INVITED COMMENTARY

New Advances in Peptide Receptor Radionuclide Therapy

Somatostatin receptors are useful drug targets for therapy aimed at the treatment of humoral effects of certain tumors. Radiolabeled somatostatin analogs, such as octreotide, with a high affinity for subtypes of these receptors are successfully being applied for visualization of somatostatin receptor–positive tumors (*1*), and the next challenge was to label these peptides with therapeutic radionuclides to perform peptide receptor radionuclide therapy (PRRT). Results from preclinical and clinical multicenter studies show that these radiolabeled agents used to treat somatostatin receptor–positive tumors provide an effective therapeutic response and, when used in conjunction with positively charged amino acids, reduce kidney uptake and therefore prevent potential damage to the kidneys.

Clinical PRRT studies are being performed using different agents. [^{111}In-diethylenetriaminepentaacetic acid (DTPA)]-octreotide was the first analog used (*2–6*), followed by [^{90}Y-dodecanetetraacetic acid (DOTA), Tyr^3]octreotide (^{90}Y-DOTATOC) (*3,7–13*), [^{90}Y-DOTA]-lanreotide (*14,15*), and [^{177}Lu-DOTA, Tyr^3]octreotate (*16*).

Various research groups have used multiple doses of [^{111}In-DTPA]octreotide, up to 160 GBq, to treat patients who have somatostatin receptor–positive tumors (*17*). The therapeutic effects included partial and minor remissions in a few patients and, mostly, stabilization of previously progressive tumors. Toxicity generally consisted of mild bone marrow toxicity, but a myelodysplastic syndrome or leukemia developed in 3 patients who received >100 GBq; therefore, a 100-GBq dose was considered the maximal tolerable dose of [^{111}In-DTPA]octreotide. No significant changes in renal parameters were observed, despite high cumulative doses in many patients. The drawback of ^{111}In, however, is the short range of the therapeutic Auger electrons emitted. The radiation emitted from a receptor-positive tumor cell cannot kill neighboring receptor-negative cells in tumors with receptor heterogeneity, because the path length of the Auger electrons is less than a cell diameter. Therefore, research groups have aimed at developing somatostatin analogs that can be linked through a chelator to a therapeutic β-emitting radionuclide, resulting in, for example, [DOTA,Tyr^3]octreotide (DOTATOC) and [DOTA,Tyr^3]octreotate. DOTA is a universal chelator capable of forming stable complexes with metals such as ^{111}In, ^{67}Ga, ^{68}Ga, ^{86}Y, and ^{64}Cu for imaging, with ^{90}Y (high-energy β-particle emitter), and with radiolanthanides such as ^{177}Lu (low-energy β-particle and γ-emitter) for PRRT.

In most radionuclide therapies, bone marrow toxicity is dose limiting. In PRRT, the bone marrow is also at risk, but after PRRT using somatostatin analogs labeled with β-emitters such as ^{90}Y and ^{177}Lu, the radiosensitive kidney is the dose-limiting organ because of high tubular reuptake of the peptide analogs after glomerular filtration and retention of the radionuclides in the tubular cells. This reuptake process can be inhibited by positively charged amino acids such as lysine and arginine (*18,19*).

The studies described below have aimed at a maximum kidney radiation dose of 23–27 Gy. On the basis of experience with external-beam radiation, this dose is expected to produce clinically significant nephrotoxicity in 5%–50% of subjects by 5 y of follow-up. The radiation dose that can be administered safely to the kidneys during PRRT remains to be established, however. A certain dose received from external-beam radiation can be expected to be different from that after PRRT, because of differences in the nature of the radiation (radiation period and dose rate), in localization, and in pathlength.

