Clinical Roundtable Monograph

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New and Emerging Treatment Options for Gastroenteropancreatic Neuroendocrine Tumors

Moderator

Alexandria T. Phan, MD
Director of GI Medical Oncology
Houston Methodist Cancer Center
Houston, Texas

Discussants

Pamela L. Kunz, MD
Assistant Professor of Medicine (Oncology)
Stanford University School of Medicine
Stanford, California

Diane L. Reidy-Lagunes, MD
Medical Oncologist
Memorial Sloan Kettering Cancer Center
New York, New York

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Abstract: Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are rare, generally indolent neoplasms that can arise throughout the gastrointestinal system. Some GEP-NETs, known as functional, secrete hormones that can lead to a complex of symptoms. Classical carcinoid syndrome is associated with flushing, diarrhea, bronchospasm, and symptoms of valvular heart disease. GEP-NETs are classified according to the primary tumor site, functionality of the disease, and histology. Treatment is guided by the resectability of the tumor, the location and extent of metastases, and the presence of clinical symptoms. Typically, first-line treatment of patients with unresectable disease includes the use of somatostatin analogs, such as octreotide LAR depot or lanreotide depot/autogel, which was recently approved by the US Food and Drug Administration for treatment of GEP-NETs. Somatostatin analogs can improve the severe diarrhea/flushing episodes that may be associated with metastatic carcinoid tumors. For patients with pancreatic NETs, additional approved treatment options include the targeted agents everolimus and sunitinib, which have demonstrated antitumor activity. Chemotherapy may also have a selective role, particularly in pancreatic NETs. Localized approaches, including cytoreductive surgery, hepatic arterial embolization, and ablative therapies, may be used for palliative treatment in patients with liver metastases.

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Target Audience

This activity has been designed to meet the educational needs of oncologists and nurses involved in the management of patients with gastroenteropancreatic tumors (GEP-NETs).

Statement of Need/Program Overview

Neuroendocrine tumors (NETs) are epithelial neoplasms that originate from neuroendocrine cells in almost any anatomic location. NETs are most likely to develop in the gastrointestinal tract and pancreas; these tumors are known as gastroenteropancreatic (GEP) NETs. Functional GEP-NETs secrete hormones that can lead to carcinoid syndrome and associated flushing, diarrhea, bronchospasm, and valvular disease. GEP-NETs are classified according to the primary tumor site, type of hormone secreted, and tumor differentiation. Treatment is guided by the resectability of the tumor, the location and extent of metastases, and the presence of clinical symptoms. Guidelines are available from several expert panels. Patients with bulky disease or functionally symptomatic disease require treatment. Options include surgery, local therapy, and pharmacotherapy, including targeted agents. The somatostatin analogs octreotide LAR depot and lanreotide depot/autogel have revolutionized the treatment of patients with carcinoid syndrome. Lanreotide depot/autogel was approved by the US Food and Drug Administration (FDA) in 2014 for the treatment of patients with unresectable, well- or moderately differentiated, locally advanced or metastatic GEP-NETs to improve progression-free survival. For patients with pancreatic NETs, other treatment options include the targeted agents everolimus and sunitinib, which have demonstrated antitumor activity. Chemotherapy can also play a role, particularly in pancreatic NETs.

Educational Objectives

After completing this activity, the participant should be better able to:

- Describe the clinical characteristics and natural history of gastroenteropancreatic neuroendocrine tumors
- Identify patients who will benefit from treatment vs a watch-and-wait approach
- Select treatment based on guidelines and disease staging
- Discuss clinical data concerning the use of somatostatin analogs and targeted therapies

Accreditation Statement

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Gastroenteropancreatic Neuroendocrine Tumors: Diagnosis and Classification

Pamela L. Kunz, MD

Neuroendocrine tumors (NETs) are epithelial neoplasms that originate from neuroendocrine cells in almost any anatomic location. NETs are generally indolent, demonstrating a slower growth pattern than their adenocarcinoma counterparts. Although the majority of NETs are sporadic, some familial syndromes have been identified, such as multiple endocrine neoplasia types 1 and 2.[1,2]

NETs are most likely to develop in the gastrointestinal tract and pancreas; these tumors are known as gastroenteropancreatic (GEP) NETs.[3,4] Approximately 10% of small intestine NETs and 40% of pancreatic NETs are functional, meaning they secrete amines and/or peptides that cause clinical symptoms.[5-7] The hormones and symptoms associated with functional GEP-NETs vary. Carcinoid syndrome is the classic example and defined by production of serotonin (frequently measured as the urinary metabolite 5-hydroxyindoleacetic acid [5-HIAA]) and symptoms of flushing, diarrhea, bronchospasm, and valvular heart disease. The most common hormones secreted by functional pancreatic NETs are insulin, gastrin, glucagon, and vasoactive intestinal polypeptide. Insulin-secreting tumors can result in hypoglycemia, and gastrin-secreting tumors (also called *Zollinger-Ellison syndrome*) can cause gastric ulcers.

