Evaluation of Safety, Biodistribution, and Dosimetry of a Long-Acting Radiolabeled Somatostatin Analog ^{177}Lu-DOTA-EB-TATE With and Without Amino Acid Infusion

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Purpose: Kidney is considered to be one of the dose-limiting organs in peptide receptor radionuclide therapy (PRRT). Amino acid cocktail infusion has been applied to reduce renal absorbed dose by inhibiting the proximal tubular reabsorption of the radiopeptide. An Evans blue-modified ^{177}Lu-labeled octreotate (^{177}Lu-DOTA-EB-TATE) has an extended circulation in the blood, which may make the amino acid infusion unnecessary. The aim of this study was to evaluate the safety, biodistribution, and dosimetry of ^{177}Lu-DOTA-EB-TATE with and without amino acid infusion.

Patients and Methods: Ten patients with metastatic neuroendocrine tumors were randomly divided into 2 groups. The effect of amino acid infusion on renal uptake was assessed in a crossover randomized setting. Group A received ^{177}Lu-DOTA-EB-TATE at a dose of 3.7 GBq without amino acid infusion for the first cycle and with amino acid infusion for the second cycle; group B received ^{177}Lu-DOTA-EB-TATE at a dose of 3.7 GBq with amino acid infusion for the first cycle and without amino acid infusion for the second cycle. All patients underwent serial whole-body planar imaging at 1, 24, 96, and 168 hours and SPECT scan at 24 hours after radioligand administration. Abdominal CT was performed 2 days before PRRT for SPECT/CT fusion. The dosimetry was calculated using the HERMES software. Dosimetry evaluation was compared on a between-group and intrapatient basis.

Results: Administrations of ^{177}Lu-DOTA-EB-TATE with or without amino acids were well tolerated. No grade 4 hematotoxicity was observed in any of the patients. Grade 3 thrombocytopenia was reported in 1 patient. No nephrotoxicity of any grade was recorded. No significant difference was observed in creatinine (75.1 ± 21.7 vs 67.5 ± 18.1 μmol/L, $P = 0.128$), blood urea nitrogen (4.5 ± 0.8 vs 5.1 ± 1.4 mmol/L, $P = 0.612$), or GFR (109.3 ± 25.2 vs 100.9 ± 24.9 mL/min, $P = 0.398$) before and after PRRT. For each cycle, there was no significant difference in whole-body effective dose, kidney effective dose, as well as residence time of the kidneys between group A and B ($P > 0.05$). By intrapatient comparison, without and with amino acid infusion also did not show significant difference in whole-body effective dose (0.14 ± 0.05 vs 0.12 ± 0.04 mSv/MBq, $P = 0.612$), kidney effective dose (1.09 ± 0.42 vs 0.73 ± 0.31 mSv/MBq, $P = 0.093$), and residence time of the kidneys (2.95 ± 1.58 vs 3.13 ± 1.11 hours, $P = 0.674$).

Conclusions: ^{177}Lu-DOTA-EB-TATE PRRT with and without amino acid infusion demonstrated a favorable safety profile in neuroendocrine tumor patients. Administration of ^{177}Lu-DOTA-EB-TATE without amino acid infusion has acceptable slightly increased kidney absorbed dose and residence time of the kidneys, and does not affect kidney function. Further investigation in a larger cohort and long-term follow-up are warranted.

Key Words: ^{177}Lu-DOTA-EB-TATE, peptide receptor radionuclide therapy, neuroendocrine tumors, amino acid infusion

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Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms arising from diffuse neuroendocrine system cells and are characterized by a high level of expression of somatostatin receptors. In somatostatin receptor–positive NETs, peptide receptor radionuclide therapy (PRRT) with targeted radiolabeled somatostatin analogs (SSAs) such as ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE produced a selective treatment effect by delivering radionuclides directly to tumor cells.