Phase I and II studies using ^{90}Y-DOTATOC are being performed (*3,7–13*). In this issue of *The Journal of Nuclear Medicine*, Waldherr et al. (*13*) report a phase II study on 39 patients with neuroendocrine gastroenteropancreatic and bronchial tumors. This phase II study was an extension of a phase I study by the same group of investigators using ^{90}Y-DOTATOC in 29 patients (*8*). These 29 patients received 4 or more single doses of ^{90}Y-DOTATOC with ascending activity at intervals of approximately 6 wk (mean cumulative dose ± SD, 6,120 ± 1,347 MBq/m^2). Of the 29 patients, 24 showed no severe renal or hematologic toxicity (toxicity ≤ grade 2 according to the National Cancer Institute grading criteria). These 24 patients received a cumulative dose of ≤7,400 MBq/m^2. Renal or hematologic toxicity developed in 5 patients. All 5 of these patients received a cumulative dose of >7,400 MBq/m^2 and no amino acid solution for kidney protection during therapy. In 4 of the 5 patients, renal toxicity developed; 2 of these patients showed stable renal insufficiency and 2 required hemodialysis. Two of the 5 patients exhibited anemia (both grade 3) and thrombocytopenia (grades 2 and 4). Twenty of the 29 patients showed disease stabilization, 2 showed partial

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remission, 4 showed a <50% reduction of tumor mass, and 3 showed progression of tumor growth.

Waldherr et al. (*12*) earlier reported a phase II study that included 41 patients (mean age, 53 y) with neuroendocrine gastroenteropancreatic and bronchial tumors. Eighty-two percent of the patients had therapy-resistant and progressive disease. The treatment consisted of 4 intravenous injections of a total of 6,000 MBq/m^2 ^{90}Y-DOTATOC, administered at intervals of 6 wk, and all patients had renal protection through intravenous amino acid infusion. The overall response rate was 24%. For endocrine pancreatic tumors, the response was 36%. Complete remissions were found in 2% (1/41), partial remissions in 22% (9/41), minor response in 12% (5/41), stable disease in 49% (20/41), and progressive disease in 15% (6/41) of the patients. The next step was the current phase II study with higher-dose ^{90}Y-DOTATOC treatment (7.4 GBq/m^2 in 4 equal injections at intervals of 6 wk, with renal protection using Hartmann-HEPA 8%) (*13*). In this study, an objective response according to WHO criteria was found in 23% of the patients, complete remission in 5%, partial remission in 18%, stable disease in 69%, and progressive disease in 8%. Furthermore, a significant reduction in clinical symptoms was found; overall clinical benefit was 63%. These results show that ^{90}Y-DOTATOC is an effective therapeutic drug, and the authors suggest that it may be an effective alternative to all chemo- and biotherapies for these tumors. These most promising tumor responses after PRRT are essentially similar to those found in other ^{90}Y-DOTATOC studies, despite differences in therapy regimens.

Paganelli et al. (*10*) treated 30 patients, who received 3 equal intravenous injections of ^{90}Y-DOTATOC over 6 mo. Cohorts of 6 patients were treated. The first cohort received 1.1 GBq per cycle, and each subsequent cohort received a dose 0.4 GBq higher than that the previous cohort had received. Up to a dose of 2.6 GBq per cycle (7.8 GBq total), no acute or delayed major adverse reactions occurred. In 1 patient, delayed grade II kidney toxicity developed after a 3.3-GBq total dose. A complete or partial reduction in tumor mass was found in 23% of patients; stable disease, in 64%; and progressive disease, in 13%.

