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Advances in Peptide Receptor Radionuclide Therapy

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Peptide receptor radionuclide therapy (PRRT) is a very effective treatment modality for advanced neuroendocrine tumors (NETs), representing a teaching model for truly targeted antitumor therapy. With the growing cumulative evidence of PRRT in various treatment settings, we are witnessing increased perception of this modality as a potent treatment option in advanced disease. Although most data derives from retrospective analyses, results from prospective comparative evaluations, such as the NETTER-1 trial, are eagerly awaited and should help to raise PRRT to a higher level of evidence. At the same time, as increased levels of evidence are anticipated by prospective evaluations, further methodological improvements are going on in different ways and aspects of radionuclide therapy, mainly regarding the radiopharmaceuticals, the combination with other radionuclides or cytotoxic drugs, and the route of administration. Although diversity of PRRT increases—not supporting cumulative evidence as opposed to uniform treatment—it is very likely to achieve significant increase of efficacy by these efforts in the near future. As the intraarterial administration of PRRT agents in liver-dominant metastatic disease has the potential to improve outcome, it would have to be shown as to which patients would benefit from this approach, to what extent the benefit would be, and to when it would justify the increased efforts for patients and treating institutes. The approach of combining cytotoxic or radiosensitizing drugs with the PRRT agents seems to trigger a major boost of efficacy in pancreatic NET. The midterm future would show the extent of benefit in terms of long-term outcome and would probably lead to inclusion into clinical routine for this particular NET entity. The translation of somatostatin-receptor antagonists into human application represents another major source of significant improvement in terms of PRRT's benefit-toxicity ratio. Eventually, it may not be completely unlikely to see another radiopharmaceutical being regarded as the PRRT agent of choice in the midterm future.
Semin Nucl Med 46:40-46 **© 2016 Elsevier Inc. All rights reserved.**

Effective treatment options for well-differentiated neuroendocrine tumors (NETs) in the stage IV disease that is in the inoperable metastatic stage are limited. Well-differentiated NETs are generally not overly sensitive to cytotoxic chemotherapy.[1-4] Although moderate response rates have been observed with novel treatments including inhibitors of tyrosine kinase or mammalian target of rapamycin in patients with pancreatic NET, survival benefit is not impressive and a considerable portion of patients discontinue treatment because of severe toxicity.[5-8] For unresectable NET of nonpancreatic origin, priorly referred to as carcinoids, treatment with somatostatin analogues is the recommended first-line therapy with predominantly antisecretory and antiproliferative effects.[9,10] This modality can prolong time-to-progression but has little cytoreductive capacity. Effective treatment options for somatostatin analogue-refractory patients with uncontrolled functional symptoms or progressive metastatic disease are limited.[10,11] Radionuclide therapy of carcinoids with ^{131}I-meta-iodobenzylguanidine (^{131}I-MIBG) has mainly resulted in symptomatic disease control with only minor cytoreductive potential.[12-14] Originating from the neural crest, a very common feature of NETs is the ability to express receptors for regulatory peptides including somatostatin receptors (SSTRs). Peptide receptor radionuclide therapy (PRRT) is a

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http://dx.doi.org/10.1053/j.semnuclmed.2015.09.005
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tumor-directed systemic treatment exploiting the abundance of SSTRs, especially sst2, on the cell membrane of well-differentiated NETs.[15-18]

Establishment of ^{177}Lu-Octreotate as the Preferred Compound for PRRT

Early experiences with PRRT using high activities of ^{111}In-DTPA-pentetreotide showed disappointing results regarding tumor response.[19,20] Subsequently, ß-emitter radionuclides have been coupled to sst2 ligands to form the radiopeptide compounds used in PRRT. First PRRT agents with ß-emitter radionuclides used ^{90}Yttrium and modified somatostatin analogue Tyr3-octreotide, with DOTA instead of DTPA as chelating molecule, to ensure stable binding. PRRT with ^{90}Y-DOTA-Tyr3-octreotide (^{90}Y-DOTATOC) resulted in considerably better response rates and replaced the treatment with ^{111}In-DTPA-0-octreotide.[21]

Incidence of severe myelosuppression and renal failure after PRRT with ^{90}Y-labeled peptides led to investigation of various strategies to reduce toxicity.[21-26] Accordingly, two amino acids in DOTATOC compound, namely phenylalanine and threoninol, were substituted with tyrosine-threonine to build DOTA-Tyr3-octreotate (DOTATATE) with significantly higher affinity to the main target somatostatin-receptor sst2.[16] Owing to lower energy and shorter particle range of the ß particles emitted by ^{177}Lutetium (^{177}Lu) compared to ^{90}Y (2 vs 11 mm), ^{177}Lu-based PRRT may be associated with lower dose to normal tissue. Labeling DOTATATE with ^{177}Lu (^{177}Lu-octreotate) has become the most important improvement of the last decade to reduce the radiation dose to the dose-limiting organs, especially kidney and bone marrow.[27-33] Furthermore, gamma emission by ^{177}Lu enables intratherapeutic whole body imaging, which can be used to visualize and quantify target uptake and absorbed dose.[34]

