Therapeutic Efficacy with Treatment-related Toxicities of ^{177}Lu-labeled Bombesin Derivative for the Peptide Receptor Radiotherapy

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1. Introduction

The gastrin-releasing peptide receptor (GRPR) has been shown to be overexpressed in many human tumours, including breast cancer, prostate cancer, small cell lung cancer, ovarian cancers, endometrial cancers, and gastrointestinal stromal tumors. In particular, GRPR expression is high in 83 % of invasive primary prostatic carcinomas. [1]. As bombesin binds to GRPR with high affinity, bombesin derivatives have been labeled with various radionuclides such as ^{99m}Tc, ^{111}In, ^{90}Y, ^{64}Cu, ^{177}Lu, ^{68}Ga, or ^{18}F and have proved to be successful candidates for peptide receptor radiotherapy (PRRT) [2,3]. ^{177}Lu was produced from the HANARO research reactor at the Korea Atomic Energy Research Institute. Present study describes the therapeutic efficacy with treatment-related toxicities of ^{177}Lu-labeled bombesin derivative.

2. Methods and Results

2.1 Preparation of ^{177}Lu-labeled bombesin derivative

Bombesin derivative was synthesized by applying a standard Fmoc (fluorenylmethyloxycarbonyl) strategy. Synthesized peptide (2.79×10^{-7} moles) in a 50 mM sodium acetate buffer (pH=5.5) was mixed with 555 MBq of ^{177}Lu which was produced at the HANARO research reactor reactor (Thermal neutron flux: 1.8×10^{14} n•cm^{-2}•s^{-1}). The mixed solution was heated to 90 °C and incubated for 30 min, and the radiochemical purity higher than 98 %.

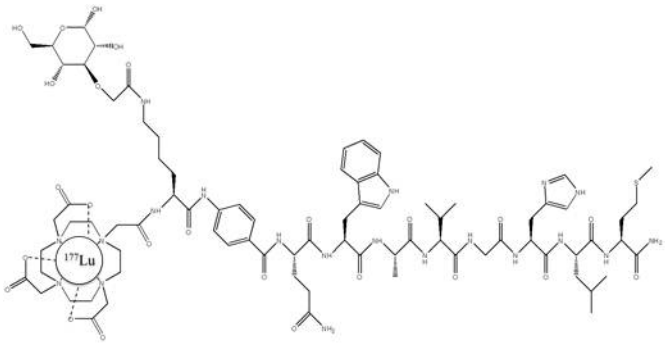

Fig. 1 The structural formula of ^{177}Lu-labeled boombesin derivative

2.2 Tumor growth inhibition by the treatment of ^{177}Lu-labeled bombesin derivative

Treatment with two doses of ^{177}Lu-DOTA-gluBBN significantly decreased the PC-3 human prostate tumor growth rate over that of the controls. The tumor size of PC-3 on 31th day in the treated group was reduced to 39 % of the control tumors in saline-treated animals. Although the PC-3 tumor size increased rapidly, 9.00 ± 3.88% of the body weight decreased in the control group. In contrast, 3.02 ± 8.00% of the body weight increased in the treated group.

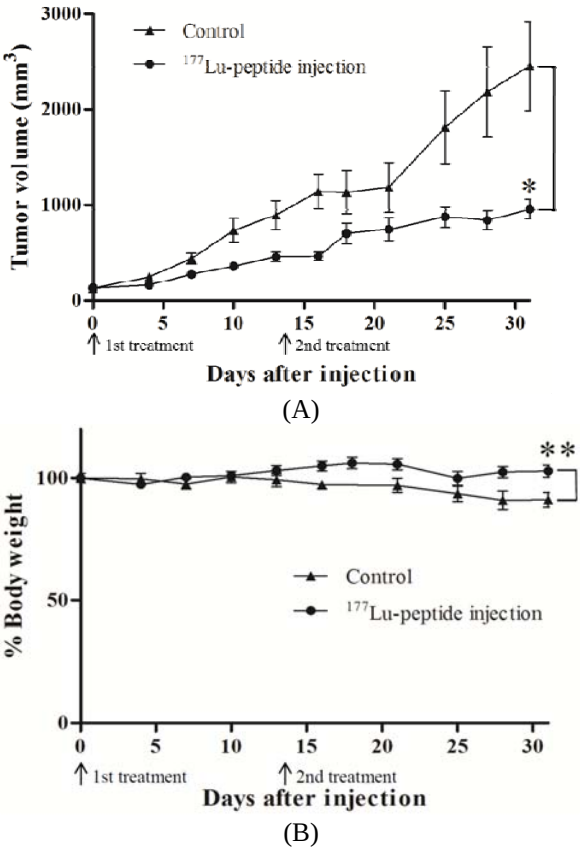

Fig. 2 Average tumor growth (A) and % Body weight (B) by treatment of ^{177}Lu-labeled in PC-3 xenografted mice