Another study with ^{90}Y-DOTATOC (OctreoTher; Novartis Pharmaceuticals Corp., East Hanover, NJ)—the phase I study under way in Rotterdam, Brussels, and Tampa (*11*)—aims to define the maximum tolerated single and 4-cycle dose of ^{90}Y-DOTATOC. Of the 42 patients (23 women, 19 men) in this study, 21 had carcinoid tumors, 10 had islet cell carcinoma, and 11 had other neuroendocrine tumors. At baseline, 34 patients had progressive disease and 8 had stable tumors. Before treatment, all patients underwent quantitative PET with ^{86}Y-DOTATOC. The cumulative radiation dose to the kidneys was limited to 27 Gy. All patients received amino acids concomitantly with ^{90}Y-DOTATOC. In 31 patients, the intention was to give 4 cycles of fixed doses per cycle. Escalating doses per cycle were 0.9, 1.8, 2.8, and 3.7 GBq/m^2, repeated every 6–9 wk. Patients received a lower dose per cycle if the cohort dose would induce renal radiation exposure beyond 27 Gy. In 11 patients, escalating single doses of 3.7, 4.6, and 5.5 GBq/m^2 were given. The median follow-up was 15 mo. With cycle doses ranging from 1.3 to 10.8 GBq and cumulative doses ranging from 1.7 to 27 GBq, the maximum tolerable dose had not been reached at the time the data were reported. Three patients had dose-limiting toxicity: 1 with grade 3 liver toxicity, 1 with grade 4 thrombocytopenia, and 1 with myelodysplastic syndrome (2 y after the start of ^{90}Y-DOTATOC and previous chemotherapy). Renal toxicity was mild: 2 patients with grade 1 proteinuria and 1 patient with grade 2 serum creatinine elevation. In 10 patients, a 37% increase in serum creatinine and a 16%–18% decrease in creatinine clearance occurred after 2 y. Thirty-two patients received the planned dose: 24 had progressive disease and 8 had stable disease at baseline. Of the 24 patients, 37% had progressive disease, 46% had stable disease, 4% had a minor remission, and 13% had a partial response after a median follow-up of 13 mo. In the group of 8 patients with stable disease at baseline, 25% showed a minor remission and 75% showed continuing disease stability after a median follow-up of 29 mo. In 2 of 2 insulinoma patients and 1 of 1 gastrinoma patients, hormone values and symptoms completely normalized. Sixteen patients (50% of the 32 patients who received the planned dose) had symptomatic improvement. Prior chemotherapy predisposed to hematologic toxicity.

Because ^{90}Y is a pure β-emitter isotope, ^{90}Y-DOTATOC cannot provide quantitative imaging outside the body. One possibility is to substitute the ^{90}Y with ^{86}Y, which is a positron emitter radioisotope (physical half-life of 14.7 h) that allows quantitative imaging with a PET scanner. This ^{86}Y isotopic surrogate, ^{86}Y-DOTATOC, can be used for pharmacokinetic and biodistribution studies (*20*). Measurement of uptake kinetics further allows calculation of the individual radiation doses to the kidney and bone marrow and estimation of the doses that would be delivered to the tumors during treatment with [^{90}Y-DOTA,Tyr^3]octreotide. Waldherr et al. (*13*) used serial images after injection of 111 MBq ^{111}In-DOTATOC to calculate the radiation dose to the kidneys. A drawback of this method is that small structural modifications in somatostatin analogs, for example, chelator substitution or metal replacement, can considerably affect the somatostatin receptor binding affinity (*21*). On the other hand, the major part of the reuptake process in the kidney is not somatostatin receptor mediated, probably resulting in a comparable kidney residence time for ^{111}In- and ^{90}Y-labeled DOTATOC.

To reduce radiation exposure to the most critical organ, that is, the kidney, several regimens of amino acid coinfusion have been tested by different groups (*9,13,16,22–24*). In one study, infusion of mixed amino acids (120 g containing 26.4 g L-lysine + L-argi-

nine, i.e., 2 L Hartmann-HEPA 8%) over 4 h starting 30 min before radiotracer injection reduced the kidney uptake at all time points (*22*). The absorbed dose to the kidneys was reduced by a mean of 27% (range, 9%–53%). Conversely, amino acid infusion and tumor uptake were not affected at either time. When the infusion was prolonged for 10 h, kidney uptake was further reduced, with absorbed doses 18% less than for a 4-h infusion scheme. Infusion of 50 g pure L-lysine was not better than infusion of mixed amino acids. Thus, the renal protection observed with amino acid infusion allowed higher activities to be administered to patients without putting a significantly higher radiation burden on the kidneys. For a 10-h infusion regimen, this increment amounted to >60% of the radioactivity that could be given without any renal protection. Amino acid infusions were relatively well tolerated, with the exception of transient hypophosphatemia, which can be lessened by phosphate supplementation, and frequent nausea and occasional vomiting. L-lysine infusion did not induce significant nausea but was sometimes accompanied by substantial hyperkalemia—up to 5.6 mmol/L (*23*).

Valkema et al. (*24*) compared the ability of various L-lysine or L-arginine concentrations to reduce renal reuptake of radiolabeled octreotide in patients. A 75-g dose of L-lysine administered over 4 h was found to be highly effective in reducing renal peptide uptake, but the severe hyperkalemia that occurred in some patients was unacceptable. Furthermore, a combination of 25 g L-lysine and 25 g L-arginine in 1 L was more effective than an equimolar dose of L-lysine, suggesting a synergistic effect.

