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61Cu-NODAGA-LM3 versus 68Ga-DOTATOC in the same patients with neuroendocrine tumors: Preliminary results of the Phase I/II COPPER-PET-in-NET Trial

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BACKGROUND

(Pre)clinical data suggest that somatostatin receptor (sstr) antagonists, when radiolabeled with gallium-68, offer superior imaging performance over agonists in patients with neuroendocrine tumors (NETs). ^{61}Cu-NODAGA-LM3 is a novel PET tracer targeting sstr2 that may overcome key limitations of [^{68}Ga]-based tracers, including production capacity, image resolution, and logistics. Cyclotron-produced ^{61}Cu and has a longer half-life compared to ^{68}Ga or ^{18}F, supporting delayed imaging and easier logistics. Additionally, ^{61}Cu has a higher positron fraction than 64Cu , enhancing image quality per administered activity. We report first-in-human data on ^{61}Cu-NODAGA-LM3 covering safety, biodistribution, dosimetry, pharmacokinetics, image quality, and lesion detection.

METHODS

In this ongoing, randomized, crossover, controlled, reader-blind, phase I/II PET/CT trial (NCT06455358), 23 patients with sstr2-positive, well-differentiated gastroenteropancreatic or bronchopulmonary NETs receive both ^{61}Cu-NODAGA-LM3 (1h and 3h post-injection) and ^{68}Ga-DOTA-TOC PET/CT (1h post-injection) on the same scanner. Imaging is conducted within 28 days and, if applicable, 14±2 days post last somatostatin analogue injection. Co-primary endpoints are safety and sensitivity of ^{61}Cu-NODAGA-LM3 with noninferiority of sensitivity against ^{68}Ga-DOTA-TOC using mixed-effects logistic regression. Biopsy and/or composite imaging during 2–7 months of follow-up serve as gold standard. Adverse events are monitored up to one day post-injection (p.i) (CTCAE v5.0). Secondary endpoints include biodistribution, pharmacokinetics, dosimetry, and lesion detection. Six patients undergo additional imaging at 18h p.i. for dosimetry, and 1h vs. 3h p.i. images are compared to define optimal imaging time.

RESULTS

To date, 20 patients completed imaging; 6 had full dosimetry. No clinically significant adverse events occurred. ^{61}Cu-NODAGA-LM3 showed rapid biexponential blood clearance (median 234 mL/min [IQR: 139–365]; R^2>0.99) and a short distribution phase (median α half-life: 34 min [IQR: 25–37]). Biodistribution was favorable, with similar bone marrow uptake at 1h p.i. (SUVmax Th6: 1.0 [IQR: 0.9–1.3] vs. 1.1 [IQR: 1.0–1.4] for ^{61}Cu-NODAGA-LM3 vs. ^{68}Ga-DOTA-TOC), but significantly lower liver (3.1 vs.

6.4) and spleen (9.0 vs. 24.0) uptake ($p < 0.001$ and 0.002). Median tumor SUVmax at 1h p.i. for the three hottest matched lesions was 12% higher with ^{61}Cu-NODAGA-LM3 (19.6 vs. 16.9), enhancing lesion detection and tumor-to-background contrast. Median effective dose was 5.0 mSv [4.2–5.7]. In blinded review, image quality was rated superior with ^{61}Cu-NODAGA-LM3 in 16 of 20 cases and equivalent in the remaining 4.

CONCLUSIONS

These preliminary data support ^{61}Cu-NODAGA-LM3 as a safe, effective sstr2-targeting tracer with favorable pharmacokinetics, biodistribution, dosimetry, with logistical and diagnostic advantages over ^{68}Ga-labeled somatostatin receptor agonist-based imaging in patients with NETs.

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