Medical management of gastrointestinal neuroendocrine tumors

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Purpose of review
To summarize the recent developments in the medical treatment of gastrointestinal neuroendocrine neoplasms.

Recent findings
The medical management of gastrointestinal neuroendocrine tumors (GI-NETs) continues to evolve with advances in the management of symptoms related to hormone hypersecretion and therapeutic control of disease progression. Systemic therapy options include somatostatin analogs (SSAs), radiolabeled SSAs, molecularly targeted agents, and cytotoxic therapy. Recent progress has focused on new targeted therapies, the sequencing of therapy and the role of immunotherapy.

Summary
This review will focus on treatment of GI-NETs and highlight new developments published over the last year.

Keywords
^{177}Lu-dotatate, carcinoid syndrome, everolimus, gastrointestinal tract, neuroendocrine tumors, somatostatin analogs, tyrosine kinase inhibitors

INTRODUCTION

Gastrointestinal neuroendocrine tumors (GI-NETs) are a heterogeneous group of tumors, which originate from enterochromaffin cells of the diffuse neuroendocrine system of the gut [1]. Because of their heterogeneity, classification based on pathologic features and clinical behavior has been utilized to guide therapeutic strategies. Important pathologic considerations include differentiation status and grade. Well differentiated NETs have a more indolent biology compared with poorly-differentiated neuroendocrine carcinomas; similarly, low-grade and intermediate-grade NETs have a lower proliferative rate and more indolent biology compared with high-grade tumors. The goals of therapy for patients with advanced disease are to improve symptoms related to hormone hypersecretion, slow disease progression, and improve survival. Multiple options are available for the management of patients with advanced, metastatic GI-NET, including surgical resection, liver-directed therapies for patients with metastases predominantly in the liver, and systemic therapy.

Advances in the understanding of the biology of well differentiated GI-NETs has resulted in an expansion of treatment options for patients over the last decade, with systemic therapy options broadening to include somatostatin analogs, radiolabeled somatostatin analogs, molecularly targeted agents including everolimus, and cytotoxic chemotherapy. Recent advances have focused on radiolabeled somatostatin analogs, molecularly targeted agents, and investigations regarding the efficacy of immunotherapy. This review will focus on the medical management of well differentiated GI-NET and recent progress in systemic therapy.

MANAGEMENT OF SYMPTOMS RELATED TO HORMONE EXCESS

Neuroendocrine cells and tumors exhibit physiological attributes of the neural and endocrine

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KEY POINTS

- Systemic treatment options for disease control in patients with advanced GI-NET include somatostatin analogs, everolimus, and ^{177}Lu-dotatate.
- In addition to somatostatin analogs, telotristat ethyl, an inhibitor of serotonin synthesis can also improve diarrhea in patients with carcinoid syndrome not well controlled with somatostatin analogs.
- Recent results have demonstrated antiproliferative activity of several tyrosine kinase inhibitors targeting VEGFR in patients with GI-NET.
- The role of immunotherapy in the treatment of GI-NET remains unclear but is under investigation.

regulatory systems. As a result, NETs are characterized by their ability to secrete peptide hormones that can lead to symptoms related to hormone excess. NETs are classified as functional tumors if patients experience symptoms because of hormone hypersecretion by the tumor cells. The most well described clinical syndrome is the classical carcinoid syndrome, with manifestations including diarrhea, flushing, and bronchospasm related to secretion of serotonin and other vasoactive peptides.

Nearly 80% of well differentiated GEP-NET cells express high levels of somatostatin receptors (SSTR) [2]. Somatostatin analogs (SSAs), including octreotide and lanreotide, bind to SSTR expressed on neuroendocrine tumor cells and can result in both antisecretory and antiproliferative actions. The efficacy of SSA for treatment of carcinoid syndrome was first noted with short-acting octreotide at a dose of 150 μg subcutaneously three times per day; 88% of patients experienced improvement in flushing and diarrhea, and 72% achieved reduction in serotonin secretion as measured by reduction in urinary levels of its breakdown product 5-hydroxyindolacetic acid (5-HIAA) [3]. Utilizing similar mechanisms of action and binding affinities to somatostatin receptor subtypes, the long-acting formulations of octreotide – long acting release (LAR) and lanreotide autogel, administered every 4 weeks, can also partially or completely improve symptoms of carcinoid syndrome and has eliminated the need for many patients to self-administer daily injections [4–6].