Epidemiology of GEP-NETs

In the United States, the incidence of NETs is approximately 5 per 100,000 individuals.[8] The incidence has been increasing relative to that of adenocarcinomas, particularly for rectal NETs.[8] This increase in the reported incidence of NETs is likely attributable to improvements in diagnostic tools, including more refined imaging modalities and better endoscopic techniques. In addition, recent introduction of pathology and American Joint Committee on Cancer (AJCC) staging guidelines have likely increased awareness. The increasing incidence of NETs, coupled with their typically indolent natural history, makes their prevalence higher than those of pancreatic and gastric adenocarcinomas combined.[8]

NETs are distributed evenly between women and men. There is a disparate racial distribution: 81% white, 12% African American, 5% Asian/Pacific Islander, 1% American Indian/Alaskan Native, and 1% unknown. The median age at diagnosis for all primary sites is 63 years, although there is considerable variation among these sites.[8] Most NETs are sporadic, and there are no known environmental or dietary risk factors. There are, however, well-described inherited genetic syndromes that predispose to the development of certain NETs, including multiple endocrine neoplasia (MEN1 and MEN2), Von Hippel–Lindau disease, neurofibromatosis, and tuberous sclerosis complex. Jejunal and rectal NETs have the highest incidence rates among GEP-NETs, at 0.67 and 0.86 per 100,000, respectively.[8] The stage at diagnosis varies considerably by primary site; the majority of patients with NETs of the stomach, rectum, and appen-

Table 1. Minimum Pathology Data Set

For Resection of Primary Tumors	For Biopsy Specimen
Anatomic site of tumor	Anatomic site of tumor
Size	Chromogranin
Presence of multicentric disease	Synaptophysin
Chromogranin	Grade (specify grading system used)
Synaptophysin	Mitotic rate
Grade (specify grading system used)	Ki-67 (if high-grade NEC cannot be excluded)
Mitotic rate (Ki-67 optional)	Presence of nonischemic tumor necrosis
Presence of nonischemic tumor necrosis	
Extent of invasion	
Presence of vascular invasion	
Presence of perineural invasion	
Number of positive nodes	
Total number of nodes examined	
TNM staging (specify staging system utilized)	
Resection margins	

NEC, neuroendocrine carcinoma; TNM, tumor, node, metastasis.

Data from Klimstra DS et al. *Am J Surg Pathol.* 2010;34:300-313.[11]

Table 2. 2010 WHO Criteria for GEP-NETs

Differentiation	Grade	Nomenclature	Proliferative Rate
Well-differentiated	G1, low grade	Neuroendocrine tumor	<2 mitoses/10 hpf AND <3% Ki-67 index
	G2, intermediate grade	Neuroendocrine tumor	2-20 mitoses/10 hpf OR 3%-20% Ki-67 index
Poorly differentiated	G3, high grade	Neuroendocrine carcinoma, small cell type	>20 mitoses/10 hpf OR >20% Ki-67 index
		Neuroendocrine carcinoma, large cell type	

hpf, high-powered field.

Data from Klimstra DS et al. Neuroendocrine neoplasms of the pancreas. In: Bosman F et al, eds. *WHO Classification of Tumours of the Digestive System*. Lyon, France: IARC Press; 2010:322-326.[12]

dix are diagnosed with localized disease, whereas patients with NETs of the small intestine and colon are diagnosed evenly among the stages.[9]

Diagnosis

The clinical presentation of patients with GEP-NETs is varied. One important first distinction is whether the tumor is functional or not. The classic example of a functional tumor is one associated with carcinoid syndrome. Patients with nonfunctional tumors are asymptomatic or have symptoms that are not attributable to hormone excess and may be related to tumor bulk. The initial diagnostic workup should include laboratory evaluation of serum chromogranin A, urinary 5-HIAA, and other clinically indicated markers (eg, insulin, gastrin, and glucagon in pancreatic NETs).[10] Cross-sectional imaging with multiphasic computed tomography or gadolinium–enhanced magnetic resonance imaging is recommended and helps define the extent of disease (localized vs metastatic, low volume vs high volume, liver-dominant vs widespread). Somatostatin scintigraphy, such as OctreoScan, is often obtained at the time of initial diagnosis but is not recommended for routine surveillance. An accurate histologic diagnosis is critical, as the grade determines the appropriate treatment. Recent guidelines for a minimum acceptable pathology data set have been developed to guide this histologic assessment (Table 1).[11]

Classification Systems for GEP-NETs

A variety of classification systems have been used for GEP-NETs, including groupings based on the primary tumor site (pancreatic vs nonpancreatic), hormone status (functional vs nonfunctional), hormone secreted (eg, insulin, gastrin), differentiation status (poorly differentiated vs well differentiated), and embryologic site of origin (the foregut [the thymus, lung, esophagus, stomach, duodenum, and pancreas], midgut [the jejunum, ileum, cecum, and ascending and traverse colon], or hindgut [the descending and sigmoid colon and rectum]). The currently accepted classification system is the 2010 World Health Organization criteria, in which NETs are classified into 3 grades, based on the Ki-67 and mitotic rate—both indices of proliferation. Well-differentiated neuroendocrine neoplasms include grades 1 and 2; grade 3 neuroendocrine carcinomas, or poorly differentiated neuroendocrine carcinoma, are further subdivided into small-cell or large-cell types (Table 2).[12] Historically, the Ki-67, mitotic rate, and overall assessment of grade were not always included in NET pathology reports, but they are now considered essential.

