# 21 Medical Treatment of Gastroenteropancreatic (GEP) Neuroendocrine Tumors

Carlo Carnaghi and Valeria Smiroldo

**Abstract**

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms that arise from the diffuse endocrine system present in various organs. These tumors are classified as functioning and nonfunctioning due to the presence of a specific syndrome determined by the production of some peptides and, due to the low incidence, they are considered rare. This landscape is going to change due to the steadily rising prevalence and incidence as reported by a recent SEER database analysis. The first aim of the treatment of patients with diagnosis of NETs is to cure, and this goal could be achieved by surgery. If patients are not suitable for surgery with curative intent, a medical management for symptom and disease is required. Somatostatin analogues are the backbone of the treatment of symptoms; a few years later after their introduction in clinical practice, the antiproliferative effects were demonstrated by two clinical trials. Significant clinical activity was also achieved with two different oral target therapies: everolimus (mTOR inhibitor) and sunitinib (multitargeted receptor tyrosine kinase inhibitor). Chemotherapy maintains a significat role for the most aggressive variants such as neuroendocrine cancers (NECs). At last, the peptide receptor radiotherapy is an innovative therapeutic approach for somatostatin receptor-positive inoperable and metastatic NETs.

## 21.1 Introduction

Neuroendocrine tumors (NETs) are an heterogeneous group of malignancies that sometimes produce peptides that cause characteristic hormonal syndromes. NETs can be clinically symptomatic (functioning) or silent (nonfunctioning); both types frequently synthesize more than one peptide,

C. Carnaghi (✉) • V. Smiroldo
Oncology and Hematology Unit, Humanitas Cancer Center, Istituto Clinico Humanitas, Rozzano, Italy
e-mail: carlo.carnaghi@cancercenter.humanitas.it


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although often these are not associated with specific syndromes. In the last years, the incidence and prevalence of NETs are increasing [1]. The primary treatment goal for patients with NETs is curative, with symptom control and the limitation of tumor progression as secondary goals. Surgery is the only possible curative approach and it represents the traditional first-line therapy. However, as most patients with NETs are diagnosed once metastases have occurred, curative surgery is generally not possible. Patients therefore require chronic postoperative medical management with the aim of relieving symptoms and improving tumor growth and survival. Descriptions of the most common treatment options for metastatic GEP-NETs will be described. Treatment options and recommendations depend on several factors, including the type and stage of neuroendocrine tumor, possible side effects, and the patient's preferences and overall health.

Unfortunately, the limited number of clinical randomized trials and the lack of sequence trials didn't allow to draw a clear therapeutic algorithm.

## 21.2 Somatostatin Analogues in Gastroenteropancreatic Neuroendocrine Tumors

*Octreotide* was the first biologically somatostatin analogue (SSA) that has been synthesized; it binds with high, low, and moderate affinity to SSTR2, SSTR3, and SSTR5, respectively [2]. Long-acting formulation of octreotide (octreotide LAR) was approved in 1995; it is a depot preparation administered by monthly intramuscular injection. The pharmacokinetics show an initial peak within 1 h of administration and a second release reaching a plateau between days 14 and 42. Steady-state serum concentrations are reached after three injections [3]. *Lanreotide* is another different somatostatin analogue with a similar receptors binding profile. The original sustained-release formulation (lanreotide SR) was later followed by lanreotide Autogel [4]. After administration, lanreotide peptide monomers are slowly released over a period of 1 month.

Somatostatin analogues have long been indicated for symptom relief associated with GEP-NET, and their clinical use has contributed to improved patient survival. The benefits related to somatostatin analogues (SSAs) were shown in three phase III randomized trials (Table 21.1). Gastrointestinal-related complaints are the most frequently reported side effects; these are related to disruption of GEP hormone signaling and reduced secretion of digestive enzymes. Altered secretion of cholecystokinin can lead to abnormalities in the biliary system and development of biliary sediment/sludge, microlithiasis, or gallstones [5].

The phase III trial (PROMID), a multicenter, randomized, double-blind, placebo-controlled trial, was the first large trial to confirm the antitumor effect of octreotide LAR in a randomized setting. In 85 treatment-naïve patients with well-differentiated metastatic GEP-NET of the midgut, functional and nonfunctional, median time to tumor progression in the octreotide LAR and

