The Latest Advances in Peptide Receptor Radionuclide Therapy for Gastroenteropancreatic Neuroendocrine Tumors

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We would like to draw attention to the latest advances in the field of peptide receptor radionuclide therapy (PRRT) of neuroendocrine tumors (NETs) of gastroenteropancreatic origin. The term *NET* refers to well-differentiated tumors that can be grade 1 (Ki-67 index, <3), 2 (Ki-67, 3–20), or 3 (Ki-67, >20); it excludes poorly differentiated grade 3 neuroendocrine carcinomas.

The seminal NETTER-1 trial has positioned PRRT with ^{177}Lu-DOTATATE at the forefront of oncologic treatments in patients with midgut NETs that have progressed on somatostatin analogs; the treatment has shown a major improvement in progression-free survival (PFS) and a positive impact on time to deterioration of quality of life. At long-term follow-up, improvement in overall survival was nonsignificant. Late serious adverse events were rare; myelodysplasia occurred in 2 of 111 (2%) ^{177}Lu-DOTATATE–treated patients, with 1 death (*1*). The disease in most patients ultimately progresses. Retreatment is not standardized, but some trials are ongoing (NCT04954820).

NETTER-1, however, did not include pancreatic NETs; also, in some countries PRRT is not reimbursed for this specific indication. Therefore, the results of the OCLURANDOM trial, recently presented at the European Society of Medical Oncology 2022 meeting, are important (*2*). On the other hand, multiple options are being actively investigated to increase the objective response rate over that obtained in NETTER-1 (18%) and further improve outcomes with PRRT.

PANCREATIC NETS

In the prospective randomized noncomparative phase II study OCLURANDOM (*2*), patients with somatostatin receptor (SSTR) imaging–positive advanced pancreatic NETs with progressive disease were randomized 1:1 to ^{177}Lu-DOTATATE, 7.4 GBq every 8 wk for 4 cycles (^{177}Lu-octreotate arm, $n = 41$), or the antiangiogenic agent sunitinib, 37.5 mg/d (sunitinib arm, $n = 43$). Among the included patients, 81% had grade 2 or 3, 37% had a Ki-67 of more than 10%, 42% had more than 25% liver involvement, 43% had received 2 or more prior systemic lines, and 57% had received prior chemotherapy. The primary endpoint was met, with a 12-mo PFS rate of 80% in the ^{177}Lu-octreotate arm and 42% in the sunitinib arm. Median PFS was 20.7 mo in the ^{177}Lu-octreotate arm and 11 mo in the sunitinib arm. Grade 3 or higher adverse events occurred less frequently in the ^{177}Lu-octreotate arm (44%) than in the sunitinib arm (60%). Other important results are expected with final trial analysis.

Some ongoing phase III trials enrolled both pancreatic NET patients and gastroenteric NET patients. COMPETE (NCT03049189) is comparing ^{177}Lu-DOTATOC with the mammalian-target-of-rapamycin inhibitor everolimus in grade 1 or 2 gastroenteropancreatic NETs, with 309 enrolled patients. Substudies within this trial are investigating the role of dosimetry. NETTER-2 (NCT03972488) and COMPOSE (NCT04919226) are exploring the role of PRRT in gastroenteropancreatic NET patients with high grade 2 or 3 tumors (Ki-67 range, 10%–55%).

SSTR ANTAGONISTS

Somatostatin antagonist analogs are not internalized but display higher occupancy and more prolonged binding to SSTR than do agonists. In a phase I study of ^{177}Lu-satoreotide tetraxetan (also called ^{177}Lu-IPN01072, ^{177}Lu-OPS201, and ^{177}Lu-DOTA-JR11) in 20 NET patients, the maximum activity was 7.4 GBq/cycle (*3*). Although response rates were encouraging, 4 of 7 patients (57%) experienced grade 4 hematologic toxicity after cycle 2, hence leading to a modification in the protocol. A phase I/II trial (NCT02592707) with ^{177}Lu-satoreotide has now completed its recruitment. Part A enrolled 15 patients who received 3 cycles of ^{177}Lu-satoreotide tetraxetan with 4.5 GBq (peptide mass, 300 μg)/cycle. Part B enrolled 25 patients who completed 1–5 cycles at different administered activities (4.5 or 6.0 GBq/cycle) and peptide masses (300, 700, or 1,300 μg/cycle). Preliminary reporting at the European Society of Medical Oncology 2020 meeting described safety and early efficacy data (*4*). The major toxicities were hematologic, the objective response rate was 21%, and for the 20 patients with adequate follow-up, the disease control rate at 12 mo was 90%.

^{177}Lu-DOTA-LM3 is another SSTR antagonist, recently evaluated in 51 metastatic NET patients (*5*). ^{68}Ga-NODAGA-LM3 PET/CT was used for patient selection. Therapy cycles ranged between 1 (half the patients) and 4, with a median of 6.1 GBq/cycle. Partial response was obtained in 36.2%. Grade 3 thrombocytopenia occurred in 5.9% of patients.

α-THERAPY AND OTHER PROMISING RADIONUCLIDES

Initial results with α-emitting radioligands are also promising. A phase 1 dose-escalation trial evaluated ^{212}Pb-DOTAMTATE in

Received Nov. 5, 2022; revision accepted Jan. 4, 2023.
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Published online Jan. 5, 2023.