Staging and Prognosis

Staging of GEP-NETs has been aided by their inclusion in the 7th edition of the Cancer Staging Manual from the AJCC. This staging system, which includes separate scales for different primary tumor sites, is modeled after the tumor/node/metastasis (TNM) staging system for adenocarcinomas and ranges from stage 0 to stage IV.[10,13] Multiple studies have confirmed the prognostic validity of the AJCC staging system for NETs of various primary sites (Figure 1).[14-16] Prognosis also varies considerably by primary site; median overall survival for patients with pancreatic NETs was reported as 42 months as compared with 88 months for jejunal/ileal NETs.[8] However, survival data vary whether they are drawn from population-based registries, such as those from the Surveillance, Epidemiology, and End Results program, or large single institution series.

Other factors that affect prognosis include the histologic classification (including tumor differentiation and tumor grade), age, sex, race, and age at diagnosis (Figure 2).[8,15,17] Molecular prognostic and predictive markers are also being explored.[18]

Disclosure

Dr Kunz has performed contracted research for Lexicon, Genentech, Merck, Advanced Accelerator Applications, and Oxigene. She is a member of the advisory boards of Ipsen and Novartis.

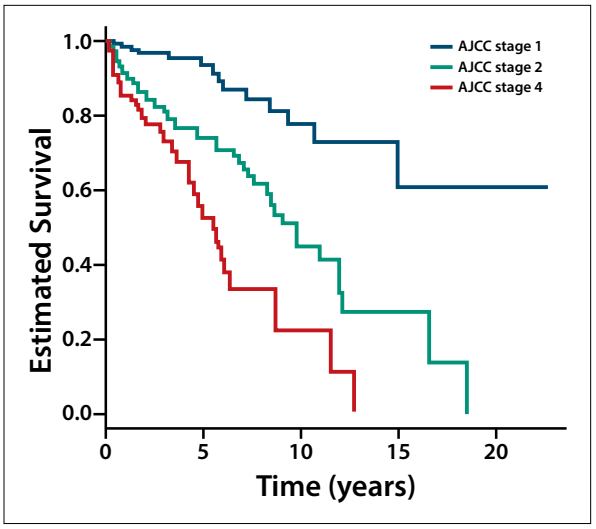

Figure 1. Kaplan-Meier survival curves in patients with pancreatic neuroendocrine tumors according to the 2010 AJCC staging system. AJCC, American Joint Committee on Cancer. Adapted from Ellison TA et al. *Ann Surg*. 2014;259(2):204-212.[16]

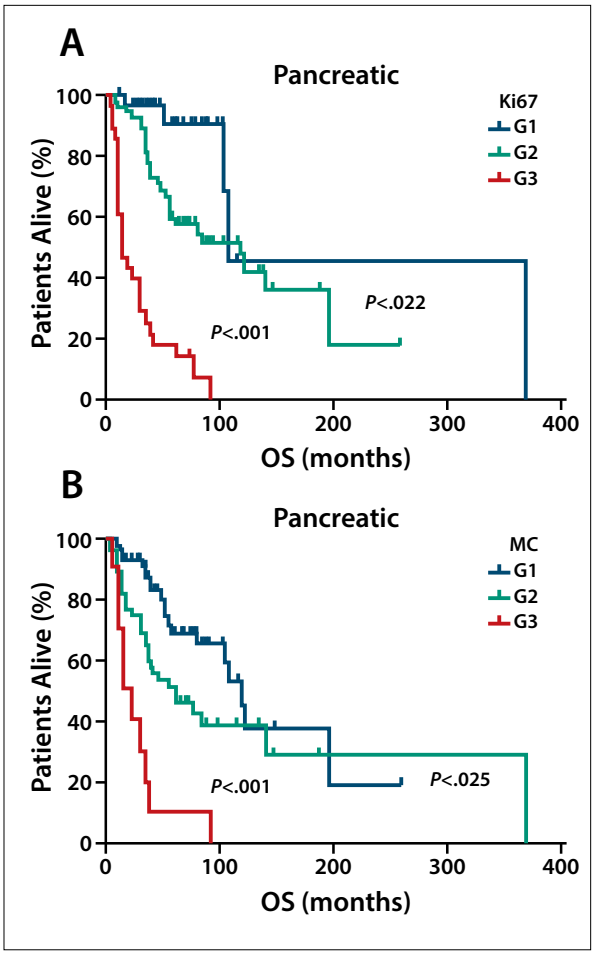

Figure 2. Kaplan-Meier survival curves in patients with pancreatic neuroendocrine tumors according to the Ki-67 index (A) and mitotic rate (B). MC, mitotic count. Adapted from Khan MS et al. *Br J Cancer*. 2013;108(9):1838-1845.[17]

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Treatment Approaches in Gastroenteropancreatic Neuroendocrine Tumors