Nephrotoxicity After PRRT With ^{177}Lu-Octreotate

High radiation doses during PRRT with ^{90}Y-labeled peptides can lead to renal impairment and even delayed end-stage renal disease.[23,26,35] The coinfusion of positively charged amino acids as competitive inhibitors of proximal tubular reabsorption may reduce the renal dose ranging from 9%-53% and is currently the established nephroprotective regimen in clinical PRRT.[25,28,36] As illustrated in Table 1, the various rates of significant renal toxicities (grades 3-4) after ^{90}Y-labeled PRRT have been reported.[21,22,32,37,38] In the current largest study on 1109 patients, Imhof et al[24] observed permanent renal toxicity of grades 4-5 in 103 patients (9.2%).

PRRT with ^{177}Lu-labeled peptides results in less propensity to renal impairment, probably due to less irradiation of the radiosensitive glomeruli during each course of treatment.[37,39] However, continuous radiation during PRRT with a relative low dose rate to arteriolar-glomerular area may lead to clinically evident impairment months after the treatment.[36,40,41] Contribution of cumulative absorbed doses to renal impairment could only be evaluated when long-term follow-up of treated patients became available (Table 1).[31,32,36,40] Furthermore, sensitive methods such as ^{99m}Tc-DTPA, ^{99m}Tc-MAG3, or ^{51}Cr-EDTA clearance tests have proved essential to capture minor PRRT-induced changes in glomerular filtration rate.[36,40,41] Serial glomerular filtration rate measurements with ^{99m}Tc-DTPA have shown slight renal impairment after treatment with ^{177}Lu-octreotate but significant nephrotoxicity (≥CTCAE, grade 3) has been rare.[42] Accordingly, in a comparative study, persistent nephrotoxicity was observed in none of 290 patients receiving ^{177}Lu-octreotate as opposed to 10 of 358 patients (2.8%) treated with ^{90}Y-DOTATOC.[43]

Neither the known risk factors for nephrotoxicity after ^{90}Y-based PRRT (eg, arterial hypertension and diabetes mellitus) nor higher cumulative activities were significantly associated with more pronounced renal function loss after ^{177}Lu-based PRRT.[32,42,44,45] This evidence of long-term renal safety disputed the need for dose reduction or strict patient selection regarding kidney function in ^{177}Lu-based PRRT.[37,44,46-48] Nevertheless, baseline impairment of renal function contributed to hematological toxicity after PRRT with ^{177}Lu-octreotate in a very recent study on 51 patients.[49]

Hematotoxicity After PRRT With ^{177}Lu-Octreotate

A limit for the maximum absorbed dose of 2 Gy to the bone marrow has been suggested to avoid bone marrow hypoplasia.[30,50,51] But all models being applied until date, including bone marrow aspiration, blood concentration of radioactivity, and the Medical Internal Radiation Dose scheme, are associated with specific difficulties and limited precision.[27,52] Furthermore, there is a high interindividual variability in hematological alterations after the same absorbed dose to the red marrow.[27,52] The limited predicting value of dosimetry measurements necessitates analysis of patients with sufficient follow-up duration to determine prognosis and clinical significance of myelosuppression after PRRT with ^{177}Lu-octreotate.

In a study of 203 patients, significant but reversible hematotoxicity occurred after 4.6% of administrations (11% of patients). Aggravation of preexisting anemia caused treatment discontinuation in one patient, and three patients (1.4%) developed myelodysplastic syndrome >14 months after termination of PRRT.[53] Similarly, satisfying results have been observed in a large cohort of 504 patients reporting significant hematotoxicity in 3.6% of administrations and 9.5% of patients (Table 1).[31] Comparing these results with those of ^{90}Y-based PRRT reporting severe hematotoxicity in 142 of 1109 patients (12.8%) underlined better tolerabilily of ^{177}Lu-based PRRT.[24] Accordingly, in a large retrospective study on 807 patients, ^{177}Lu-octreotate proved to be safer than ^{90}Y-DOTATOC regarding both hematological and renal toxicity.[43] These findings have underlined the outstanding toxicity profile of PRRT with ^{177}Lu-octreotate, which also compares favorably with reported toxicities of common chemotherapy regimens

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