During PRRT, the kidney is the dose-limiting organ since it excretes and reabsorbs radiolabeled SSA, leading to a high renal radiation dose, which may cause kidney injury.[1,2] Megalin/cubilin play an important role for renal proximal tubule reabsorption of the radiolabeled SSA.[3,4] Studies have shown that infusion of amino acids (lysine and arginine) significantly reduced the renal reuptake of radiolabeled SSA, by competing with the megalin/cubilin complex on the membrane of proximal tubular cells.[5,6]

However, amino acid infusion may also have some disadvantages, for example, their hyperosmolarity and their propensity to cause nausea and vomiting.[7] The coadministration of amino acids also complicates the PRRT procedure. The radiopharmaceutical infusion alone is usually completed within 30 minutes. While with amino acid infusion, the whole procedure takes more than 4 hours. At present, ^{177}Lu is the most frequently used radionuclide in PRRT, and the renal toxicity with ^{177}Lu-PRRT is much less common than

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Trial registration treatment using ^{177}Lu-DOTA-EB-TATE in patients with advanced neuroendocrine tumors (NCT03478358)

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TABLE 1. Demographic and Clinical Characteristics of the Enrolled Patients

Patient No.	Age, y	Sex	Primary Site	Grade (Ki-67 Index)	Previous Treatment	Injected Dose for the First Cycle, GBq	Injected Dose for the Second Cycle, GBq
1	49	M	Pancreas	G2 (5%)	SSA, chemotherapy	3.96	3.77
2	41	F	Pancreas	G2 (15%)	Surgery, SSA	4.14	3.77
3	45	F	Pancreas	G3 (25%)	Surgery, chemotherapy, tyrosine kinase inhibitor	4.07	NA
4	34	M	Pancreas	G2 (10%)	Surgery, SSA, chemotherapy, everolimus, tyrosine kinase inhibitor	3.85	3.81
5	39	M	Pancreas	G2 (3%)	SSA, TACE, PRRT	3.74	NA
6	60	M	Rectum	G2 (9%)	SSA	3.19	3.33
7	57	F	Pancreas	G2 (5%)	Surgery, SSA, everolimus	3.40	3.29
8	43	M	Pancreas	G2 (10%)	SSA, chemotherapy, tyrosine kinase inhibitor	3.17	3.37
9	60	M	Pancreas	G2 (3%)	SSA, chemotherapy, tyrosine kinase inhibitor	3.42	3.67
10	55	F	Pancreas	G2 (20%)	Surgery, SSA, PRRT	3.32	3.11

M, male; F, female; SSA, somatostatin receptor; TACE, transarterial chemoembolization; NA, not applicable.

^{90}Y-PRRT.[8–12] A study of 807 patients reported that PRRT with ^{177}Lu was less likely to result in renal toxicity than PRRT with ^{90}Y. The rate of occurrence of renal toxicity in patients treated with ^{177}Lu-PRRT was 13.4% in comparison to 33.6% with ^{90}Y-PRRT.[13] This is because ^{177}Lu emits lower energy β-particles with shorter range than ^{90}Y, leading to lower irradiation of the kidneys. ^{177}Lu-DOTA-EB-TATE is based on a modification of ^{177}Lu-DOTATATE with Evans blue (EB), which binds reversibly to serum albumin to greatly extend the circulation half-life.[14,15] Compared with ^{177}Lu-DOTATATE, ^{177}Lu-DOTA-EB-TATE will have much less renal clearance due to the larger size of the EB-TATE/albumin complex. Taken together, the amino acid infusion in^{177}Lu-DOTA-EB-TATE PRRT seems unnecessary. We thus hypothesize that ^{177}Lu-DOTA-EB-TATE PRRT without amino acid infusion may also demonstrate acceptable renal toxicity profile. The aim of this study was to evaluate the safety, biodistribution, and dosimetry of ^{177}Lu-DOTA-EB-TATE with and without amino acid infusion.

PATIENTS AND METHODS

Patients

This study was approved by the Institutional Review Board of Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, and registered at the Clinicaltrials.gov (NCT03478358). A total of 10 patients with advanced metastatic NETs were prospectively recruited in this study. All patients gave written informed consent. The inclusion criteria were the same as in our prior study.[16] The patients were randomly divided into 2 groups: group A (n = 5; male/female = 3/2; mean age, 43 ± 7 years) and group B (n = 5; male/female = 3/2; mean age, 56 ± 8 years).