Alexandria T. Phan, MD

The treatment approach for patients with GEP-NETs varies based on multiple factors related to both the disease and the patient. Disease-related factors include the location and extent of metastases, resectability of the tumor, and presence of symptoms. Patient-related factors include goals of treatment, concomitant medical conditions, and access to therapy. For example, patients presenting with bulky and/or symptomatic GEP-NETs will require initiation of therapy to control symptoms or cytoreduce bulky disease. Although advanced unresectable/metastatic GEP-NETs remain incurable, the goals of therapy are to improve progression-free survival (PFS)—and possibly, overall survival—by controlling the symptoms and growth of the disease/tumor. Therapeutic modalities include surgery, interventional radiology for liver-directed therapy, and pharmacotherapy.[1] Pharmacotherapy for the management of GEP-NETs now includes cytotoxic chemotherapy, targeted therapies, biological agents, and radioisotope radiotherapy. Recent advances through several pivotal clinical studies have expanded and transformed the landscape of systemic treatment options in the management of GEP-NETs as a whole. Two targeted agents were approved for pancreatic NETs. The somatostatin analog lanreotide depot/autogel was approved by the US Food and Drug Administration (FDA) in December 2014 for the treatment of patients with unresectable, well- or moderately differentiated, locally advanced or metastatic GEP-NETs to improve PFS.[2] Another somatostatin analog, octreotide long-acting release (LAR) depot, is approved for symptom control of severe diarrhea/flushing episodes associated with metastatic midgut well-differentiated NETs (carcinoid tumors) or functional pancreatic NETs producing vasoactive intestinal peptide (VIPomas).[3] Sunitinib is an oral multitargeted tyrosine kinase inhibitor, approved by the FDA in 2011 for progressive, advanced, unresectable, and metastatic pancreatic NETs.[4] The mammalian target of rapamycin inhibitor everolimus was approved in 2011 for progressive pancreatic NETs.[5]

The Role of Multidisciplinary Care

Optimal care of patients with GEP-NETs involves a multidisciplinary team with experience and expertise in NETs. The traditional solo practice in oncology, which involves medical oncologists providing chemotherapy, is no longer adequate to manage the care of patients with complex and rare malignancies, such as GEP-NETs. Patients with GEP-NETs will frequently present with advanced or metastatic disease involving other organs. Therapeutic options involve disciplines such as surgery, radiotherapy, nuclear medicine, interventional radiology, and medical oncology. Furthermore, because GEP-NETs are generally heterogeneous and indolent—with a long natural history of disease—management must be individualized to the goals of therapy for each patient. Different treatment modalities may be necessary at certain times or to achieve various therapeutic objectives. A common feature and fundamental requirement of all centers of excellence in NETs is a multidisciplinary approach to patient care.

The Role of Surgery

Surgery plays an important role in the management of GEP-NETs, whether for curative intent or palliation of symptoms. Durable survival remains possible only with curative surgery for patients with localized resectable disease. For example, in metastatic or advanced well-differentiated midgut NETs (carcinoid tumors), mesenteric and/or primary resection may be an important consideration to palliate or alleviate symptoms of bowel ischemia or bowel obstruction, such as abdominal pain, diarrhea, malabsorption, and malnutrition. Although prospective data are needed, complete surgical resection of oligometastases has been reported to improve PFS and, possibly, overall survival. Retrospective case series reviews have suggested that surgical debulking of heavy burden metastatic GEP-NETs can be an effective method for palliation of disease-related symptoms for selected patients. Whether or not patients with advanced, unresectable, metastatic GEP-NETs require surgery at presentation or sometime later during their disease process, surgical assessment is recommended in all clinical practice guidelines (National Comprehensive Cancer Network [NCCN], European Neuroendocrine Tumor Society [ENETS], and the North American Neuroendocrine Tumor Society [NANETS]).

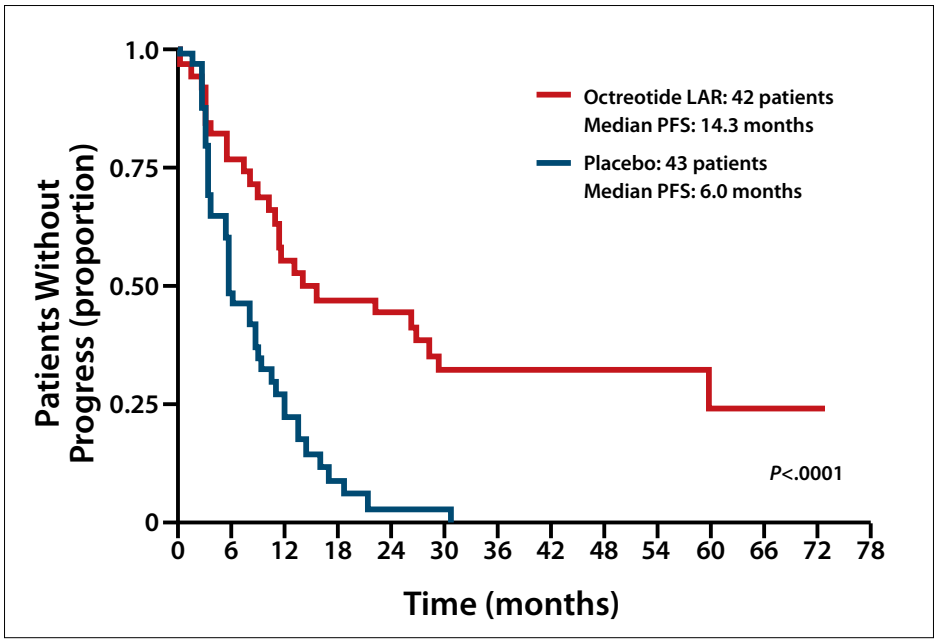

Figure 3. PFS in the PROMID trial, which enrolled patients with advanced midgut neuroendocrine tumors.

