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

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In this Hot Topic, we would like to draw the attention to the latest advances in the field of peptide receptor radionuclide therapy (PRRT) of neuroendocrine tumors (NET) of gasteroenteropencreatic (GEP) origin. The term NET refers to well-differentiated tumors that can be of grade G1 (Ki67 index: <3), G2 (Ki67: 3-20) or G3 (Ki67: >20); it excludes poorly differentiated G3 neuroendocrine carcinomas.

As a reminder, the seminal NETTER-1 trial has positioned PRRT with ^{177}Lu-DOTATATE at the forefront of oncologic treatments in patients with midgut NET progressing on somatostatin analogs (SSA), showing major improvement in progession-free survial (PFS) and a positive impact on time to deterioration of quality of life. At long-term follow-up, improvement in overall survival was non-significant. Late serious adverse events were rare; myelodysplasia occurred in 2/111 (2%) ^{177}Lu-DOTATATE treated patients, with one death (*1*). The majority of patients ultimately progress. Retreatment is not standardized, but some trials are ongoing (NCT04954820).

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

PANCREATIC NET

In the prospective randomized non-comparative phase II study OCLURANDOM (*2*), patients with somatostatin receptor imaging (SRI)-positive advanced panNET with progressive disease were randomized 1:1 to ^{177}Lu-DOTATATE 7.4 GBq every 8 weeks for 4 cycles (OCLU arm; n=41), or the antiangiogenic agent sunitinib 37.5 mg/d (SUN arm; n=43). Among included patients, 81% had grade 2-3, 37% had a Ki67 >10%; 42% had >25% liver involvement; 43% had received two or more prior systemic lines and 57% a prior chemotherapy. The primary endpoint was met, with a 12-months PFS rate of 80% in the OCLU arm and 42% in SUN arm. Median PFS was 20.7 months in the OCLU arm and 11 months in the SUN arm. Grade 3 or higher adverse events occurred less frequently in the OCLU arm (44%) compared to the SUN arm (60%). Other important results are expected with final trial analysis.

Some phase III trials are ongoing that enrolled both panNET and gastroenteric (GE) NET. COMPETE (NCT03049189) is comparing ^{177}Lu-DOTATOC to the mTOR inhibitor everolimus in G1/G2 GEP-NET, 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 GEP-NET patients with high grade G2 or G3 tumors (Ki67 range: 10% to 55%).

SOMATOSTATIN RECEPTOR (SSTR) ANTAGONISTS

Somatostatin antagonist analogs are not internalized but display higher occupancy and more prolonged binding to SSTR compared to agonists. In a phase I study of ^{177}Lu-satoreotide tetraxetan (also called ^{177}Lu-IPN01072, ^{177}Lu-OPS201, ^{177}Lu-DOTA-JR11) in 20 NET patients, the maximum activity was 7.4 GBq per cycle (*3*). Although response rates were encouraging, 4/7 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 ESMO 2020 described safety and early efficacy data (*4*). The major toxicities were hematological, the ORR was 21% and for the 20 patients with adequate follow-up, disease control rate at 12 months 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 of 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.

ALPHA 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 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 2.50 MBq/kg of ^{212}Pb-DOTAMTATE administrated 4 times at 8-week intervals. For the first 10 subjects treated at this recommended activity, the ORR was 80%. There were two cases of transient

renal toxicity and one case of renal toxicity that did not recover, but this patient had several confounding factors. A phase II study of ^{212}Pb-DOTAMTATE (NCT05153772) is ongoing.

In a single-centre study, 91 patients received ^{225}Ac-DOTATATE (100-120 kBq/kg body weight) 8-weekly (median four cycles; range 1-10). All patients received concomitant capecitabine therapy (*7*). Fifty-seven had received prior ^{177}Lu-DOTATATE therapy with 33 of them being considered progressive/refractory to ^{177}Lu-PRRT. Treatment-related toxicities were deemed minimal. Among 79 patients with assessable disease, the ORR was 51%. The 24-month 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 GEP-NET patients who progressed after ^{177}Lu-SSA therapy is ongoing.

Based on preclinical studies, the combined β- and Auger-emitter terbium-161 also appears promising, especially so when coupled to an SSTR antagonist, probably leading to substantial damage to cell membranes of tumor cells (*8*).

^{67}Cu-SARTATE PRRT can be paired with ^{64}Cu-SARTATE with the potential for dosimetry planning (*9*). The chelator MecoSAR offers improved retention of copper compared to previous chelators. ^{67}Cu-SARTATE 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 intra-arterial PRRT after selective catheterization of the hepatic artery. A “non-head-to-head” comparison of intra-arterial PRRT (15 patients) vs. standard intravenous route (14 other patients) found that intra-arterial PRRT was associated with higher concentration and absorbed dose in liver metastases (*10*). Whether higher response rate was achieved was not reported. Prospective studies are needed since earlier reports were not uniformly positive. Trials with intra-arterial ^{177}Lu-dotatate are ongoing (NCT03590119, NCT04837885).

COMBINATION THERAPY

Many studies investigated PRRT combined with chemotherapy, notably in higher grade tumors or FDG-avid metastatic disease as it is associated with poorer prognosis (*11*). A phase II study evaluated ^{177}Lu-DOTATATE (five cycles of 5.5 GBq each) plus oral capecitabine in the

inter-cycle in patients with FDG-positive advanced GEP-NET (*12*). Of 37 enrolled patients, 68% had G2 or G3 NET and 68% had panNET. Grade 3 or 4 adverse events included hematological toxicity (16.2%), diarrhea (5.4%) and asthenia (5.4%). Five patients (13%) discontinued the protocol. No renal toxicity was observed. Partial response 3 months after end of the 5 cycles was obtained in 10 out of 33 evaluable patients (30%). The median PFS was 31.4 months, but still difficult to interpret in the absence of randomization. The phase II CONTROL NET trial presented at ASCO 2022, evaluated the combination of PRRT (^{177}Lu-DOTATATE) and CAPTEM (capecitabine plus temozolomide) in 75 patients with advanced progressive NET (45 midgut NET and 27 PanNET) (*13*). Patients with midgut NET were randomized 2/1 to PRRT+CAPTEM (n=33) or PRRT alone (n=14) and those with PanNET to PRRT+CAPTEM (n=19) or CAPTEM alone (n=9). A non significant trend for better PFS (HR 0.41, p=0.08) with PRRT+CAPTEM was observed for PAnNET patients, suggesting continuing investigations in this subgroup of NET patients, only (*13*). The risk of long-term hematological toxicity should be taken into consideration (*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 PARP inhibitors olaparib (NCT04086485, NCT04375267) and talazoparib (NCT05053854), the DNA-dependent protein kinase (DNA-PK) inhibitor peposertib (NCT04750954), or the ribonucleotide reductase (RR) inhibitor triapine (NCT04234568).

No doubt that 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 further reinforce the role of PRRT in GEP-NET patients in the years to come.

DISCLOSURE

^{177}Lu-DOTATATE for the academic OCLURANDOM trial was supplied by AAA/Novartis. Eric Baudin is advisor for AAA/Novartis. Rodney Hicks is a shareholder of Telix Pharmaceuticals. David Taieb is advisor for AAA/Novartis. No other potential conflicts of interest relevant to this article exist.

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