Treatment Regimen and Safety Evaluation

The preparation of DOTA-EB-TATE and labeling of ^{177}Lu were performed as published previously.[17] The treatment was planned for 2 cycles at 8–12 weeks intervals. Group A received ^{177}Lu-DOTA-EB-TATE without amino acid infusion for the first cycle (IV administration of 500 mL of 0.9% NaCl starting 30 minutes before ^{177}Lu administration) and with amino acid infusion (25 g lysine + 25 g arginine diluted in 2 L of normal saline infused over 4 hours, starting 30 minutes before ^{177}Lu administration) for the second cycle; group B received ^{177}Lu-DOTA-EB-TATE with amino acid infusion for the first cycle and without amino acid infusion for the second cycle. ^{177}Lu-DOTA-EB-TATE diluted in 100 mL of normal saline was coadministered slowly in an IV infusion for over 30 minutes. The dose of ^{177}Lu-DOTA-EB-TATE was empirically set to be 3.7 GBq/cycle. The average administered activity was 3.58 ± 0.32 GBq per cycle.

Hematological parameters, liver, and renal function (creatinine and blood urea nitrogen [BUN]) at baseline, 1 week, and 4 weeks after PRRT were tested. ^{99m}Tc-DTPA dynamic renal imaging for the determination of the GFR was performed at baseline and 8 weeks after each cycle of PRRT. Treatment-related adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

SPECT/CT

Administration of ^{177}Lu-DOTA-EB-TATE was followed by serial whole-body planar imaging at 1, 24, 96, and 168 hours with a standard marker of 11.1 MBq at the level of lateral malleolus. SPECT imaging at 24 hours was acquired. Whole-body scintigraphy and SPECT imaging were performed with a dual-head SPECT scanner (E.CAM; Siemens Medical Solutions), a low-energy high-resolution collimator, a 20% energy window, a peak at 140 keV, a scan speed of 15 cm/min for whole-body imaging, and 32 frames with a 40-second exposure time per frame for each tomographic scan. Abdominal CT was performed 2 days before PRRT for SPECT/CT image fusion.

Dosimetry Calculation

Dosimetry calculations were performed using the HERMES software (HERMES Medical Solutions, Stockholm, Sweden) based on the hybrid planar-SPECT/CT method. The quantitative dosimetry analysis was performed on the 24 hours whole-body images by drawing regions of interest manually over the source organs, including kidneys, liver, spleen, and urinary bladder. The regions of interest drawn on the 24 hours images were then replicated on the remaining whole-body images acquired at different times. Source organ volumetric contours were delineated manually on SPECT/CT fusion images. The time-activity curves obtained were using biexponential functions. The integration of these curves provided

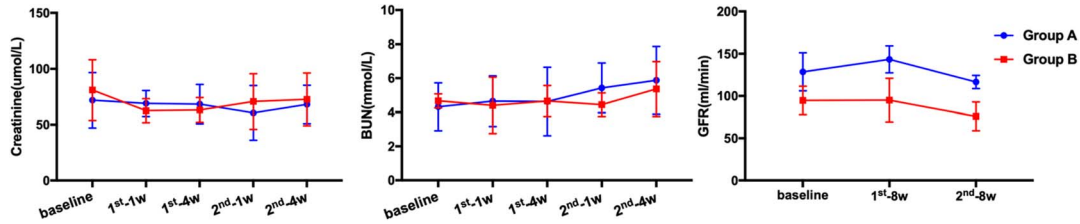

FIGURE 1. Changes in creatinine, BUN, and GFR at baseline, 1 week, and 4 weeks after each cycle of PRRT.

the residence times of the region. Absorbed dose for kidney and whole-body effective dose were determined with HERMES software.

Statistical Analysis

Calculations were performed using SPSS Statistics for Windows version 26.0 (IBM Corp, Armonk, NY). Quantitative data were expressed as mean ± standard deviation. Two sample *t* tests were used to evaluate differences between the 2 groups. Intrapatient comparisons within each group were performed using the nonparametric Wilcoxon signed rank test. A *P* value less than 0.05 was considered statistically significant.

RESULTS

Patients

All 10 patients received the first cycle of PRRT. Eight patients received the second cycle, including 3 in group A and 5 in group B. One patient in group B died of pulmonary infection 1 month after the second cycle, thus hematological parameters, and liver and renal function after therapy were not available. This patient was included for dosimetry calculation but excluded from the safety analysis of the second cycle. The details of patients' clinical characteristics were listed in Table 1.