LAR, long-acting release; PFS, progression-free survival; PROMID, Placebo Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors. Adapted from Rinke A et al. *J Clin Oncol.* 2009;27(28):4656-4663.[7]

Somatostatin Analogs

All patients with functional or symptomatic GEP-NETs should be considered for a somatostatin analog.[1] Currently, 2 somatostatin analogs, octreotide LAR depot and lanreotide depot/autogel, are available. Both agents predominantly target the somatostatin receptor type 2 (SSR2). Somatostatin receptors (SSRTs) are receptors on many organs, but are especially overexpressed in GEP-NETs, particularly SSRT2 and 5.

Octreotide LAR Depot

Octreotide LAR depot is FDA-approved for treatment of severe diarrhea/flushing episodes associated with metastatic midgut well-differentiated NETs (carcinoid tumors) or functional pancreatic NETs producing VIPomas.[3] In a study by Modlin and colleagues, octreotide LAR depot controlled symptoms of carcinoid syndrome in more than 75% of patients.[6]

Octreotide LAR depot does not have an indication for treatment, but there is a study in patients with midgut NETs. The single-country, double-blind, placebo-controlled, randomized PROMID (Placebo Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors) trial enrolled 85 patients with well-differentiated, metastatic midgut NETs.[7] At baseline, carcinoid syndrome was reported in 41% of patients in the octreotide LAR depot arm and 37% in the placebo arm. Baseline disease status was not defined in the study. The patients were randomly assigned to octreotide LAR depot 30 mg (n=42) or placebo (n=43) administered monthly via intramuscular injections.[7] Octreotide LAR depot demonstrated significant antiproliferative effects in patients with GEP-NETs.[7] The study's primary endpoint—median time to tumor progression—was significantly longer with octreotide LAR depot vs placebo (14.3 months vs 6 months; hazard ratio [HR], 0.34; 95% CI, 0.20-0.59; *P*=.000072; Figure 3).[7] In a subgroup analysis, patients with minimal liver involvement (<10%) appeared to have statistically improved benefit compared with those with high liver involvement (>10%). Improved time to tumor progression was not observed in patients with high liver tumor burden or grade 2 tumors. The presence of carcinoid syndrome did not impact antitumor responses. As a result of these findings, the NCCN guidelines include the use of octreotide LAR depot for cytostatic control.[1]

Serious adverse events occurred in 11 patients receiving octreotide LAR depot and 10 receiving placebo. The most common of these events affected the gastrointestinal tract (in 6 octreotide LAR depot patients vs 8 placebo patients), the hematopoietic system (5 vs 1), and general health status (eg, fatigue and fever; 8 vs 2). Treatment discontinuation based on adverse events was reported in 5 octreotide LAR depot patients vs no placebo patients. No treatment-related deaths occurred. Quality of life was comparable in both treatment arms.