Many patients with carcinoid syndrome treated with SSAs have sub-optimal control or become refractory to SSAs over time. An option that can be considered in these patients includes telotristat ethyl, which inhibits tryptophan hydroxylase, the rate-liming enzyme in serotonin biosynthesis. In the phase III TELESTAR and TELECAST trials, patients with carcinoid syndrome diarrhea experienced significant reduction in bowel movement frequency with the use of telotristat [7,8]. The TELESTAR trial enrolled patients with more than four bowel movements per day on a stable dose of SSA, whereas TELECAST was open to patients with less than four bowel movements per day and did not require SSA therapy. In the TELESTAR and TELECAST trials, telotristat ethyl resulted in at least 30% reduction in daily bowel movement as well as a decrease in urine-5HIAA compared with placebo. Data from a recent follow-up analysis demonstrated that sustained reduction in bowel movement frequency of more than 30% was achieved with telotristat 250 mg three times a day (TID) after a median of 19 days in the TELESTAR and 34 days in the TELECAST trials. The timing of response varied among patients. The earliest and latest sustained improvements in the TELESTAR and TELECAST trials were 3 and 73 days, respectively [9▪]. This data provides an expectation regarding time to onset of improvement in bowel movement frequency with use of telotristat, and can be used as a guide in the initial assessment of drug benefit in patients with carcinoid syndrome diarrhea.

SYSTEMIC TREATMENT OF ADVANCED GASTROINTESTINAL NEUROENDOCRINE TUMORS

Somatostatin analogs and radioactive somatostatin analogs

The antiproliferative effects of SSAs were demonstrated in the placebo-controlled phase III PROMID and CLARINET trials [10–12]. In the PROMID trial, treatment of patients with midgut NETs with octreotide LAR 30 mg every 28 days was associated with an improvement in time to progression (TTP) of 14.3 months compared with 6 months in the placebo arm [hazard ratio 0.34; 95% confidence interval (CI) 0.2–0.59; $P = 0.000072$] [11]. In the CLARINET trial, treatment of patients with pancreatic and midgut NETs treated with lanreotide 120 mg every 28 days was associated with a median progression-free survival (PFS) of 32.8 months compared with 18 months for the placebo arm (hazard ratio 0.47; 95% CI 0.30–0.73) [12]. Because of their antiproliferative and antisecretory effects, and also ease of administration and tolerability, SSAs are generally considered as a first-line therapeutic option in well differentiated gastroenteropancreatic NETs (Table 1).

Peptide receptor radionuclide therapy (PRRT) is a therapeutic strategy in which SSAs are conjugated with a chelator and a radionuclide to deliver tumoricidal doses of radiation. In the NETTER-1 trial, 229 patients with well differentiated, metastatic midgut NETs were randomized to receive either ^{177}Lu-

Table 1. Key randomized trials of approved agents for tumor control in gastrointestinal neuroendocrine tumors

Trial Name	Agent	Number of patients	Tumor type	Study arms	RR (%)	Median TTP or PFS (months)
PROMID [11]	Octreotide LAR	85	Midgut	Octreotide vs. placebo	2%	14.3 vs. 6 HR 0.34; 95% CI 0.2–0.59
CLARINET [12]	Lanreotide	204	GI and pancreatic NET	Lanreotide vs. placebo	Not reported	Not reached vs. 18 HR 0.47; 95% CI 0.30–0.73
RADIANT-2 [21]	Everolimus with octreotide	429	NET with carcinoid syndrome	Everolimus with octreotide vs. placebo with octreotide	2%	16.4 vs. 11.3 HR 0.77; 95% CI 0.59–1.00
RADIANT-4 [20]	Everolimus	302	GI and lung NET	Everolimus vs. placebo	2%	11.0 vs. 3.9 HR 0.48; 95% CI 0.35–0.67
NETTER-1 [13]	^{177}Lu-Dotatate	229	Midgut	^{177}Lu-Dotatate vs. Octreotide LAR 60 mg	18%	40 mo. (expected) vs. 8 HR 0.21; 95% CI 0.13–0.33

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; RR, radiographic response rate; TTP, time to progression.