Safety

Administrations of ^{177}Lu-DOTA-EB-TATE with or without amino acids were well tolerated. No life-threatening grade 4 hematotoxicity was observed in any of the patients. Grade 3 hematotoxicity (thrombocytopenia) was reported in 1 patient. No nephrotoxicity or hepatotoxicity of any grade was recorded. There was also no nephrotoxicity of any grade observed during the follow-up after the completion of PRRT (follow-up period, 8 months). Compared with baseline, no significant change was observed in creatinine, BUN, or GFR after the first cycle (creatinine: 75.9 ± 23.2 vs 67.0 ± 13.9 μmol/L, $P = 0.114$; BUN: 4.8 ± 1.5 vs 5.6 ± 3.3 mmol/L, $P = 0.515$; GFR: 105.2 ± 26.1 vs 109.9 ± 33.0 mL/min, $P = 0.953$) and the second cycle (creatinine: 75.1 ± 21.7 vs 67.5 ± 18.1 μmol/L, $P = 0.128$; BUN: 4.5 ± 0.8 vs 5.1 ± 1.4 mmol/L, $P = 0.612$; GFR: 109.3 ± 25.2 vs 96.9 ± 29.0 mL/min, $P = 0.237$). The mean creatinine, BUN, and GFR at baseline, 1 week, and 4 weeks after each cycle are shown in Figure 1.

Dosimetry

For the first cycle, whole-body effective dose (0.13 ± 0.25 vs 0.11 ± 0.31 mSv/MBq, $P = 0.117$) and kidney effective dose (1.10 ± 0.43 vs 0.62 ± 0.26 mSv/MBq, $P = 0.076$) in group A (without amino acids) were not significantly different from those in group B (with amino acids). The residence times of the kidneys were 3.72 ± 1.49 hours in group A and 2.12 ± 0.96 hours in group B ($P = 0.076$). As to the second cycle, there was also no significant difference in whole-body effective dose (0.15 ± 0.02 vs 0.14 ± 0.07 mSv/MBq, $P = 0.881$) and kidney effective dose (0.91 ± 0.34 vs 0.98 ± 0.41 mSv/MBq, $P = 0.655$) between group A (with amino acids) and group B (without amino acids). The residence times of the kidneys were 2.98 ± 0.97 hours in group A and 3.23 ± 1.29 hours in group B ($P = 0.881$). By intrapatient comparison, without and with amino acid infusion also did not show significant difference in whole-body effective dose (0.14 ± 0.05 vs 0.12 ± 0.04 mSv/MBq, $P = 0.612$), kidney effective dose (1.09 ± 0.42 vs 0.73 ± 0.31 mSv/MBq, $P = 0.093$), and residence time of the kidneys (2.95 ± 1.58 vs 3.13 ± 1.11 hours, $P = 0.674$) (Fig. 2). A representative example of ^{177}Lu-DOTA-EB-TATE with and without amino acid infusion is shown in Figure 3. Estimated effective doses of ^{177}Lu-DOTA-EB-TATE with and without amino acid infusion in normal organs are shown in Figure 4.

DISCUSSION

^{177}Lu-DOTA-EB-TATE was based on the modification of ^{177}Lu-DOTATATE with EB motif, which binds reversibly to serum albumin, leading to extended circulation half-life and much increased tumor uptake.[14] Our prior dosimetry study showed that absorbed dose to the kidneys from ^{177}Lu-DOTA-EB-TATE was 1.15 ± 0.92 mSv/MBq, which is 3.2 times higher than that of ^{177}Lu-DOTATATE,[15] but still far less than the maximum absorbed

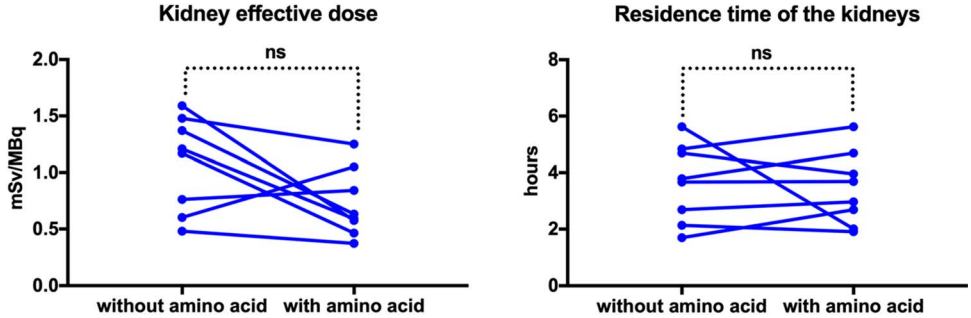

FIGURE 2. Intrapatient comparison of effective dose and residence time of the kidneys of ^{177}Lu-DOTA-EB-TATE with and without amino acid infusion.