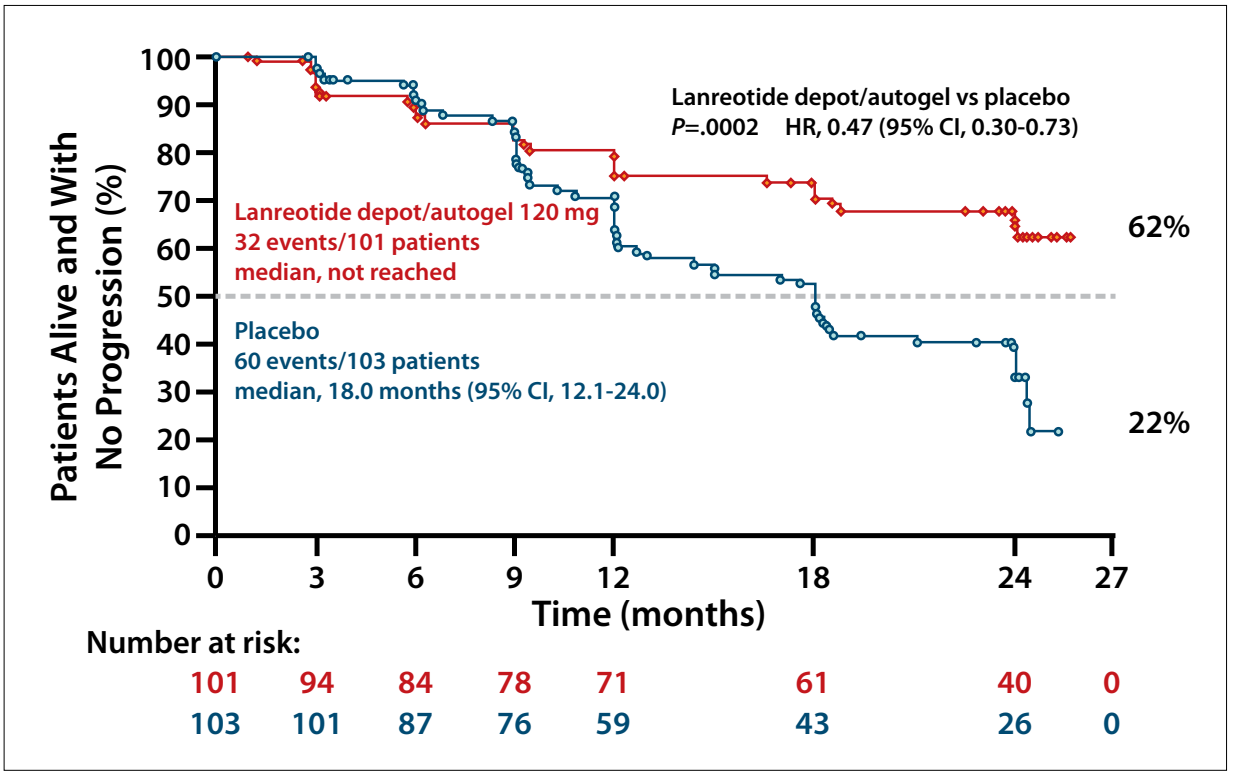

Figure 4. Progression-free survival among the intent-to-treat population in the CLARINET trial, which enrolled patients with grade 1 or 2 GEP-NETs that were well-differentiated or moderately differentiated, nonfunctioning, and locally inoperable or metastatic.

CLARINET, Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors. GEP-NETs, gastroenteropancreatic neuroendocrine tumors. Adapted from Caplin ME et al. *N Engl J Med*. 2014;371(3):224-233.[8]

Lanreotide Depot/Autogel

In 2007, lanreotide depot/autogel was approved by the FDA to treat acromegaly. The 2014 approval of lanreotide depot/autogel for GEP-NETs was based on the results of the international, randomized, double-blind, placebo-controlled CLARINET (Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors) trial, which evaluated the efficacy and safety of lanreotide depot/autogel in patients with advanced, well-differentiated or moderately differentiated, nonfunctioning grade 1 or 2 GEP-NETs.[8] The CLARINET trial included patients with tumors that originated in the pancreas, midgut, or hindgut, or were of unknown origin. A total of 204 patients were randomly assigned to subcutaneous lanreotide depot/autogel 120 mg (101 patients) or placebo (103 patients) administered every 28 days for 96 weeks. More than 95% of the patients at baseline had stable disease as defined by the Response Evaluation Criteria In Solid Tumors (RECIST), and all tumors were nonfunctional. Treatment with lanreotide depot/autogel reduced the risk of disease progression or death by a significant 53% vs placebo.[8] The median PFS was not reached in the lanreotide depot/autogel group (ie, greater than 24 months) vs 18 months in the placebo group (HR, 0.47; 95% CI, 0.30-0.73; *P*<.001; Figure 4). The estimated 2-year PFS rates were 65% and 33%, respectively. Treatment with lanreotide depot/autogel resulted in improved PFS, demonstrating its antiproliferative effect in the overall population, as well as in predefined subgroups, such as grade 1 vs grade 2 tumors and low (≤20%) vs high (>25%) hepatic tumor load. There was a trend toward improved PFS in patients with midgut and pancreatic tumors, but the difference did not reach statistical significance.

No unexpected or new adverse events were observed among patients receiving lanreotide depot/autogel. Serious adverse events related to study treatment occurred in 3 patients in the lanreotide depot/autogel arm and 1 patient in the placebo arm. These treatment-related adverse events included hyperglycemia, diabetes, nausea, vomiting, abdominal pain, biliary fistula, and cholelithiasis in the lanreotide depot/autogel group and bile duct stenosis in the placebo group. They led to treatment discontinuation by 1 patient receiving lanreotide depot/autogel and no patients receiving placebo. Quality of life did not differ between the treatment arms.

The long-term safety and efficacy of lanreotide depot/autogel in patients with GEP-NETs were evaluated