Paganelli et al. (*9*) determined in a phase I clinical trial the maximum dose of ^{90}Y-DOTATOC, also after an infusion of L-lysine and L-arginine, in 40 patients divided into 8 groups who received 2 increasing doses of the tracer. All patients received the amino acid infusion just before therapy. Sixty percent of the patients reported nausea and vomiting after the amino acid infusion but no side effects from the ^{90}Y-DOTATOC injection up to a dose of 5.6 GBq per cycle, and no kidney damage was noted.

Waldherr et al. (*13*) infused 2.5 L Hartmann-HEPA 8% over 3 h to inhibit tubular reuptake of ^{90}Y-DOTATOC. The percentage reduction of renal uptake is not described. With a single exception, serum creatinine values in the patients remained normal during and after treatment. One patient showed an increase in serum creatinine to 230 μmol/L (reference range, 45–93) after therapy. On the basis of this single patient, the authors conclude that dose-limiting toxicity (renal insufficiency) starts at 7.4 GBq/m^2, limiting further dose escalation. However, the estimated kidney radiation dose for this patient and other patients is not given. In most oncologic trials, evidence of toxicity in additional patients would be required before this conclusion could be drawn, because renal uptake ranges widely between patients, with radiation doses to kidneys ranging from 0.94 to 4.7 mGy/MBq (*11*). The problem of balancing benefits (clinical response to radionuclide therapy) and risks (renal radiotoxicity) is significant; therefore, careful renal dosimetry and coinfusion of protective amino acids during therapy is important, preferably on an individualized basis.

New is the use for PRRT of [^{177}Lu-DOTA,Tyr^3]octreotate (*16*), which shows the highest tumor uptake of all tested octreotide analogues so far, not only in rats but also in patients with neuroendocrine tumors (*25–27*). Radiotherapy with this analog started recently in 63 patients (238 administrations). Interim analysis was performed on 18 patients with neuroendocrine tumors who had received at least 22–30 GBq and were followed up for at least 3 mo. Most patients had progressive disease before enrollment. All had amino acid coinfusion to reduce the kidney dose to ≤23 Gy. Mild nausea, vomiting, and mild abdominal discomfort were present in 29%, 14%, and 11%, respectively. According to the World Health Organization toxicity criteria, no dose-limiting toxicity was observed. The serum creatinine level did not change significantly in any patient. By CT assessment, minor tumor shrinkage was seen in 6% of 18 patients; partial remission, in 39%; tumor progression, in 11%; and no change, in 44%. These interim results show that [^{177}Lu-DOTA,Tyr^3]-octreotate is also most promising for PRRT of somatostatin receptor–positive tumors.

In preclinical studies tumor responses were also good—up to 100% cure—both for [^{177}Lu-DOTA,Tyr^3]octreotate (*27*) and for ^{90}Y-DOTATOC (*28,29*). Tumor response was dependent on tumor size, in accordance with a computer model of tumor cure (*30*) that had calculated that ^{177}Lu would be optimal for small tumors whereas ^{90}Y would be better for large tumors. Rats with tumors of more than one size treated with the combination of ^{90}Y-DOTATOC and [^{177}Lu-DOTA,Tyr^3]octreotate indeed survived longer (area under survival curve, 146 d) than those treated with ^{90}Y-DOTATOC (57 d) or [^{177}Lu-DOTA,Tyr^3]octreotate (50 d) only (M. de Jong, unpublished data, January 2002). In patients with tumors of more than one size, use of combinations of radionuclides would thus be of the greatest interest, to obtain the widest range of tumor curability.

In conclusion, these early results of antitumor PRRT effects are most encouraging and more statistically significant than the results of studies using nonradiolabeled somatostatin analogs (*31*). Patients with neuroendocrine tumors are an important population that would benefit from such therapy. In addition, a variety of other peptide-based radioligands are under development, including bombesin, gastrin/cholecystokinin, and neurotensin, which are receptors expressed on a variety of common cancers, and Arg-Gly-Asp peptides, which, because they bind to receptors expressed on newly formed blood vessels, can be targeted to many common tumors.

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