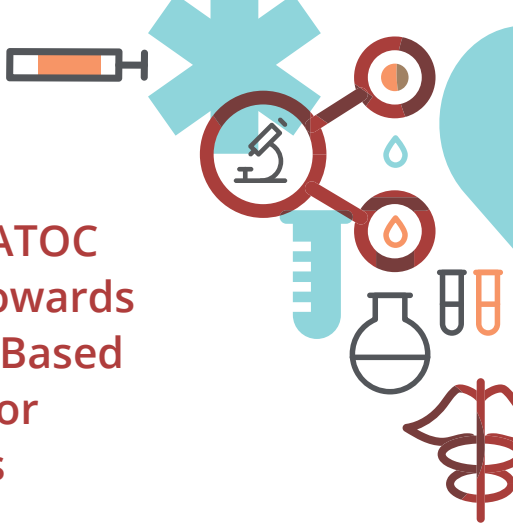

B-14

Dosimetry and Potential Toxicities of 212Pb-DOTATOC in a Preclinical Model: Towards Personalized Dosimetry Based Alpha-Particle Therapy for Neuroendocrine Tumors

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BACKGROUND: Emerging evidence suggests that alpha particle therapy has the potential to improve tumor response compared to beta particle therapy. However, concerns regarding potential toxicities to normal organs and tissues mandate development of personalized dosimetry approaches. In this study, a dosimetry-based dose escalation study was performed with 212Pb-DOTATOC in an animal model to examine the relationship between localized alpha dose and pathological changes in kidneys.

METHODS: 203Pb-DOTATOC was administered to eight CD1-Elite (SOPF) mice and SPECT/CT images were obtained at 1.5h and 20h post-injection. The mice were divided into four groups and injected with escalating activities of 212Pb-DOTATOC (0.037–0.178 MBq/g). Absorbed doses arising from 212Pb-DOTATOC were estimated by OLINDA software. Blood or urine were collected up to 16 weeks for analyses of nephrotoxicity parameters NGAL (neutrophil gelatinase-associated lipocalin) and cystatin C, and kidneys were harvested at 7 months post-injection for histopathological analyses. Four mice were injected with the highest dose (0.178 MBq/g), and hematological toxicity was evaluated by complete blood counts.

Results: Escalated 212Pb-DOTATOC activities linearly increased alpha dose in kidneys (6.6 Gy to 35.2 Gy) with minimal contributions from beta particles (<4%). We found evidence for acute tubular injury and renal function reduction by 50% (5 of 8 treated mice) with higher prevalence in males. Chronic renal toxicity was observed in the treated mice with a higher degree of tubular/glomerular damages in males compared to females. 50% and 40% average declines were observed in platelets and white blood cells respectively within 2–3 weeks in mice, which returned to baseline levels at 5 weeks post administration.

CONCLUSION: 203Pb imaging-based dosimetry can inform personalized dosimetry-guided therapy with 212Pb-based therapeutics. Administration of 212Pb-DOTATOC (0.037–0.178 MBq/g) resulted in acute/chronic renal toxicity and reversible hematological toxicity. NGAL is a sensitive biomarker for acute tubular injury, but observed levels were not proportional to increased alpha doses in this study.