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Current Opinion in
Endocrine and Metabolic Research

Review

Medical treatment of neuroendocrine neoplasms

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Abstract

Medical therapy of clinically nonfunctioning (nonsecreting) low grade (grade 1–2) neuroendocrine neoplasms consists of first-line first generation somatostatin analogs and second-line or third-line peptide receptor radiotherapy with radiolabeled beta-emitting somatostatin analogs, Everolimus, Sunitinib, and interferon-α. Second-generation somatostatin analogs like Pasireotide have no proven superiority over first-generation somatostatin analogs. Chemotherapy is usually reserved as second-line therapy in pancreatic neuroendocrine neoplasms and neuroendocrine carcinomas.

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Current Opinion in Endocrine and Metabolic Research 2021, **18:**139–144

This review comes from a themed issue on **Neuroendocrine Tumors**

Edited by **Gregory Kaltsas** and **Ashley Grossman**

For complete overview of the section, please refer the article collection - Neuroendocrine Tumors

Available online 6 April 2021

https://doi.org/10.1016/j.coemr.2021.03.019

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Keywords

Neuroendocrine, Somatostatin, Receptor, Octreotide, Lanreotide, Chemotherapy, Interferon, Sunitinib, Everolimus, Pasireotide, PRRT, Peptide receptor radiotherapy, DOTATATE, DOTATOC, Telotristat.

Watchful waiting might still be an option in patients with unresectable (metastatic) neuroendocrine neoplasms (NEN)

Given the indolent nature of a subset of low-grade well-differentiated neuroendocrine neoplasms (NEN), which may show an indolent growth pattern, not all patients with irresectable or metastasized NEN may require antiproliferative therapies, especially not in the absence of hormonal hypersecretion [1]. In this paper, only the different medical options will be discussed [2].

Somatostatin analogs (SSAs) are the preferred first-line therapy in differentiated gastroenteropancreatic neuroendocrine neoplasms (GEP NEN)

The first-generation, currently used, somatostatin analogs (SSAs) act through binding to somatostatin receptor subtypes (SSTs), particularly SST_2, and to a lesser extent, SST_3 and SST_5. These receptors are generally widely expressed on well-differentiated grade 1–2 (G1-2) NEN, as well as on a proportion of G3 NEN [3,4]. Two randomized placebo-controlled phase 3 trials, PROMID, including 85 treatment-naive patients with locally inoperable or metastatic G1 midgut neuroendocrine tumors (NET), and CLARINET, including 204 patients with nonfunctioning, SST-positive, GEP NET, and a Ki67 index below 10% have confirmed the growth-stabilizing effect of these first-generation SSAs in NET [5,6]. In the PROMID trial, the median time since diagnosis was 4.3 months, 66% of patients had undergone resection of the primary tumor, and carcinoid syndrome was diagnosed in 39% of patients. Patients treated with octreotide LAR 30 mg every 4 weeks had significantly prolonged time to progression (TTP) (median 14.3 months) as compared with placebo-treated patients (median 6.0 months). However, the overall survival (OS) was equal in both groups, and objective response (OR) was only seen in 2% of patients treated with octreotide LAR [6,7]. In the CLARINET trial, the median time since diagnosis was >1 year, 39% of patients had undergone resection of the primary tumor, only 4% of patients had documented progression at baseline, and 16% had received prior treatment. Again, similar to the PROMID trial, patients treated with Lanreotide Autogel 120 mg every 4 weeks had significantly longer progression-free survival (PFS) (median 32.8 months) as compared with placebo-treated patients (median 18.0 months). In the CLARINET trial, the great majority of patients (69%) had G1 tumors [5]. There is, however, a striking difference between the PFS and TTP in the placebo arms of both trials, stressing the importance of selecting appropriate study groups. In the CLARINET trial, patients progressing on placebo were allowed to switch to lanreotide, which resulted in a PFS of 14.0 months after cross-over [5,8]. Both studies led to the

international approval of both SSAs as first-line treatment in nonfunctioning/nonsyndromic midgut NET (octreotide LAR 30 mg every 4 weeks) and GEP NET (Lanreotide Autogel 120 mg every 4 weeks) [9].

