Usability of ^{67}Cu as a therapeutic radioisotope for peptide receptor radionuclide therapy

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Copper-67 is an attractive radionuclide for nuclear medicine therapy, which has an emitted β-particle energy suitable for applying to small tumors and a physical half-life of 61.8 hours long enough to damage them. Recently, radiolabeled somatostatin (SST) analogues targeting SST receptor-2 are useful for diagnosis and therapy of neuroendocrine tumors (NETs). And peptide receptor radionuclide therapy (PPRT) has become one of the most promising treatments for patients with well to moderately differentiated unresectable or metastatic NETs. High energy β-particle-emitting ^{90}Y (2.28 MeV) becomes available for this therapy and shows high efficacy, but its application is limited by adverse effects.[1] ^{67}Cu emits middle energy β-particles (0.39–0.58 MeV), and its maximal tolerated activity dose is much higher than ^{90}Y. So, ^{67}Cu may have an advantage in treating relatively small tumor masses.[2]

In this study, we prepared a novel SST derivative, ToDBTTATE, labeled with ^{67}Cu (Fig. 1), and evaluated its potential for cancer therapy in mice bearing AR42J rat pancreatic tumor cells. ToDBTTATE has a ligand, diacetyl-bis (N^4-methylthiosemicarbazone) (ATSM), which releases a copper in hypoxic condition such as tumor in its structure and the copper will remain at the site.[3]

The ligand which was synthesized from 4-Methyl-3-thiosemicarbazide according to the procedure reported by Paterson *et al.*[4] was bound to TATE, a most frequently used SST analog in clinical practice and ^{67}Cu-ToDBTTATE was obtained from reaction with ^{67}Cu with microwave synthesis system. Tumor-bearing mice were prepared by implantation of AR42J tumor cells (5×10^6 cells) in 0.1 mL PBS into the flanks of nude mice (BALB/c-nu/nu, male). Biodistribution experiments were performed by intravenously administering

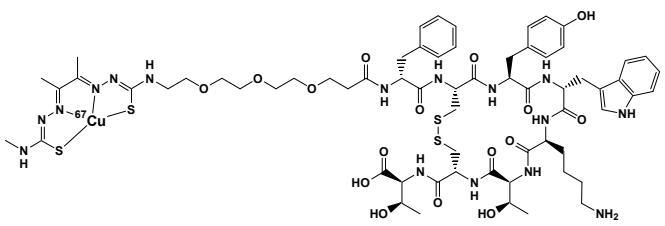

Fig. 1. Chemical structure of ^{67}Cu-ToDBTTATE.

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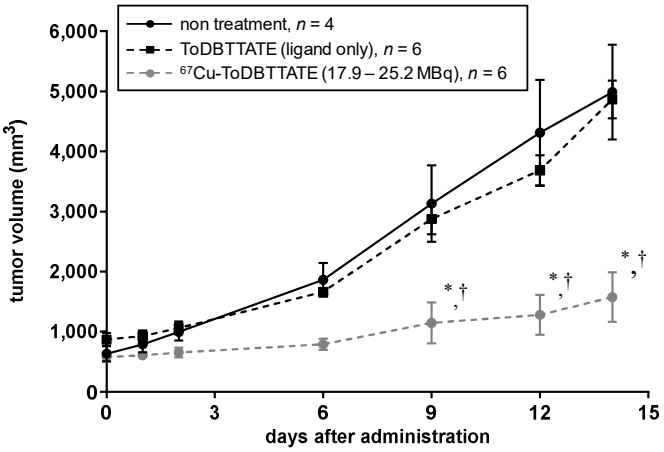

Fig. 2. Therapeutic studies of ^{67}Cu-ToDBTTATE. *, † Differences between the group of ^{67}Cu-ToDBTTATE and non-treatment (*)/ligand only (†) were determined at $p < 0.05$ by using Graph Pad PRISM ver. 6.05 (ANOVA followed by Tukey's test).

^{67}Cu-ToDBTTATE. The mice were killed at 1, 24 and 48 h after administration, and tissue of interest were excised and weighed after which their radioactivity was measured. For therapeutic studies, AR42J tumors were grown in BALB/c mice in the same way. Mice were intravenously administered with 17.9–25.2 MBq of ^{67}Cu-ToDBTTATE. Untreated mice were used as a control. Mice were weighed and tumor diameters were recorded regularly. The diameters of tumors were measured with a caliper, and tumor volumes were determined using the following formula: (longer diameter) $\times$ (shorter diameter)^2/2.

^{67}Cu-ToDBTTATE showed high accumulation in the tumor, 2.62 ± 0.46, 1.75 ± 1.20 and 1.80 ± 0.44% ID/g at 1, 24 and 48 h after administration, respectively. Substantial tumor size reduction was observed in all mice treated with ^{67}Cu-ToDBTTATE (Fig. 2). As this result, ^{67}Cu-ToDBTTATE is a promising agent for the treatment of NETs and ^{67}Cu is expected to be suitable for treatment of relatively small tumor. The use of ^{67}Cu for cancer therapy has also potential for efficient tailor-made therapy.

References

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