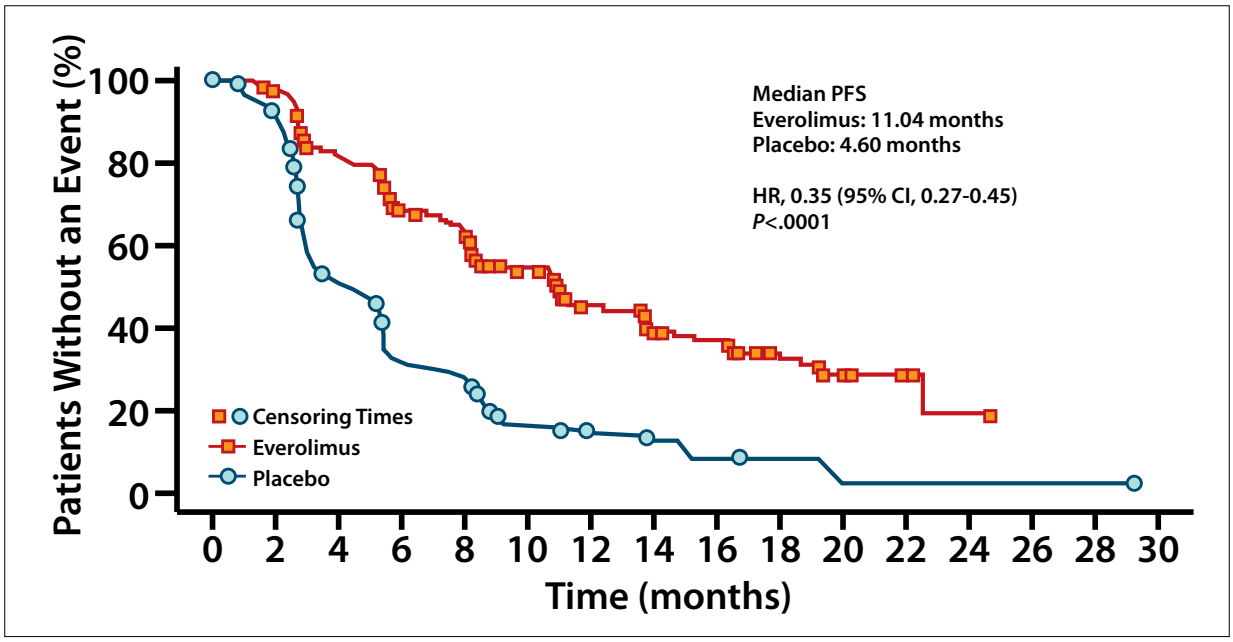

Figure 5. Median PFS in the RADIANT-3 trial, which enrolled patients with advanced low-grade or intermediate-grade pancreatic neuroendocrine tumors who had experienced radiographic progression in the previous 12 months.

PFS, progression-free survival; RADIANT-3, RAD001 in Advanced Neuroendocrine Tumors, Third Trial. Adapted from Yao JC et al. *N Engl J Med.* 2011;364(6):514-523.[10]

in an open-label extension study of CLARINET patients that collected data for up to 6 years.[9] Enrolled patients included those from the lanreotide depot/autogel group with stable disease who continued treatment and those in the placebo group, with or without progressive disease, who received open-label lanreotide depot/autogel. The median PFS was 32.8 months in the lanreotide depot/autogel group vs 18.0 months in the placebo group.[9] Among patients in the placebo arm who switched to lanreotide depot/autogel after documented radiologic disease progression, the median time to second progression after starting therapy was 14 months.

The results of both PROMID and CLARINET are important in validating the antiproliferative effects of somatostatin analogs in NETs. A clinically meaningful difference in antitumor efficacy and level of cross-resistance between lanreotide depot/autogel and octreotide LAR depot will likely not be definitively resolved without a head-to-head comparison. However, there were important differences between the studies that can help guide the selection of lanreotide depot/autogel vs octreotide LAR depot. The CLARINET trial showed improved PFS with lanreotide depot/autogel in 204 international patients with relatively indolent, therapy-naive, nonprogressing GEP-NETs (pancreatic NET and midgut NET/carcinoid tumors).[8] The PROMID study showed improved time to tumor progression with octreotide LAR depot in 85 German patients with midgut NET (carcinoid tumors), whose disease status was unknown at baseline.[7]

Targeted Agents

Two targeted agents, everolimus and sunitinib, have demonstrated antitumor activity and improved PFS in patients with advanced pancreatic NETS.

Everolimus

Everolimus was evaluated in the randomized, double-blind, placebo-controlled, phase 3 RADIANT-3 (RAD001 in Advanced Neuroendocrine Tumors) trial, which randomly assigned 410 patients with advanced pancreatic NETs to everolimus 10 mg once daily or placebo with best supportive care.[10] Median PFS was 11.04 months with everolimus vs 4.60 months with placebo (HR, 0.35; 95% CI, 0.27-0.45; *P*<.001; Figure 5).[10] Most drug-related adverse events were grade 1 or 2. The most common adverse events of all grades were stomatitis (occurring in 64% of everolimus patients vs 17% of placebo patients), rash (49% vs 10%), diarrhea (34% vs 10%), fatigue (31% vs 14%), and infections (23% vs 6%).

The randomized, double-blind, phase 3 RADIANT-2 trial evaluated everolimus plus octreotide LAR depot in 429 patients with advanced midgut NETs/carcinoid tumors.[11] The median PFS was 16.4 months with everolimus plus octreotide LAR depot vs 11.3 months with placebo plus octreotide LAR depot (HR, 0.77; 95% CI, 0.59-1.00; 1-sided log-rank test, *P*=.026). There was a trend toward improved survival with the addition of everolimus to octreotide LAR depot. Most treatment-

related adverse events were grade 1 or 2. The most common adverse events of all grades included stomatitis (62% with everolimus plus octreotide LAR depot vs 14% with placebo plus octreotide LAR depot), rash (37% vs 12%), fatigue (31% vs 23%), and diarrhea (27% vs 16%).