The efficacy of SSAs in NEN of another primary origin, like the respiratory tract, is investigated in ongoing prospective trials, like the SPINET trial (NCT02683941). SSAs should not be considered as a primary antiproliferative treatment for patients with fast-growing NET, massive bulky disease, or neuroendocrine carcinoma (NEC) [1]. Over time, the SSA-treated NEN may become refractory to the antigrowth effects of the somatostatin analogs [10]. However, it seems that their efficacy may be (temporarily) restored by either increasing the dosage or shortening the time interval between dosages, as shown in the CLARINET Forte (NCT02651987) trial and the control arm of the NETTER-1 trial [11].

At present, the immediate-release, short-acting form of octreotide is indicated in the management of refractory carcinoid syndrome as an adjunct to longer-acting formulations or in the treatment of carcinoid crisis and in the peri-interventional setting to prevent the occurrence of carcinoid crisis [12,13].

For many years, SSAs have been the principal treatment for hormonal hypersecretion in the carcinoid syndrome, VIPoma syndrome, and other selected hyperfunctioning pancreatic NEN, like glucagonomas, somatostatinomas, and selected insulinomas [4,14,15]. Our meta-analysis has shown clinical response rates in 65–70% of carcinoid syndrome patients with equal efficacy of the two major SSAs, octreotide LAR and Lanreotide autogel [16]. There is an ongoing debate whether perioperative infusion with octreotide is needed in symptomatic patients with the carcinoid syndrome who are already treated with long-acting SSAs in order to prevent a carcinoid crisis, but most studies recommend this approach [12,13,17,18].

Side effects that finally lead to discontinuation of SSA therapy are rare and include increased abdominal pain and other gastrointestinal symptoms. Long-term side-effects apart from GI symptoms include the development of biliary sludge/gallstones that cause symptomatic disease in <1%, hypoglycemia or hyperglycemia, arrhythmia (long QT), pancreatic enzyme insufficiency (causing steatorrhea), and vitamin deficiencies (predominantly vitamins B12 and D) [1,3,19,20].

The second-generation, multi-SST agonist, Pasireotide, which has a high affinity for all SSTs, except SST_4, has regretfully not shown superiority to 40 mg octreotide LAR every 4 weeks in patients with GEP NET, including patients with refractory symptoms of hormonal hypersecretion [21,22]. As Lung NET generally express lower levels of SST_2, Pasireotide might be a better candidate SSA for patients with these tumors. At 9 months in the prospective, multicenter, randomized, open-label, phase 2 trial of patients with advanced, progressive, well-differentiated carcinoid tumors of the lung or thymus (LUNA trial), disease control was found in 16 of 41 patients (39%) treated with Pasireotide LAR (60 mg/4 weeks) [23]. In the COOPERATE-2 study, the efficacy and safety of Pasireotide LAR (60 mg every 4 weeks) plus Everolimus (10 mg q.d.) to Everolimus (10 mg q.d.) alone in patients with advanced, well-differentiated, progressive panNEN was studied. Seventy-nine patients were randomized to the combination trial arm and 81 to the Everolimus arm. The addition of Pasireotide to Everolimus was not associated with the improvement in PFS as compared with Everolimus alone in this study (16.8 months versus 16.6 months, respectively) [24]. Pasireotide is currently not registered for the treatment of NEN patients.

Second-line and third-line therapies in differentiated gastroenteropancreatic neuroendocrine neoplasms (GEP NEN)

Radionuclide therapy

Peptide receptor radionuclide therapy (PRRT) with beta-emitting SSAs: yttrium-90 (^{90}Y) coupled to Tyr3-octreotide (^{90}Y-DOTATOC) and lutetium-177 (^{177}Lu) coupled to octreotate, or Tyr^3-octreotide (^{177}Lu-DOTATATE, or ^{177}Lu-DOTATOC) are effective second-ine or third-line treatment options for metastasized or unresectable SST-positive NEN. At present, mostly ^{177}Lu-coupled radiochemicals are used [25].

