Preclinical study of boron neutron capture therapy for bone metastasis using a human lung cancer cell line

Tooru Anfoh
Faculty of Pharmaceutical Sciences, Kobe Gakuin University, Japan
Email: t.andoh@pharm.kobegakuin.ac.jp

Takuya Fujimoto
Department of Orthopaedic Surgery, Hyogo Cancer Center, Japan

Yuki Nagasaki
Faculty of Pharmaceutical Sciences, Kobe Gakuin University, Japan

Minoru Suzuki
Particle Radiation Oncology Research Center, Institute for Integrated Radiation and Nuclear Science, Kyoto University, Japan

Hiroki Tanaka
Division of Radiation Life Science, Institute for Integrated Radiation and Nuclear Science, Kyoto University, Japan

Takushi Takata
Division of Radiation Life Science, Institute for Integrated Radiation and Nuclear Science, Kyoto University, Japan

Yoshinori Sakurai
Division of Radiation Life Science, Institute for Integrated Radiation and Nuclear Science, Kyoto University, Japan

Hideki Ichikawa
Faculty of Pharmaceutical Sciences, Kobe Gakuin University, Japan

Introduction: Metastasis is the greatest contributor to cancer-related deaths. For most cancer patients, a diagnosis of metastatic disease indicates a terminal illness. Pathological fracture of bone metastasis has a major impact on the quality of life of patients with advanced cancer; therefore, it is important to prevent it. Although radiation therapy is an effective treatment for patients with painful bone metastases, it cannot completely prevent a pathological fracture. However, we have previously demonstrated the effectiveness of bone neuron capture therapy (BNCT) with the use of p-borono-L-phenylalanine (L-BPA) on tumors of human clear cell sarcoma-bearing nude mouse models [1]. Therefore, BNCT may become the local treatment option for bone metastasis. In the present study, we established a bone metastasis model for lung cancer and investigated the in vivo biodistribution of L-BPA and its antitumor effects after BNCT.

Materials and Methods: A549-luc cells, a lung cancer cell line of human origin, were suspended in Matrigel® and injected into the tibia of the left hind leg of nude mice [2]. After 3–4 weeks, a tumor mass was observed in the tibia of the mice, and computed tomography and luminescence imaging were performed. The biodistribution of 10B was explored by the intravenous administration of BPA-fructose complex (BPA-Fr, 24 mg 10B/kg) to a bone metastasis mouse model of lung cancer. At a predetermined time after administration, the mice were sacrificed, and the blood and tissue samples were immediately collected. The concentration of 10B in the samples was then measured using inductively coupled plasma atomic emission spectroscopy. Mice were allocated to either the

BNCT or the control group. The tumors in the hind legs were exposed to thermal neutron irradiation at the Institute for Integrated Radiation and Nuclear Science, Kyoto University.

Results: Bone metastasis was successfully induced in the mouse model of human lung cancer. The formation of a solid tumor mass in the left tibia of the mice was confirmed by macroscopic observation, micro-computed tomography scans, and luminescence imaging. At 1.5 hours after the administration of BPA-Fr, the concentration of 10B in the bone metastasis model tumor tissue reached 41 μg 10B/g wet tumor tissue. The tumor-to-blood and tumor-to-normal tissue (normal bone) ratios 1.5 hours after the injection were 4.7 and 4.3, respectively. In the BNCT trial, the irradiation doses absorbed by the mice were 5.49 and 0.78 Gy in the BNCT and control group, respectively. Tumor growth was observed in the control group, while the BNCT group displayed suppressed tumor growth. These results suggested that 10B accumulated specifically in the bone tumor and that BNCT eliminated the tumor cells at this site.

Conclusion: BNCT was effective in the treatment of bone metastasis in a lung cancer mouse model. Further research is warranted for its application in the clinical setting.

Acknowledgments: This work was supported in part by JSPS KAKENHI Grant Number 16K10860 and 17K16708.

References:
1. T. Fujimoto et al. Appl. Radiat. Isot. 73, 96-100 (2013).
2. J.P. Campbell et al., J. Vis. Exp., 4(67), e4260 (2012).