial injection of the WOW emulsion.

2. Case report

2.1. Human subject protection

This pilot study was reviewed and approved by the institutional review board of Kojin-kai Medical City East Hospital, Japan. In addition, the institutional review board of Kyoto University Research Reactor Institute (KURRI), Japan, judged the eligibility of each patient for this pilot study.

2.2. Case presentation

A 63-year-old man underwent right lobectomy of the liver (not involving segment 5) in October 2006. The patient received eight rounds of trans-catheter arterial chemotherapy involving an epirubicin-containing WOW emulsion for intrahepatic metastasis in the residual liver. However, new metastatic lesions that were judged to be refractory to this treatment developed, and so the patient was referred to Kojin-kai Medical City East Hospital for BNCT and was informed of this pilot study.

The patient was informed about the study procedure, the expected effects and risks of the planned treatment, other treatment options, and the data management protocols. He provided written informed consent for all of the activities performed at the two institutions; i.e., Kojin-kai Medical City East Hospital and Kyoto University Research Reactor Institute, and voluntarily agreed to participate in this trial.

Laboratory tests performed 1 week before the BNCT demonstrated the following findings: total bilirubin: 1.0 mg/dl, aspartate aminotransferase (AST): 99 IU/l, alanine aminotransferase (ALT): 58 IU/l, total protein: 7.7 g/dl, serum creatinine: 0.8 mg/dl, blood urea nitrogen: 19 mg/dl. In addition, the patient had Child–Pugh grade B cirrhosis and was hepatitis B virus-positive.

2.3. BNCT procedure

Preparation of the boron compound-containing WOW emulsion: 500 mg of $^{10}B_{12}H_{11}SH$ (^{10}BSH) were dissolved in 5 ml of 10% glucose solution, and the resultant solution was filtrated through a controlled pore glass membrane, emulsified into 5 ml of IPSO-containing surfactant, and used to produce a water-in-oil emulsion (WO). The WO emulsion was emulsified again with an aqueous phase containing 5 ml of saline and surfactant. The ^{10}BSH-containing WOW emulsion was prepared using a previously described double emulsifying technique (Higashi et al., 1995; Fig. 1). ^{10}B concentration of the injected solution was 13,000 ppm, and the lipid microdroplets in the WOW emulsion measured 70 μm in diameter.

On 30 July 2011, the patient received a superselective intra-arterial injection of the ^{10}BSH-containing WOW emulsion through a catheter lodged in the tumor-feeding branch of the left hepatic artery. Six mililiter of the ^{10}BSH-containing WOW emulsion were administered. The selective accumulation of the ^{10}BSH-containing WOW emulsion in the tumor cells in the left lobe of the liver was observed on a computed tomography (CT) scan performed 3 days after the intra-arterial injection. Increases in the patient's AST and ALT levels were detected, but these soon recovered to within the normal range and the patient's general condition was good, so the patient was transported to KURRI to undergo irradiation 5 days (4th August 2011) after the injection of the ^{10}BSH-containing WOW emulsion.

Whilst positioning the patient in the irradiation room, we referred to four lines marked on his skin, which indicated the upper, lower, right, and left margins of the tumorous region, and a central point, which indicated its center. The lines had been drawn at Kojin-kai Medical City East Hospital. The patient was treated with frontal neutron beams. A 20-cm circular collimator, which encompassed the left lobe, was used to direct the beams. In this pilot study, the dose and irradiation time were restricted based on the dose delivered to the normal liver. In this case, the irradiation time was set so that a maximum radiation dose of 5.0 Gy-Eq would be delivered to the normal liver tissue (Figs. 2 and 3). According to the method described by Suzuki, compound biological effectiveness (CBE) factors were used as an alternative to

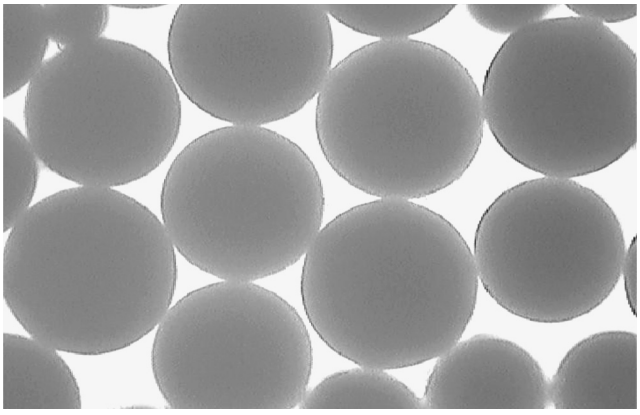

Fig. 1. Microphotograph of the ^{10}BSH-containing WOW emulsion. Emulsification using a fine-pore glass membrane containing equally sized pores is a new technique for preparing lipid microdroplets of equal size containing fine aqueous microdroplets, which can be used to produce WOW emulsions. The prepared WOW emulsion was observed using a BHS-323 optical microscope (Olympus Optics Co., Tokyo, Japan).