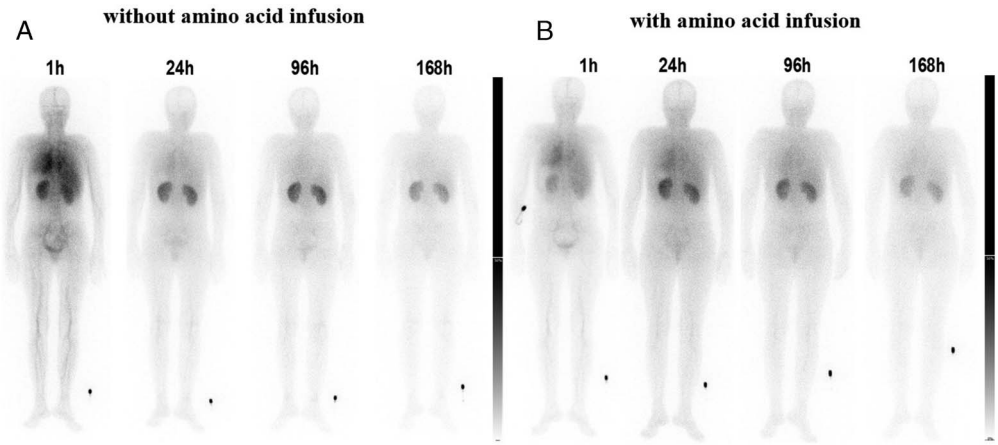

FIGURE 3. Representative whole-body posterior projection images of a 41-year-old woman at 1, 24, 96, and 168 hours after IV administration of ^{177}Lu-DOTA-EB-TATE with and without amino acid infusion. The renal uptake was somewhat lower at 1 hour after administration with amino acid infusion, but the accumulation in the kidneys from 24 hours to 168 hours was similar with or without amino acid infusion.

doses.[18–20] The subsequent dose escalation study with multiple cycles further supported the safety of ^{177}Lu-DOTA-EB-TATE. In that study, none of the patients experienced grade 2/3/4 nephrotoxicity, suggesting that ^{177}Lu-DOTA-EB-TATE is well tolerated and produces no nephrotoxicity with a cumulative activity of up to 11 GBq.[21] In the present study, similarly, none of the patients had nephrotoxicity of any grade during PRRT or on follow-up. This indicated that ^{177}Lu-DOTA-EB-TATE without amino acid infusion is also safe with no renal toxicity observed. This finding was expected as ^{177}Lu-PRRT generally induces very low rate of nephrotoxicity in comparison to ^{90}Y-PRRT. As the radiosensitive glomerulus is approximately 6 mm far from the inner cortex boundary, its crossfire irradiation by the radioactivity reabsorbed by the proximal tubules depends on the radionuclide β range.[22] The range of β-particles emitted by ^{177}Lu is shorter than that of ^{90}Y (0.2 vs 1.1 cm), thus leading to lower irradiation of the glomerulus and overall lower risk of nephrotoxicity.

In this study, between-group and intrapatient comparisons revealed that, without amino acid infusion, the absorbed dose to the kidneys was slightly increased, but the difference was not statistically significant. A probable explanation was that, as the inhibitory effect of amino acids on renal uptake of radioactivity dramatically decreased over time, ^{177}Lu-DOTA-EB-TATE was still retained in the kidneys due to prolonged circulation time, renal clearance, and reabsorption in the proximal tubule, thus, the absorbed dose to the kidneys after amino acid infusion was stopped might not be influenced. Our data showed that, without amino acid infusion, the absorbed dose to the kidneys was 1.09 ± 0.42 mSv/MBq. On the basis of a generally accepted maximum absorbed dose of 23–29 Gy to the kidneys, a maximal dose of 21 GBq of ^{177}Lu-

