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Pre-Clinical Evaluation of 225Ac-DOTATOC Pharmacokinetics, Dosimetry, and Histopathology to Enable Phase-1 Clinical Trial in Patients with Neuroendocrine Tumors

Objectives: Evaluate pharmacokinetics of 225Ac-DOTATOC with and without kidney protection (KP); to compare 225AcNO3 or "free"225Ac derived from accelerator production versus stockpile extraction; to estimate predicted radiation absorbed dose (RAD) to humans receiving 225Ac-DOTATOC; and to evaluate histopathology 90 days post-administration.
Methods: 225AcNO3-accelerator, 225AcNO3-stockpile, or 225Ac-DOTATOC prepared using 225AcNO3-stockpile, with and without KP, was administered IV to male Sprague Dawley rats, n= 5 per cohort per time point. At 1-hour to 90-days post-administration, rats were euthanized. Blood was collected for CBC and metabolic testing. Organs were collected, weighed, evaluated for radioactivity using a gamma counter and processed for histopathological examination. Cumulative organ radioactivity was used as the input function to estimate mean radiation absorbed tissue dose in humans (OLINDA 1.0). Mean Residence Times (Mbq-h/Mbq) were determined to allow estimation of RAD in mSv/MBq.
Results: 225Ac-DOTATOC (10uCi +KP, 3uCi +KP, 10uCi, 3uCi), 225AcNO3-accelerator, and 225AcNO3-stockpile RAD to kidneys were (1.09E+02, 7.39E+01, 1.39E+02, 1.37E+02, 1.83E+02, 1.29+E02, respectively). KP decreased RAD 22% and 46% following 10uCi and 3uCi 225Ac-DOTATOC, respectively. 225Ac-DOTATOC treated animals showed similar CBC to controls. Untargeted 225AcNO3 from either accelerator or stockpile significantly decreased white and red blood cells, and overall survival. Three rats that received 225AcNO3-stockpile and two rats that received 225AcNO3- accelerator did not survive 90 days. The 225AcNO3 stockpile and accelerator groups each had a single rat found dead which was not necropsied. Over the entire study, vehicle control rats continuously gained weight, while the groups receiving either 225AcNO3 stockpile or accelerator gained weight slower, with body weights remaining almost unchanged. There was no bone marrow hypoplasia in vehicle control, DOTATOC control, or 3 μCi-KP DOTATOC rats. Rats receiving 3 μCi+KP DOTATOC, 10 μCi+KP DOTATOC, and 10 μCi-KP DOTATOC developed mild to moderate bone marrow hypoplasia. All DOTATOC groups showed normal pattern of fat replacement in bone marrow consistent with normal aging. Bone marrow hypoplasia was marked to very marked in rats receiving 225AcNO3-accelerator and was slightly less severe in 225AcNO3-stockpile. All treatment groups showed evidence of previous or ongoing renal tubular nephrosis. All treatment groups except 3 μCi-KP DOTATOC group showed evidence of renal glomerulopathy; lesions were most severe in 225AcNO3 stockpile and accelerator groups. Cardiac lesions of myofiber and epicardial mineralization were seen only in 225AcNO3- accelerator group. The histological impact in control and 225Ac-DOTATOC groups was negligible at all timepoints.
Conclusion: The estimated radiation absorbed dose from 225Ac-DOTATOC was low in all critical organs. Accelerator produced 225Ac contains 227Ac (t½ ~ 21yrs) as a trace impurity, resulting in increased radiation dose when compared to stockpile-derived 225AcNO3. The histopathological results show moderate impact from untargeted 225AcNO3. The clinical impact is believed to be insignificant, since patients will receive targeted 225Ac-DOTATOC which showed negligible toxicity at all timepoints.

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