Dotatate at a dose of 7.4 GBq every 8 weeks followed by maintenance octreotide LAR 30 mg (LU arm) or high-dose octreotide LAR at a dose of 60 mg every 4 weeks (OCT arm). PFS was significantly improved in the LU arm compared with OCT arm; the median PFS was not reached in the LU arm compared with 8.4 months in the OCT arm (hazard ratio 0.21; 95% CI 0.13–0.33) [13]. In the final analysis of overall survival (OS), median OS was 48 months in the LU arm and 36.3 months in the OCT arm. This difference was not statistically significant, possibly related to a high rate of cross-over from the control arm to radioligand therapy after progression. To address this issue and nonproportional hazards, an analysis of restricted mean survival time at various time intervals was conducted. This demonstrated a numerically longer survival at all time points in patients receiving ^{177}Lu-dotatate compared with those receiving high-dose octreotide, suggesting not only PFS benefit but also OS benefit with ^{177}Lu-Dotatate in patients with metastatic midgut NET [14▪▪,15▪▪].

A major secondary endpoint of the NETTER-1 trial was measurement of health-related quality of life (HRQoL) utilizing the EORTC QLQ C-30 and G.I.NET-21 questionnaires. Time to deterioration (TTD) in HRQoL was significantly longer in the LU arm compared with the OCT arm in the global health, physical functioning, role functioning, diarrhea, pain, body image, disease-related worries, and fatigue domains. The most striking improvement was noted in the global health domain, with a 22.7 month prolongation in global health TTD compared with octreotide (hazard ratio 0.41, 95% CI 0.24–0.69; $P < .001$) [16]. A similar study of 70 patients utilizing EORTC QLQ-C30 questionnaire in patients with midgut NET demonstrated an improvement in global health status after each treatment cycle, with notable improvement of emotional functioning ($P < 0.001$) and cognitive functioning ($P = 0.003$ after the first cycle; $P = 0.05$ after the second cycle) [17].

Mechanistic target of rapamycin inhibitors

The mechanistic target of rapamycin (mTOR) is an intracellular serine/threonine kinase that regulates key cell functions involved in cell survival, proliferation, and metabolism [18]. mTOR mediates downstream signaling from a number of pathways, including VEGF and insulin-like growth factor (IGF) that are implicated in neuroendocrine tumor growth [19]. The activity of the mTOR inhibitor everolimus has been investigated in GI-NETs in two key phase III randomized trials. In the RADIANT-2 and RADIANT-4 trials, everolimus was evaluated in different patient groups: advanced grade 1–2 NET associated with carcinoid syndrome (RADIANT-2) and advanced nonfunctioning gastrointestinal and lung NETs (RADIANT-4) [20,21]. The RADIANT-2 trial enrolled patients with low and intermediate grade NETs with carcinoid syndrome who were randomized to receive octreotide LAR with everolimus vs. octreotide LAR with placebo. Fifty-eight percent of patients in this trial had GI-NETs. Although median PFS by central radiology review was longer in patients receiving octreotide and everolimus (16.4 vs. 11.3 months; hazard ratio 0.77; 95% CI 0.59–1.00), the result did not meet the predefined level of statistical significance [21]. Treatment with everolimus and octreotide LAR was associated a larger decline in 24 h urine 5-HIAA

and chromogranin A levels compared with placebo and octreotide LAR but the impact of everolimus on control of symptoms of carcinoid syndrome was not reported. In the RADIANT-4 trial, everolimus was associated with an improved median PFS of 11 months compared with 3.9 months for placebo (hazard ratio 0.48; 95% CI 0.35–0.67) [20]. On the basis of these clinical trial results, everolimus is currently Food and Drug Administration (FDA)-approved for the treatment of patients with non-functional GI-NET and lung NET.