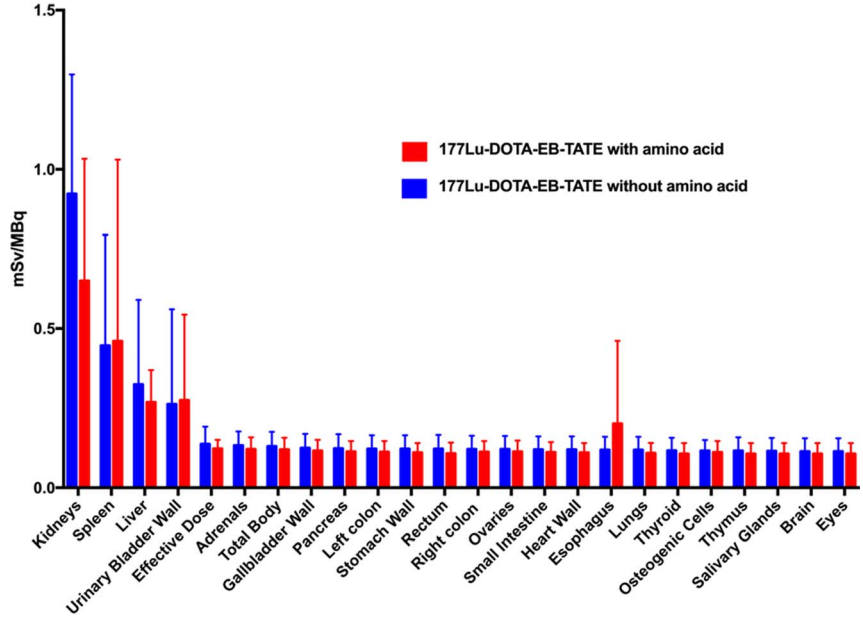

FIGURE 4. Estimated effective dose of ^{177}Lu-DOTA-EB-TATE with and without amino acid infusion in normal organs.

DOTA-EB-TATE can be given to a patient if the amino acid cocktail was not administered. Our prior study showed that 1.85 GBq or 3.7 GBq/cycle of ^{177}Lu-DOTA-EB-TATE appeared as effective as the standard ^{177}Lu-DOTATATE PRRT of 5.5–7.4 GBq/cycle.[16,21] Therefore, ^{177}Lu-DOTA-EB-TATE without amino acid infusion was able to achieve satisfactory therapeutic efficacy with an administered activity, which is much lower than the dosage that delivers the maximum absorbed dose of 23 Gy to the kidneys. Without amino acid infusion, the infusion period is shortened by 3 hours; the procedure is thus greatly simplified and clinically more suitable. Although conventional amino acid infusion regimen seems not to show enough effect on inhibiting the renal reuptake of radioactivity in ^{177}Lu-DOTA-EB-TATE PRRT, other strategies are still needed to be investigated to reduce renal retention, thus enabling even higher dose of ^{177}Lu-DOTA-EB-TATE to be administered.

One limitation of this study is that the number of patients is rather small. Future studies with more patients treated with ^{177}Lu-DOTA-EB-TATE without amino acid infusion are necessary to consolidate our findings. Another limitation of this study is that whole-body and SPECT imaging were performed using a low-energy collimator rather than a medium-energy collimator. The dose calculation of kidneys may be somewhat affected. Even so, our results were still valid to reflect insignificant difference in kidney dose calculated with and without amino acid infusion.

CONCLUSIONS

The administration of ^{177}Lu-DOTA-EB-TATE without amino acid infusion has acceptable slightly but insignificantly increased kidney absorbed dose and residence time of the kidneys, which does not affect kidney function. Without amino acid infusion, the infusion period could be considerably shortened, the procedure is thus greatly simplified, and the adverse effects of amino acid infusion might be avoided. Further investigation in a larger cohort and long-term follow-up are warranted.

