

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 (t_{1/2} ~ 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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Email Address

jnorenberg@salud.unm.edu

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Primary author: Prof. NOREMBERG, Jeffrey (Radiopharmaceutical Sciences Program, UNM HSC)

Co-authors: Ms GOFF, Chelsea (Radiopharmaceutical Sciences Program, UNM HSC); Dr KUSEWITT, Donna (UNM Comprehensive Cancer Center); Dr HESTERMAN, Jacob (inviCRO); Dr FAIR, Joanna (UNM Comprehensive Cancer Center); Dr ORCUTT, Kelly (inviCRO); Dr JOHN, Kevin (Los Alamos National Laboratory); Ms NYSUS, Monique (Radiopharmaceutical Sciences Program, UNM HSC); Dr RIXE, Olivier (UNM Comprehensive Cancer Center); Mrs JACQUEZ, Quiteria (Radiopharmaceutical Sciences Program, UNM HSC); Dr HELOISA, Soares (UNM Comprehensive Cancer Center); Mrs DANIELS, Tamara (Radiopharmaceutical Sciences Program, UNM HSC)

Presenter: Prof. NOREMBERG, Jeffrey (Radiopharmaceutical Sciences Program, UNM HSC)