**Table 21.1** Published phase III trials with SSAs

| Study | N of pts. | Tumor origin | Treatment | Primary endpoint | Prior therapy | Results (mo) | HR, *p*-value |
|---|---|---|---|---|---|---|---|
| PROMID [6] | 85 | G1 metastatic GEP-NET of the midgut | Octreotide LAR vs placebo | TTP | No | 14.3 vs 6 | HR 0.34; 95% CI 0.20–0.59; *P* 0.000072 |
| RADIANT-2 [13] | 429 | NETs | EVE 10 mg/day + octreotide LAR vs placebo + octreotide LAR | PFS | Yes | 16.4 vs 11.3 | HR 0.77; 95% CI 0.59–1.00; *P* 0.026 |
| CLARINET [8] | 204 | G1-G2, nonfunctional NETs | Lanreotide Autogel vs placebo | PFS | Yes | NR vs 18 | HR 0.47; 95% CI 0.30–0.73; *P* < 0.001 |

*mo* months, *TTP* time to progression, *GEP* gastroenteropancreatic, *GI* gastrointestinal, *BSC* best supportive care, *SSAs* somatostatin analogues, *PFS* progression-free survival, *NR* not reached

placebo groups was 14.3 and 6 months, respectively (HR 0.34; CI 0.20–0.59; $P = 0.000072$) [6]. Authors concluded that due to the low number of observed deaths, the survival analysis was not confirmatory, and the extent of tumor burden is a predictor for shorter survival. Overall survival was similar in patients receiving octreotide LAR or placebo treatment [7]. The Lanreotide Antiproliferative Response in Patients with GEP-NET (CLARINET) trial is a randomized, double-blind, placebo-controlled, multinational study of the somatostatin analogue lanreotide in patients with advanced, well-differentiated, or moderately differentiated, nonfunctioning, somatostatin receptor-positive neuroendocrine tumors. Patients were randomly assigned to receive lanreotide Autogel Depot at a dose of 120 mg or placebo once every 28 days for 96 weeks. The primary endpoint of progression-free survival (PFS) was met, lanreotide Autogel was superior to placebo in prolonging PFS, and median PFS was not reached with lanreotide Autogel vs 18 months with placebo (HR 0.47; 95% CI 0.30–0.73; $P < 0.001$). After 2 years of treatment, estimated rates of PFS were 65.1 and 33.0% in the lanreotide Autogel and placebo groups, respectively [8].

*Pasireotide* is a next-generation, multi-receptor-targeted somatostatin analogue with high affinity for SSTR1, SSTR2, SSTR3, and SSTR5. Binding affinity to SSTR5 is 39-fold higher than octreotide [9]. Pasireotide long-acting formulation (pasireotide LAR) is administered by monthly intramuscular injection. It has a similar safety profile as that of first-generation SSAs, except for a higher frequency and degree of hyperglycemia [10].

A phase III multicenter, randomized, double-blind clinical trial evaluated pasireotide LAR (160 mg) vs increased dose of octreotide LAR (40 mg) in patients with metastatic GEP-NETs with carcinoid symptoms failing at standard dose of octreotide LAR (30 mg). Pasireotide LAR and octreotide LAR showed similar effects on symptom control, and the trial was earlt stopped due to the higher toxicity profile of pasireotide. This trial was not designed for evaluating survival data, but in the analysis, pasireotide LAR was associated with a longer PFS compared with octreotide LAR; these data warrant further investigation into the role of pasireotide LAR in the treatment of GEP-NETs [11].

## 21.3 Targeted Therapies

*Everolimus* is a serine-threonine kinase inhibitor of mammalian target of rapamycin (mTOR) downstreamer of the PI3K/AKT pathway. Everolimus binds to an intracellular protein, FKBP-12, resulting in an inhibitory complex formation with mTOR complex 1 (mTORC1) and thus inhibition of mTOR kinase activity. Everolimus efficacy was investigated in four trials (Table 21.2).

**Table 21.2** Published trials with everolimus

| Study | Phase | N of pts. | Tumor origin | Treatment | Primary endpoint | Results | HR, *p*-value |
|---|---|---|---|---|---|---|---|
| RADIANT-1 [12] | II | 160 | pNETs | EVE 10 mg/day | ORR | 8.7% | – |
| RADIANT-2 [13] | III | 429 | NETs | EVE 10 mg/day + octreotide LAR vs placebo + octreotide LAR | PFS | 16.4 vs 11.3 mo | HR 0.77; 95% CI 0.59–1.00; *P* 0.026 |
| RADIANT-3 [14] | III | 410 | pNETs, G1-G2 | EVE 10 mg/day or placebo + BSC (±SSAs) | PFS | 11 vs 4.6 mo | HR 0.35; 95% CI 0.27–0.45; $P < 0.001$ |
| RADIANT-4 [15] | III | 205 | G1 nonfunctional NETs of the lung or GI | EVE 10 mg/day or placebo | PFS | 11.0 vs 3.9 mo | HR 0.48; 95% CI 0.35–0.67; $P < 0.00001$ |

*GI* gastrointestinal, *BSC* best supportive care, *SSAs* somatostatin analogues, *PFS* progression-free survival, *ORR* objective response rate, *EVE* everolimus, *mo* months

RADIANT-1 is a multinational, single-arm phase II trial that evaluated everolimus 10 mg/day in patients with *advanced pNETs* refractory to cytotoxic chemotherapy. Patients who were previously on SSAs were continued on this regimen. This trial demonstrated an 8.7% objective response rate, and 84.7% of patients had at least stable disease. Median PFS was 9.7 months in patients receiving everolimus alone and 16.7 for everolimus and octreotide treatment. Median overall survival was 24.9 months in the everolimus group and had not yet been reached at the time of publication in the everolimus plus octreotide group [12].