REFERENCES

1. Otte A, Herrmann R, Heppeler A, et al. Yttrium-90 DOTATOC: first clinical results. *Eur J Nucl Med*. 1999;26:1439–1447.
2. Moll S, Nickeleit V, Mueller-Brand J, et al. A new cause of renal thrombotic microangiopathy: yttrium 90-DOTATOC internal radiotherapy. *Am J Kidney Dis*. 2001;37:847–851.
3. Barone R, Van Der Smissen P, Devuyst O, et al. Endocytosis of the somatostatin analogue, octreotide, by the proximal tubule-derived opossum kidney (OK) cell line. *Kidney Int*. 2005;67:969–976.
4. de Jong M, Barone R, Krenning E, et al. Megalin is essential for renal proximal tubule reabsorption of (111)In-DTPA-octreotide. *J Nucl Med*. 2005;46:1696–1700.
5. Jamar F, Barone R, Mathieu I, et al. (86Y-DOTA0)-D-Phe1-Tyr3-octreotide (SMT487)–a phase 1 clinical study: pharmacokinetics, biodistribution and renal protective effect of different regimens of amino acid co-infusion. *Eur J Nucl Med Mol Imaging*. 2003;30:510–518.
6. de Jong M, Rolleman EJ, Bernard BF, et al. Inhibition of renal uptake of indium-111-DTPA-octreotide in vivo. *J Nucl Med*. 1996;37:1388–1392.
7. Rolleman EJ, Valkema R, de Jong M, et al. Safe and effective inhibition of renal uptake of radiolabelled octreotide by a combination of lysine and arginine. *Eur J Nucl Med Mol Imaging*. 2003;30:9–15.
8. Marincek N, Jörg AC, Brunner P, et al. Somatostatin-based radiotherapy with [^{90}Y-DOTA]-TOC in neuroendocrine tumors: long-term outcome of a phase I dose escalation study. *J Transl Med*. 2013;11:17.
9. Pfeifer AK, Gregersen T, Grønbæk H, et al. Peptide receptor radionuclide therapy with Y-DOTATOC and (177)Lu-DOTATOC in advanced neuroendocrine tumors: results from a Danish cohort treated in Switzerland. *Neuroendocrinology*. 2011;93:189–196.
10. Bergsma H, Konijnenberg MW, van der Zwan WA, et al. Nephrotoxicity after PRRT with (177)Lu-DOTA-octreotate. *Eur J Nucl Med Mol Imaging*. 2016;43:1802–1811.
11. Kwekkeboom DJ, de Herder WW, Kam BL, et al. Treatment with the radiolabeled somatostatin analog [^{177}Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. *J Clin Oncol*. 2008;26:2124–2130.
12. Romer A, Seiler D, Marincek N, et al. Somatostatin-based radiopeptide therapy with [^{177}Lu-DOTA]-TOC versus [^{90}Y-DOTA]-TOC in neuroendocrine tumours. *Eur J Nucl Med Mol Imaging*. 2014;41:214–222.
13. Bodei L, Kidd M, Paganelli G, et al. Long-term tolerability of PRRT in 807 patients with neuroendocrine tumours: the value and limitations of clinical factors. *Eur J Nucl Med Mol Imaging*. 2015;42:5–19.
14. Tian R, Jacobson O, Niu G, et al. Evans blue attachment enhances somatostatin receptor subtype-2 imaging and radiotherapy. *Theranostics*. 2018;8:735–745.
15. Zhang J, Wang H, Jacobson O, et al. Safety, pharmacokinetics, and dosimetry of a long-acting radiolabeled somatostatin analog (177)Lu-DOTA-EB-TATE in patients with advanced metastatic neuroendocrine tumors. *J Nucl Med*. 2018;59:1699–1705.
16. Liu Q, Cheng Y, Zang J, et al. Dose escalation of an Evans blue-modified radiolabeled somatostatin analog (177)Lu-DOTA-EB-TATE in the treatment of metastatic neuroendocrine tumors. *Eur J Nucl Med Mol Imaging*. 2020;47:947–957.
17. Wang H, Cheng Y, Zhang J, et al. Response to single low-dose (177)Lu-DOTA-EB-TATE treatment in patients with advanced neuroendocrine neoplasm: a prospective pilot study. *Theranostics*. 2018;8:3308–3316.
18. Cives M, Strosberg J. Radionuclide therapy for neuroendocrine tumors. *Curr Oncol Rep*. 2017;19:9.
19. Rolleman EJ, Kooij PP, de Herder WW, et al. Somatostatin receptor subtype 2-mediated uptake of radiolabelled somatostatin analogues in the human kidney. *Eur J Nucl Med Mol Imaging*. 2007;34:1854–1860.
20. Forrer F, Krenning EP, Kooij PP, et al. Bone marrow dosimetry in peptide receptor radionuclide therapy with [^{177}Lu-DOTA(0),Tyr(3)]octreotate. *Eur J Nucl Med Mol Imaging*. 2009;36:1138–1146.
21. Liu Q, Zang J, Sui H, et al. Peptide receptor radionuclide therapy of late-stage neuroendocrine tumor patients with multiple cycles of (177)Lu-DOTA-EB-TATE. *J Nucl Med*. 2021;62:386–392.
22. Walrand S, Jamar F. Renal and red marrow dosimetry in peptide receptor radionuclide therapy: 20 years of history and ahead. *Int J Mol Sci*. 2021;22.