Vascular endothelial growth factor pathway and multitargeted tyrosine kinase inhibitors

NETs are characterized by their hypervascular nature and expression of vascular endothelial growth factor (VEGF), a potent regulator of tumor angiogenesis [22]. Agents including monoclonal antibodies against VEGF and tyrosine kinase inhibitors (TKIs) with activity against VEGF receptors have demonstrated antitumor activity in phase II and phase III trials (see Table 2). The activity of bevacizumab, a monoclonal antibody, which directly targets VEGF, was suggested in a phase II and subsequent phase III trial, both demonstrating a radiographic partial response rate of 12–18% [23,24]. In the phase III trial, patients with advanced high-risk grade 1–2 NETs were randomized to receive bevacizumab with octreotide LAR vs. interferon alpha with octreotide LAR. The primary endpoint of PFS was not significantly different between the bevacizumab and interferon arms (median PFS 16.6 with bevacizumab vs. 15.4 months for interferon; hazard ratio 0.93; 95% CI 0.73–1.18) [24]. Interpretation of these trial results is complicated because of the use of an active control arm. This suggests that there may be efficacy for bevacizumab in this population of patients; nonetheless, a role for bevacizumab has not been established in patients with advanced GI-NET.

Multiple clinical trials have evaluated the role of multitargeted TKIs, which inhibit multiple receptors including VEGF receptors in patients with advanced GEP-NET. Although sunitinib is approved for patients with pancreatic NETs, its activity in GI-NET has not been established [27,28]. More recently, other TKIs, including pazopanib, surufatanib, and axitinib have been studied in randomized clinical trials compared with placebo. Pazopanib was evaluated in a randomized phase II clinical trial vs. placebo in patients with advanced well differentiated extrapancreatic NETs (Alliance A021202). Median PFS was 11.6 months in patients receiving pazopanib compared with 8.5 months for placebo (hazard ratio 0.53, one-sided 90% upper confidence limit 0.69, $P = 0.0005$) [29]. In the SANET-ep phase III trial comparing surafatinib to placebo in patients with advanced extrapancreatic NETs, median PFS by investigator assessment was significantly longer in patients receiving surufatanib compared with placebo (9.2 vs. 3.8 months, hazard ratio 0.33, 95% CI 0.22–0.5; $P < 0.0001$) [30▪▪] . In the randomized phase II/III AXINET trial (GETNE1107), 256 patients with extrapancreatic NET were randomized to

Table 2. Trials evaluating vascular endothelial growth factor pathway inhibitors in gastrointestinal neuroendocrine tumors

Agent	Target	Trial phase	Number of total patients	Number (%) with GI primaries	RR (%)	PFS (months)
Bevacizumab [24]	VEGF	III vs. placebo	427	143 (36%) small bowel, cecum, appendix	12 vs. 4%	16.6 vs. 15.4 (HR, 0.93; 95% CI 0.73–1.18)
Surufatanib [30▪▪]	VEGFR, FGFR-1, CSF-1R	III vs. placebo	198	93 (47%) GI	10 vs. 0%	9.2 vs. 3.8 (HR 0.33; 95% CI 0.22–0.50)
Axitinib [32]	VEGFR1–3, PDGFR	II/III vs. placebo	256	151 (59%) GI	17.5 vs. 3.8%	17.2 vs. 12.3 (HR 0.82; 95% CI 0.61–1.09))
Pazopanib [29]	VEGFR-1/2/3, PDGFR-α/β, c-KIT	II vs. placebo	171	(66%) small bowel	2%	11.6 vs. 8.5 (HR 0.53)
Lenvantinib [25]	VEGFR1–3, FGFR1–4	II	111	56 (50%) GI	16.4% in GI-NET cohort	15.7 (95% CI 12.1–19.5)
Cabozantinib [26]	VEGFR, MET, AXL, RET	II	61	41 (67%) nonpancreatic	15%	31.4 (95% CI, 8.5-NR) for nonpancreatic NET cohort