The efficacy of PRRT with ^{177}Lu-DOTATATE was shown in the phase III NETTER-1 randomized controlled trial in 229 patients with metastasized midgut NET progressive on first-line therapy with a standard dose of octreotide LAR (30 mg every 4 weeks). In this trial, 80% of patients had undergone resection of the primary tumor, and 69% of tumors were classified as G1. Approximately half of the patients had been treated with another line of therapy. The risk of PD or death was 79% lower in patients treated with PRRT in combination with octreotide LAR 30 mg/4 weeks than those treated with a double dose (60 mg every 4 weeks) octreotide LAR [11,26]. In a large series of 443 NEN patients from our institution treated with ^{177}Lu-DOTATATE, the objective response rate was 39%. SD was reached in 43% of patients, PFS and overall survival (OS) for all NEN patients were 29 and 63 months, respectively [27]. PRRT also gave a clinically significant improvement in quality of life [25,28,29]. The combined data from the NETTER-1 trial and the Erasmus MC, Rotterdam, the Netherlands, finally led to the approval of PRRT with ^{177}Lu-DOTATATE for the treatment of patients with unresectable, progressive, G1 and 2 SSTR-positive GEP NEN and bronchopulmonary

NEN (USA) in adults by the FDA and EMA. Apart from its effects on tumor progression, PRRT with ^{177}Lu-DOTATATE can also result in the reduction of hormonal hypersecretion in hormone-producing GEP NEN [30](Zandee et al. submitted).

Relevant adverse effects of ^{177}Lu-DOTATATE include nausea associated with the infusion of kidney-protective amino acids, renal toxicity, transient bone marrow suppression, and the development of myelodysplastic syndrome or acute myeloid leukemia in 2% of cases [25,27,31].

Salvage treatment with additional cycles of PRRT with ^{177}Lu-DOTATATE is considered a relevant option after renewed progression of the disease [32].

Everolimus

Activation of the mTOR cascade plays an important role in the proliferation, growth, and apoptosis of GEP and bronchopulmonary NEN through the downstream effects of the phosphatidylinositol 3-kinase/AKT pathway [9]. The mTOR inhibitor Everolimus can be currently considered as a registered second-line therapy in patients with unresectable G1-2 GEP and bronchial NEN. The antiproliferative effect of Everolimus was studied in three randomized controlled RADIANT trials. In the RADIANT-3 trial, including 410 low-grade panNEN patients with PD, Everolimus (10 mg q.d.) increased PFS to 11.0 months as compared to 4.6 months in the placebo group. About 83% of patients had a G1 pancreatic NET (panNET), while 24% of panNENs were hormone-secreting [33]. Similarly, in the RADIANT-2 in patients with advanced low-grade NEN and carcinoid syndrome, Everolimus (10 mg/day) plus octreotide LAR (30 mg/week) prolonged PFS to 16.4 months compared with 11.3 months for placebo plus octreotide LAR. However, there was no significant difference in OS between the Everolimus arm and treatment arm in this study [34,35]. In the EVERLAR study, results in nonfunctioning gastrointestinal NETs were similar to the RADIANT-2 trial [36]. Again, in the RADIANT-4 trial in 302 patients with advanced nonfunctional well-differentiated NEN of the respiratory and GI tract, the PFS was 11.0 in the patients treated with Everolimus (10 mg q.d.) compared to 3.9 months in the placebo group. All study patients had documented PD at baseline; 54% had been treated with SSA, 25% with chemotherapy, and 21% with radiotherapy; 65% of tumors were G1 [37]. In the abovementioned LUNA trial, Everolimus treatment (10 mg q.d.) resulted in an objective response in 14 of 42 patients (33%), and the combination of the same dose of Everolimus and pasireotide LAR (60 mg every 4 weeks) resulted in an objective response in 24 of 41 patients (58%). In hormone-producing NEN, Everolimus treatment can also reduce hormonal hypersecretion in parallel with inhibition of tumor progression [38]. Both Pasireotide and Everolimus, and particularly their combination, can lead to severe hyperglycemia, making these drugs less attractive, except for patients with metastatic insulinomas [39]. Long-term treatment with Everolimus is associated with primary and acquired resistance, which limits its long-term benefit for NEN [40,41].

Frequent adverse effects reported with Everolimus include stomatitis, rash, diarrhea, fatigue, infections, diabetes mellitus, and pneumonitis [14].

