A Multi-dosing Strategy Improves the Efficacy of SSTR2-targeted Alpha-particle Therapy for Neuroendocrine Tumors with a Low Toxicity Profile

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Background: Somatostatin Receptor Subtype 2(SSTR2)-targeted alpha-particle therapy using lead-212 (^{212}Pb) is emerging as a potentially highly effective treatment for neuroendocrine tumors (NETs). Our previous studies suggested that a newly-developed Tyr^3-octreotide (TOC) variant (VMT-**α**-NET) enhanced tumor targeting and reduced renal accumulation and retention of the ^{212}Pb-labeled peptide compared to DOTATOC. In this study, we investigated the potential benefit of the multi-dosing strategy over a single administration of [^{212}Pb]VMT-**α**-NET with regard to tumor control and renal/hematologic toxicity.

Materials and methods: VMT-**α**-NET was labeled with ^{212}Pb (1–5 MBq/nmol) in pH=5.4 sodium acetate buffer (75 °C; 30 min). For a therapy study, AR-42J tumor-bearing athymic female nude mice were administered with 3.7 MBq of ^{212}Pb-VMT-α-NET either by 3 fractionated doses over the course of 4 weeks with 1.22 MBq per each fraction or by single dose. All doses were given with i.v. co-injection with kidney protectant (DL-Lysine) in saline. A toxicity study was separately conducted with tumor-free female CD-1 Elite mice by the same dosing design to evaluate renal/hematologic toxicities (No DL-Lysine). A biodistribution study was also conducted by injecting 0.37 MBq (i.v.) of ^{212}Pb-VMT-α-NET in female CD-1 Elite mice.

Results: As of 51 days post-administration, all control mouse tumors had reached an endpoint of 1500 mm^3 tumor volume. While tumors in the 3.7 MBq (single-administration) group were observed to progress, 8 out of 10 mice in the multi-administration group were tumor-free (*i.e.*, apparent complete responses). No significant bodyweight loss was observed in both single- and multi-administration therapy cohorts. However, in the toxicity study cohort, there were initial bodyweight decreases (at day 5) in the single-administration group that recovered after 1 week. Platelet counts decreased at week 1, but recovered at 5 weeks post the single administration. However, no significant platelet response was observed in response to fractionated administration. The biodistribution study indicated that the kidney is the major organ of accumulation, but the clearance was relatively rapid, having <5% injected dose at 6 h

post injection and <2% ID/g in the kidneys after 24 hours. No significant difference was observed in the biodistribution of ^{212}Pb vs. ^{212}Bi in the kidneys and the bone, indicating that recoil/redistribution of ^{212}Bi is minimal (at least at the whole-organ level).

Conclusion: These studies suggest that multi-administration of radiopharmaceutical strategy may improve the efficacy of [^{212}Pb]VMT-**α**-NET with reduced toxicity (at least hematologic toxicity). Ongoing kidney pathology analysis will provide more information about renal toxicity arising from single- vs. multi-doses of [^{212}Pb]VMT-**α**-NET.

Keywords: PRRT, Multi-administration, VMT-**α**-NET, ^{212}Pb, Alpha-particle therapy