AXL, AXL receptor tyrosine kinase; CI, confidence interval; c-KIT, c-KIT receptor tyrosine kinase; CSF-1R, colony stimulating factor 1 receptor; FGFR, fibroblast growth factor receptor; GI, gastrointestinal; HR, hazard ratio; MET, MET receptor tyrosine kinase; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; RET, RET receptor tyrosine kinase; RR, radiographic response rate; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

receive axitinib or placebo in combination with octreotide LAR. Although the primary endpoint of improvement in median PFS by investigator assessment did not meet the criteria for statistical significance, median PFS by blinded independent radiology review was longer for patients receiving axitinib and octreotide LAR compared with those receiving placebo (16.6 vs. 9.9 months, hazard ratio 0.687, $P = 0.01$) [31,32]. The results of these studies provide evidence that the VEGF signaling pathway is a valid target for therapy in well differentiated GI-NETs. On the basis of the results of these trials, TKIs may become an option for therapy.

Cytotoxic chemotherapy

Cytotoxic chemotherapies have been evaluated in advanced well differentiated NETs. Although alkylating agents are active against pancreatic NET, the efficacy of cytotoxic chemotherapy appears to be lower in well differentiated GI-NET [33,34]. Thus, chemotherapy is not typically utilized for well differentiated GI-NET, except in cases with higher grade disease or more unfavorable biology [35▪,36▪].

Immunotherapy

Immunotherapy-based treatments remain under investigation in GI-NETs. Studies evaluating the role of single agent anti-PD-1 antibodies, including spartalizumab and pembrolizumab, have demonstrated limited activity in well differentiated NET [37,38]. Given the limited efficacy of single-agent checkpoint inhibitors, trials evaluating immunotherapy have focused on combinations with other immunomodulatory agents. The results of early-phase trials suggest that there may be activity of combination therapy with VEGF pathway inhibitors and immunotherapy. For example, in the extrapancreatic NET cohort of a phase II basket study evaluating the anti-PD-L1 antibody atezolizumab with bevacizumab in patients with rare cancers, the objective response rate was 15% (95% CI 3–38%) and median PFS 14.9 months (95% CI 6.1 to NR) [39]. The combination of TKIs with immunotherapy is also being evaluated in well differentiated NET. In addition to their ability to independently slow progression of well differentiated neuroendocrine tumors, TKIs also have immunomodulatory properties [40]. There are ongoing trials evaluating the clinical efficacy of checkpoint inhibitors with TKIs, including a phase II of pembrolizumab and lenvantinib in nonlung NETs (NCT03290079) and a phase II of nivolumab and cabozantinib in advanced extrapancreatic NETs (NCT04197310).

CONCLUSION

Gastrointestinal neuroendocrine tumors are increasing in incidence. Advances in treatment for GI-NETs over the last decade have translated into improved survival and patient outcomes. Systemic treatment options for disease control in patients with advanced GI-NET include SSAs, everolimus, and ^{177}Lu-dotatate. In addition, recent results from phase II and III trials have demonstrated antiproliferative activity of several tyrosine kinase inhibitors targeting VEGFR in patients with GI-NET. Control of carcinoid syndrome is an important aspect of patient care. SSAs can improve symptoms including flushing and diarrhea in patients with carcinoid syndrome. Telotristat ethyl, an inhibitor of serotonin synthesis, can also improve diarrhea in patients with carcinoid syndrome not well controlled with SSAs. Areas of investigation in the future include identifying predictors of response to treatment and investigation of novel agents.

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Conflicts of interest

K.P. has received a one-time Pancreatic Advisory Board fee for Celgene (5/2019); one-time HCC Advisory Board fee for Eisai (11/2019); and one-time Infigratinb Launch Preparation Advisory Board fee for Helsinn/QED (5/2021). J.C. has received consulting fees from Advanced Accelerator Applications, Crinetics, Ipsen, Lexicon/TerSera, and Novartis (spouse has consulted for Bayer and Pfizer); has received royalties from UpToDate; and has stock in Merck.

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- ▪ of special interest
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