Sunitinib

Sunitinib is an oral multitargeted tyrosine kinase inhibitor (TKI) that inhibits PDGFR, VEGFR1/2, c-KIT, FLT-3, among others. Production and effects of VEGF have been demonstrated in NEN, which are generally highly vascularized [9]. In a phase 3 randomized clinical trial in 171 PanNET patients with documented PD at baseline, Sunitinib (37.5 mg q.d.) treatment prolonged the PFS to 11.4 months (later adjusted to 12.6 months) as compared with 5.5 months (5.8 months) for placebo-treated patients. OS improved nearly by 10 months—38.6 months. Approximately half of the patients had a functioning tumor, and more than 80% had a G2 tumor, while 43% had used or were still using SSAs during the study, and 81% of patients had been treated with chemotherapy in the past. However, quality of life did not improve [42,43]. This study led to the approval of Sunitinib for the treatment of progressive well-differentiated nonresectable panNEN. Other TKIs like Axitinib, Cabozantinib, Nintedanib, Pazopanib, Sorafenib and Sulfatinib may have similar actions on panNEN but are not yet approved for therapy [44,45]. Like with Everolimus, long-term treatment with Sunitinib is associated with primary and acquired resistance, which limits its long-term benefit for NEN [40,41].

Adverse effects of Sunitinib include neutropenia, hypertension, diarrhea, nausea, fatigue, thyroid dysfunction, palmar—plantar erythrodysesthesia, and hypertension [14,46].

Immunotherapy

Interferon-α was a once more popular treatment for metastasized GEP NETs or carcinoid syndrome. The limited efficacy combined with the poor tolerability of this drug has restricted its use to selected patients with refractory functional midgut NET with doses ranging from 3 to 5 million U 3 times per week. In a meta-analysis on the effects of interferon-α in NEN, tumor response rates were found to be only 11% [47], which explains the diminished popularity of this treatment nowadays. The Southwest Oncology Group (SWOG) S0518 study was conducted to determine whether depot octreotide (20 mg every 21 days) plus Bevacizumab

(15 mg/kg every 21 days) prolonged PFS compared with octreotide LAR (20 mg every 21 days) plus interferon-α (5 million U t.i.w.) in patients with advanced G1-2 NEN; 213 patients were allocated to octreotide LAR and interferon-α. The median PFS by central review was 15.4 months, and by site review, 10.6 months. The confirmed radiologic response rate was 4% for the combination of octreotide LAR and interferon-α [48].

Interferon-α treatment has unfavorable, sometimes intolerable side effects like fatigue, fever, and flu-like symptoms, autoimmune disorders, thyroid dysfunction, and liver enzyme abnormalities [47,48].

The efficacy of immune checkpoint inhibitors is most probably restricted to a subset of higher grade NEN with high numbers of tumor-infiltrating lymphocytes [49], but clinical trials are ongoing.

Chemotherapy

Chemotherapy has a poor response rate in well-differentiated (G1-2) NEN in the gastrointestinal tract. Better response rates can be achieved in metastatic well-differentiated grade 2 panNEN. Until recent years, the most used chemotherapeutical for panNEN was streptozotocin (STZ) in combination with doxorubicin, 5-fluorouracil, or cyclophosphamide. More recently, it was shown that temozolomide and capecitabine may be superior and less toxic [50]. The response to temozolomide most probably depends on the expression of the DNA repair enzyme, O6-methylguanine DNA methyltransferase (MGMT) in these tumors; tumors with high MGMT levels show a lower response rate [51]. This might also explain why panNET responds better to this alkylating agent than midgut NET. In NEC, platinum-based regimens historically constitute the first line of choice. The reader is referred to the widely available oncology literature [52–54].

Serotonin pathway inhibitors

The serotonin synthesis inhibitor telotristat ethyl is registered for its use in the treatment of carcinoid syndrome-related diarrhea. In a placebo-controlled trial, telotristat ethyl 250 mg tid was shown to reduce the daily bowel movements by almost one in patients with four or more stool episodes per day [16,55,56]. The drug does not seem to exert antineoplastic activity in neuroendocrine tumors [57].

Conflict of interest statement

WWH received speaker fees from Novartis – AAA, Ipsen and Pfizer and research support from Ipsen.

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