DOI: 10.2967/jnumed.122.264422

PRRT-naïve NET patients (*6*). In the absence of dose-limiting toxicity, the recommended phase 2 dose was established at the highest activity tested, defined as a 2.50 MBq/kg dose of ^{212}Pb-DOTAMTATE administered 4 times at 8-wk intervals. For the first 10 subjects treated at this recommended activity, the objective response rate was 80%. There were 2 cases of transient renal toxicity and 1 case of renal toxicity that did not recover, but that patient had several confounding factors. A phase II study of ^{212}Pb-DOTAMTATE (NCT05153772) is ongoing.

In a single-center study, 91 patients received ^{225}Ac-DOTATATE (100–120 kBq/kg of body weight) at 8-wk intervals (median, 4 cycles; range, 1–10). All patients received concomitant capecitabine therapy (*7*). Fifty-seven had received prior ^{177}Lu-DOTATATE therapy, with 33 being considered to have progressive disease or disease refractory to ^{177}Lu-PRRT. Treatment-related toxicities were deemed minimal. Among 79 patients with assessable disease, the objective response rate was 51%. The 24-mo PFS was 67.5%. Prior ^{177}Lu-PRRT–refractory disease was associated with poorer PFS. A prospective phase 1b/3 trial (NCT05477576) of ^{225}Ac-DOTATATE in gastroenteropancreatic NET patients who experienced progression after ^{177}Lu-somatostatin analog therapy is ongoing.

From preclinical studies, the combined β- and Auger-emitter ^{161}Tb also appears promising, especially when coupled to an SSTR antagonist, probably leading to substantial damage to tumor cell membranes (*8*).

^{67}Cu-SARTATE PRRT can be paired with ^{64}Cu-SARTATE with the potential for dosimetry planning (*9*). The chelator MeCOSar (5-(8-methyl-3,6,10,13,16,19-hexaaza-bicyclo[6.6.6]icosan-1-ylamino)-5-oxopentanoic acid) offers improved retention of copper compared with previous chelators. ^{67}Cu-SARTATE has entered clinical trials, albeit in neuroblastoma (NCT04023331).

LIVER-DOMINANT DISEASE

A subtle way to increase the uptake of radioligands in liver metastases could be the use of intraarterial PRRT after selective catheterization of the hepatic artery. A non–head-to-head comparison of intraarterial PRRT (15 patients) versus the standard intravenous route (14 other patients) found that intraarterial PRRT was associated with a higher concentration and absorbed dose in liver metastases (*10*). Whether a higher response rate was achieved was not reported. Prospective studies are needed since earlier reports were not uniformly positive. Trials with intraarterial ^{177}Lu-DOTATATE are ongoing (NCT03590119, NCT04837885).

COMBINATION THERAPY

Many studies have investigated PRRT combined with chemotherapy, notably in higher-grade tumors or ^{18}F-FDG–avid metastatic disease. as it is associated with a poorer prognosis (*11*). A phase II study evaluated ^{177}Lu-DOTATATE (5 cycles of 5.5 GBq each) plus oral capecitabine in the intercycle in patients with ^{18}F-FDG–positive advanced gastroenteropancreatic NETs (*12*). Of 37 enrolled patients, 68% had G2 or G3 NETs and 68% had pancreatic NETs. Grade 3 or 4 adverse events included hematologic toxicity (16.2%), diarrhea (5.4%), and asthenia (5.4%). Five patients (13%) discontinued the protocol. No renal toxicity was observed. A partial response 3 mo after the end of the 5 cycles was obtained in 10 of 33 evaluable patients (30%). The median PFS was 31.4 mo but still was difficult to interpret in the absence of randomization. The phase II CONTROL NET trial presented at 2022 meeting of the American Society of Clinical Oncology evaluated the combination of PRRT (^{177}Lu-DOTATATE) and capecitabine plus temozolomide (CAPTEM) in 75 patients with advanced progressive NETs (45 midgut NETs and 27 pancreatic NETs) (*13*). Patients with midgut NETs were randomized 2 to 1 to PRRT + CAPTEM (n = 33) or PRRT alone (n = 14), and those with pancreatic NETs were randomized 2 to 1 to PRRT + CAPTEM (n = 19) or CAPTEM alone (n = 9). A nonsignificant trend for better PFS (hazard ratio, 0.41; P = 0.08) with PRRT + CAPTEM was observed for pancreatic NET patients, suggesting continuing investigations in this subgroup of NET patients only (*13*). The risk of long-term hematologic toxicity should be considered (*14*).

There is also a lot of exciting preclinical work and ongoing trials in NET patients on the combination of PRRT with immune checkpoint inhibitors, such as pembrolizumab (NCT03457948) or nivolumab (NCT04525638), or with DNA-damage response-modifying agents, such as the poly(adenosine diphosphate-ribose) polymerase inhibitors olaparib (NCT04086485, NCT04375267) and talazoparib (NCT05053854), the DNA-dependent protein kinase inhibitor peposertib (NCT04750954), or the ribonucleotide reductase inhibitor 3-aminopyridine-2-carboxaldehyde thiosemicarbazone (Triapine; Nanoshift, LLC) (NCT04234568).

The mentioned clinical trials, and others investigating the role of dosimetry and predictive imaging and blood biomarkers to improve patient selection and precision medicine approaches to personalized treatment, will no doubt further reinforce the role of PRRT in gastroenteropancreatic NET patients in the years to come.

DISCLOSURE

^{177}Lu-DOTATATE for the academic OCLURANDOM trial was supplied by AAA/Novartis. Eric Baudin and David Taïeb are advisors for AAA/Novartis. Rodney Hicks is a shareholder of Telix Pharmaceuticals. No other potential conflict of interest relevant to this article was reported.

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