The RADIANT-2 trial is a multicenter, randomized, placebo-controlled phase III trial looking at the role of adding everolimus 10 mg/day or placebo to octreotide LAR 30 mg every 28 days in patients with *advanced NETs and carcinoid syndrome*. Median PFS was 16.4 months in the everolimus group compared with 11.3 months in the placebo group. Although this trial demonstrated that treatment with everolimus was associated with a reduced risk of progression of 23%, the hazard ratio (0.77; $p = 0.026$) fell short of achieving statistical significance based on the prespecified cutoff value ($p = 0.0246$) [13].

RADIANT-3 is a multicenter, double-blind, randomized phase III trial that evaluated everolimus in patients with unresectable or *metastatic low- or intermediate-grade pNETs* progressing to prior chemotherapy or other systemic treatments. Patients received either everolimus 10 mg/day or placebo in addition to best supportive care, including SSAs in 40% of cases. PFS was 11 months for the everolimus group versus 4.6 months in the placebo group, with a hazard ratio for disease progression or death with everolimus of 0.35 ($p < 0.001$); no significant difference was documented in overall survival between the two treatment arms of the RADIANT-3 trial, since the trial design allowed crossover at disease progression [14].

RADIANT-4 is a randomized, double-blind, placebo-controlled, phase III trial that evaluated the PFS in patients with *advanced, progressive, well-differentiated, nonfunctional neuroendocrine tumors of the lung or gastrointestinal origin* treated with everolimus 10 mg/day or placebo. At central review analysis, everolimus-treated patients showed a prolonged median PFS, as compared with those receiving placebo (11.0 vs 3.9 months; HR 0.48; 95% CI 0.35–0.67; $p < 0.00001$); similar results were observed at investigator assessment (14.0 vs 5.5 months; HR 0.39; 95% CI 0.28–0.54; $p < 0.00001$). This benefit in PFS was achieved in all subgroup analyses. The first pre-planned interim OS analysis suggested that everolimus might be associated with a reduction in the risk of death (HR 0.64; 95% CI 0.40–1.05; $p = 0.037$, whereas the boundary for statistical significance was 0.0002) compared with placebo [15].

*Sunitinib malate* is a multitargeted tyrosine kinase inhibitor, whose targets include vascular endothelial growth factor receptors (VEGFRs) and stem cell factor receptor (c-KIT). A phase III (SUN-1111), randomized, double-blind, placebo-controlled trial was conducted to assess the efficacy and safety of continuous daily administration of sunitinib 37.5 mg/day in patients with advanced pancreatic neuroendocrine tumors. The study was discontinued early after the observation of serious adverse events and deaths in the placebo group as well as a difference in progression-free survival favoring sunitinib. Median progression-free survival was 11.4 months in the sunitinib group as compared with 5.5 months in the placebo group (hazard ratio for progression or death, 0.42; 95% confidence interval [CI], 0.26–0.66; $P < 0.001$) [16].

In 2016, the updated progression-free survival and the final overall survival of SUN-1111 were published. Five years after study closure, median OS was 38.6 months for sunitinib and 29.1 months for placebo (HR 0.73; 95% CI 0.50–1.06; $P = 0.094$), with 69% of placebo patients having crossed over to sunitinib; median PFS was 12.6 months for sunitinib and 5.8 months for placebo (HR 0.32; 95% CI 0.18–0.55; $P = 0.000015$). The authors conclude for the doubling of PFS with sunitinib compared with placebo [17].

*Cabozantinib* (XL-184) is a potent inhibitor of MET, VEGFR2/KDR, RET, and other receptor tyrosine kinases, such as KIT, AXL, and

FLT3. In an open-label phase II trial, cabozantinib demonstrated clinical activity in patients with advanced carcinoid and well or moderately differentiated pNET. Patients received cabozantinib 60 mg daily in 28-day cycles. A somatostatin analogue was allowed if the dose was stable for 2 months. There was no limit to prior therapy. The primary objective was to evaluate the overall response rate. Partial responses were observed in 15% of each cohort treated with cabozantinib, and stable disease was the best response in about two-thirds of patients. Median progression-free survival was 21.8 months (95% CI 8.5–32.0). Adverse events were consistent with those reported with the use of cabozantinib in other diseases. Grade 3/4 toxicity included hypertension in 13% of patients, hypophosphatemia in 11%, diarrhea in 10%, lymphopenia in 7%, thrombocytopenia in 5%, fatigue in 5%, and increased lipase or amylase in 8%. At present, a confirmation of cabozantinib activity in a randomized phase III trial in carcinoid tumors and pNETs is in development [18].