2.3 Treatment-related toxicities of of ^{177}Lu-labeled peptide bombesin derivative

The pancreas did not differ among the three groups, including the islet cells and granules. The kidneys also lacked significant toxicity, except for slight glomerulopathy with an increase in the mesangial matrix. The spaces between Bowman's capsule and the glomerulus slightly decreased in the treated kidneys. However, basophilic areas were absent in all slides of the kidneys, and significant nephrotoxicities, such as degeneration and infarction, were not observed.

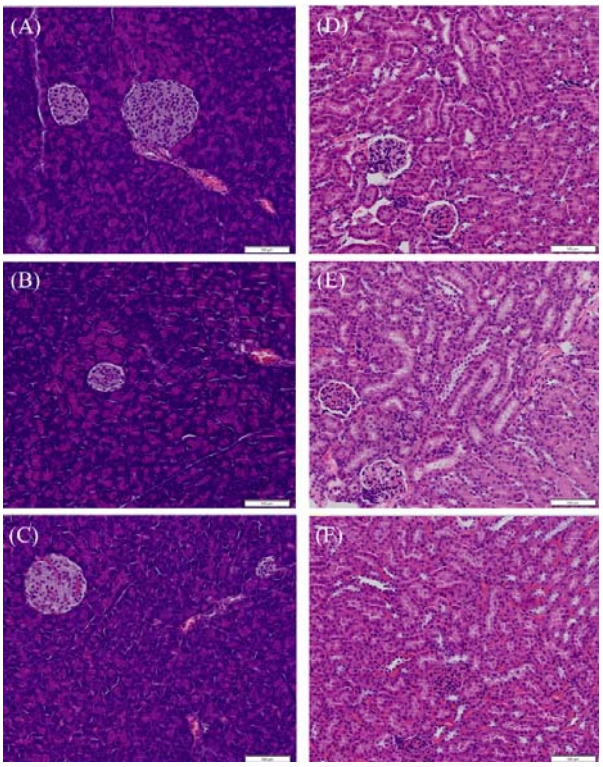

Fig. 3 Histological evaluation of the toxicity of ^{177}Lu-labeled peptide treatments in the pancreas (A-C) and kidneys (D-E). Normal represents the non-tumor-xenografted mice (A, D), and control (B, E) and treated (C, F) represent the PC-3-xenografted mice.

2.4 GRPR over-expression of Korean prostate patients

GRPR-expression in a prostate adenocarcinoma from Korean patients was compared with a normal prostate gland. Immunohistochemistry staining for GRPR was performed using commercially available prostate adenocarcinoma tissues of Korean patients. GRPR over-expression was observed in prostate adenocarcinoma under a microscope.

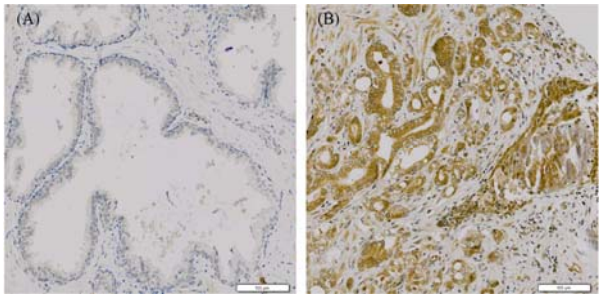

Fig. 4 GRPR expression in prostate cancer tissue from Korean prostate patients. Normal prostate (A) and prostate adenocarcinoma (B) tissue

3. Conclusions

These results suggest that ^{177}Lu-labeled bombesin derivative has promising characteristics as a novel nuclear medicine, especially for the treatment of GRPR over-expressing prostate tumors.

Acknowledgement

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