Effect of tumor size on the therapeutic effect of ^{67}Cu-labeled compounds targeting the somatostatin receptor

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Nuclear medicine therapy, wherein a radiopharmaceutical is administered to patients for treatment, is an effective medical treatment that targets cancer cells in the body; it has garnered significant attention in recent years as an effective treatment process that places less burden on patients. Four nuclides are available in Japan, namely, ^{131}I, ^{90}Y, and ^{177}Lu, which are β-particle emitting nuclides, and ^{223}Ra, which is an α-particle emitting nuclide. ^{90}Y has a high energy β-particle of 2.28 MeV and exhibits good therapeutic effect; however, it has a significant impact on the surrounding tissues and the injected dose is limited by exposure to other organs.[1] Several other nuclides can be potentially used for nuclear medicine therapy. For example, ^{67}Cu has a low energy β-particle of 0.392 MeV; it can be administered in large doses but its effectiveness has not yet been sufficiently analyzed. Therefore, depending on the property of cancer tissue, effective and efficient treatment can be realized. It should be noted that the effectiveness of nuclear medicine therapy is affected by the properties and size of target cancer tissue, radiation quality, and energy, suggesting that the most efficient radiation energy may exist for each target.[2] In other words, although the range of therapeutic effect is limited owing to low energy, sufficient effects can be obtained with low-energy β-particles for small tumors, thus leading to effective treatment.[3] We previously synthesized ^{67}Cu-ToDBTTATE targeting the somatostatin receptor and demonstrated that this compound constricts tumor growth in model mice bearing AR42J rat pancreatic tumor cells.[4] Further investigations regarding the characteristics of ^{67}Cu may contribute to effective and efficient treatment and/or customized medicine according to patient conditions.

In this study, we prepared model mice with tumors of various sizes and attempted to investigate the differences in the therapeutic effect of ^{67}Cu-ToDBTTATE on the tumor size to clarify the relationship between tumor size and the therapeutic effects of ^{67}Cu-ToDBTTATE.

Tumor-bearing mice were prepared by implanting AR42J tumor cells (5×10^6 cells), in 0.1 mL PBS, into the flanks of nude mice (BALB/c-nu/nu, male). After the tumor grew to various sizes, 16.0–25.2 MBq of ^{67}Cu-ToDBTTATE was injected into the mice from the tail vein. Saline or non-labeled ToDBTTATE-administered mice were used as the control. All mice were weighed and the tumor diameters were regularly measured using a caliper; the tumor volumes were determined using the following formula: (longer diameter) × (shorter diameter)^2/2. This study was performed in accordance with the recommendations by the Guide for the Care and Use of Laboratory Animals of Suzuka University of Medical Science.

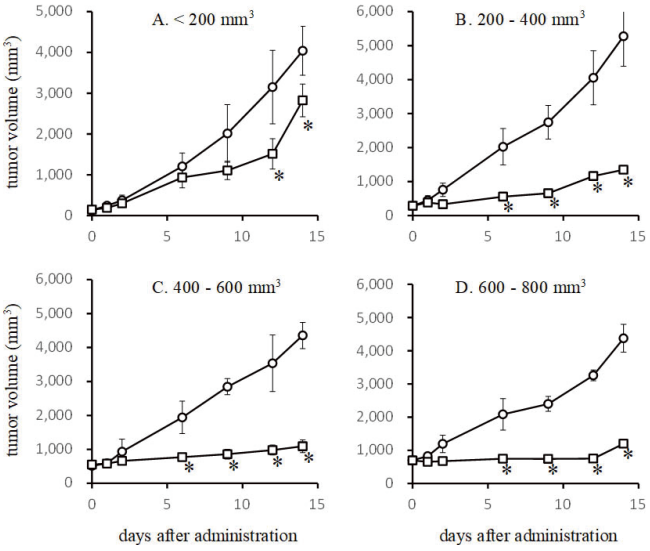

Fig. 1. Relationship between tumor size and the therapeutic effect of ^{67}Cu-ToDBTTATE (○: control, □: ^{67}Cu-ToDBTTATE). *: $p < 0.05$ (2-way ANOVA, sidack-test).

The mice were divided into four groups according to the tumor size, *i.e.*, less than 200, 200 to 400, 400 to 600, and 600 to 800 mm^3; then, the ^{67}Cu-ToDBTTATE-administered mice were compared with the control in each group. A tumor growth constricting effect was observed in the ^{67}Cu-ToDBTTATE-administered mice in all groups compared with the control (Fig. 1). Some tumor growth was observed in the group with a tumor size of less than 200 mm^3, which may be because the days after cell implantation were short and the targeted somatostatin receptor was not well expressed. No difference in the therapeutic effect of ^{67}Cu-ToDBTTATE on the tumor size was observed in this study. In future works, we plan to conduct comparative studies using model mice with larger tumors.

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References
1) G. A. Wiseman *et al.*, Eur. J. Nucl. Med. **27**, 766 (2000).
2) K. Fujimori *et al.*, Kaku Igaku **31**, 241 (1994).
3) E. B. van Dieren *et al.*, Int. J. Radiat. Oncol. Biol. Phys. **36**, 197 (1996).
4) Y. Fujisawa *et al.*, RIKEN Accel. Prog. Rep. **53**, 175 (2019).