## 21.4 The Role of Chemotherapy in Advanced and Metastatic GEP-NETs

The majority of well-differentiated GEP-NETs have an indolent behavior, but in patients who develop clear tumor progression, systemic chemotherapy may be useful. Cytotoxic chemotherapy has been tested in GEP-NETs since the 1980s, but treatment recommendations are controversial in many instances.

*Streptozotocin* (STZ) was the most studied chemotherapy agents in NETs. The efficacy of STZ alone or in combination with 5FU and doxorubicin is documented by several small nonrandomized trials.

A recent systematic review and meta-analysis try to evaluate the role of "standard" combination of STZ and 5FU comparing its activity with the other available chemotherapy regimens. The results do not show any significant differences in terms of overall response rate, progression-free survival, and overall survival [19–24].

Other drugs that showed efficacy in NETs are dacarbazine, cisplatin, capecitabine, etoposide, carboplatin, temozolomide, and irinotecan, but due to the lack of data, also ENETS, NANETS, and NCCN guidelines do not give any clear suggestion about the ideal schedules and specific indication [25–27].

Differently to NETs, chemotherapy is the standard treatment for metastatic poorly differentiated neuroendocrine carcinoma (NEC) in which it represents the only therapeutic option. The standard combination is cisplatin and etoposide or irinotecan. Although these neoplasms are more chemosensitive than NETs (ORR about 55%), the prognosis is extremely poor [28].

## 21.5 Treatment Selection and Sequences

Considering the long median survival, documented in patients with diagnosis of locally advanced and metastatic NETs, one of the aims of treatment is the continuum of care that could be achieved by the individualization of the best therapy sequence. Comparing the different available guidelines, we could find some suggestions about the selection for first, second, and further lines of treatment, but the ideal sequence and how one therapy could influence the subsequent treatment outcomes are unknown. If we take, for example, NETs of the midgut, the favorable toxicity profile of somatostatin analogues makes them a good first choice for many patients [6, 8], but beyond first-line, physicians and patients often face decisions regarding where to proceed next, and for some patients with liver-dominant disease, liver-directed therapies are still an option. For others, everolimus is a systemic option, and then lutetium dotatate will be an option based on approval of the drug. Knowing how to choose among these three treatments is going to be a challenge. It's even more complicated for pancreatic NETs. Beyond somatostatin analogues, we have several strategies: everolimus, sunitinib, cytotoxic chemotherapy, liver-directed therapy, and peptide receptor radiotherapy. The use of everolimus or sunitinib is supported by

randomized data, and their use is appropriate in this setting [14, 17]. Although no large, randomized trials have yet been completed with streptozocin- or temozolomide-based regimens, these are clearly active in pancreatic NETs and are associated with higher tumor response rates than somatostatin analogues or the biological agents. Cytotoxic therapies may also be an upfront treatment for highly symptomatic patients when tumor shrinkage rather than disease stabilization is the primary objective [19–24]. Moreover concomitant diseases of the patient and the different toxicity profiles could help clinicians to personalize treatment strategy. Combination therapies may be feasible, and effective but randomized trials are clearly needed to assess the safety and the efficacy of these regimens when compared with single-agent therapy.

At present, the landscape of therapeutic options for patients with poorly differentiated neuroendocrine carcinomas (NECs) is still lacking. For metastatic NECs the combination of cisplatin/etoposide is considered a standard option offering high rate of tumor response, but at the same time, short-lasting duration of response and high toxicity are reported [28].

There are a number of trials taking place looking at immunotherapy. If these agents work anywhere in the neuroendocrine field, they are more likely to work in poorly differentiated or high-grade tumors given the high mutational burden of these cancers.

In conclusion, there is a lack of real standard approaches and therapeutic sequences for metastatic GEP-NETs and NECs, and the appropriate selection and sequencing of treatments currently depend on clinical judgment.

Due to the complexity and heterogeneity of NETs, every treatment choice should take place in the setting of a multidisciplinary neuroendocrine tumor board.

To date research efforts are focused on translational studies in order to better select the patients who could benefit from different treatment options. Furthermore clinical trials comparing one agent to another would be beneficial in order to find the best treatment strategy.

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