Sunitinib

Sunitinib was evaluated in the A6181111 study, a randomized, double-blind, placebo-controlled trial in patients with pancreatic NETs.[12] The study enrolled 171 patients with advanced, well-differentiated pancreatic NETs, who were randomly assigned to sunitinib 37.5 mg daily or placebo with best supportive care. PFS was 11.4 months with sunitinib vs 5.5 months with placebo (HR, 0.42; 95% CI, 0.26-0.66; $P<.001$).[12]

Most adverse events were grade 1 or 2. The most common adverse events of all grades in the sunitinib arm were diarrhea (49% vs 32% in the placebo arm), nausea (37% vs 24%), asthenia (28% vs 22%), vomiting (28% vs 25%), and fatigue (27% vs 22%). Grade 3 or 4 adverse events were more frequent among patients receiving sunitinib. Serious adverse events, however, were more common with placebo, occurring in 41% of patients (vs 26% of the sunitinib arm). During the trial period, 5 patients receiving sunitinib died vs 9 patients receiving placebo. The trial was discontinued early based on the rate of serious adverse events and deaths in the placebo group and the PFS advantage seen with sunitinib.

Selecting a Treatment Approach

Scientific advancements and clinical research have transformed our understanding of NETs and introduced more therapeutic options for managing patients with advanced NETs. Results of pivotal clinical trials, such as A6181111,[12] RADIANT-3,[10] and CLARINET,[8] provided evidence of meaningful improvement in PFS, which led to the FDA approval of sunitinib, everolimus, and lanreotide depot/autogel in NETs. Sunitinib and everolimus share the same FDA indication for pancreatic, but not midgut, NETs that are progressing, whereas lanreotide depot/autogel is FDA-approved for frontline or progressing GEP-NETs inclusive of pancreatic and midgut NETs. Given the growing number of therapeutic options now available for the treatment of patients with GEP-NETs, it is important to select therapy based on the treatment goals individualized to the patient. Careful consideration of patient-related, disease-related, and treatment-related factors is the optimal approach to individualizing therapeutic selection. Disease-related factors include the location and extent of metastases, resectability of the tumor, and presence or absence of symptoms. Patient-related factors include goals of therapy, concomitant medical conditions, and access to therapy. Treatment-related factors include side effects relating to the therapy.

The goals of therapy for management of advanced GEP-NETs are twofold: symptom control and cancer/tumor control. Surgical evaluation should be an integral part of management of patients with GEP-NETs. Patients with resectable disease should have the tumor completely resected when it is medically stable to do so. Patients with borderline resectable disease may need cytoreduction or a bridge therapy; if tumor reduction is attained, reassessment for surgery may be appropriate. In pancreatic NETs, the objective tumor responses (tumor reduction) with sunitinib and everolimus were 9.3%[12] and 5%,[10] respectively. Tumor reduction in pancreatic NETs is best observed with cytotoxic chemotherapy, such as streptozocin-based chemotherapy regimens.[13-17]

The approach to patients with unresectable, advanced, or inoperable GEP-NETs can start with determining whether the disease is bulky or functional. Patients with functional NETs will require hormonal control with somatostatin analogs and/or cytoreduction of tumor burden. In patients with nonfunctional NETs, the goal of tumor control should be balanced with the need to maintain quality of life by minimizing the toxic effects of therapy.

Selection of the optimal therapies requires consideration of a potential agent's safety profile and the overall treatment strategy in terms of a sequential approach. In patients with unresectable, symptomatic, bulky disease, the goal of systemic therapy is cytoreduction: shrinking the tumor to palliate symptoms relating to hormones being oversecreted or to alleviate symptoms relating to bulk of disease as the size of the tumor regresses. With appropriate patient selection, chemotherapy regimens, such as those incorporating streptozocin or temozolomide, continue to play an important role in patients with pancreatic NETs, based on the cytoreductive potential. For asymptomatic patients, the goal is to maintain disease stability. Therefore, cytostatic therapies with nominal objective tumor response, such as targeted agents (eg, everolimus or sunitinib) and somatostatin analogs may be preferable to more cytotoxic therapies because tumor shrinkage is not necessarily the treatment goal. There is a subset of patients who have well-differentiated GEP-NETs with asymptomatic, indolent, low-volume disease, in whom a watch-and-wait approach may be preferable. However, the decision of when to initiate therapy may be influenced by the recent approval of lanreotide depot/autogel in the frontline setting. The FDA-approved indication for other agents, such as everolimus and sunitinib, is limited to patients with disease progression. Given the relative rarity of the condition, it is important to seek the advice of a NET specialist who understands the natural history of the disease.

Other Therapeutic Approaches

In addition to systemic therapies, various localized approaches may be used in the treatment of patients with GEP-NETs. Localized therapies may provide symptomatic improvement in patients with functional tumors that are refractory to systemic therapy or in patients with bulky tumors causing symptoms. Options for unresectable liver metastases include arterial embolization, chemoembolization, and radioembolization.[1] The goal of these palliative liver-directed therapies is to reduce symptoms rather than to attain cytoreduction. Often, symptomatic control requires very little tumor shrinkage; one treatment may provide significant hormonal control.

A variety of investigational approaches are being evaluated in the treatment of GEP-NETs. One popular and promising approach involves the administration of radiolabeled somatostatin analogs via peptide receptor radionuclide therapy.[18] A study by Kwekkeboom and colleagues identified an overall survival benefit of several years from the time of diagnosis in patients treated with [(177)Lu-DOTA(0),Tyr(3)]octreotate.[19] This therapy is limited to patients with diffuse somatostatin-avid disease. It is readily available in Europe, but remains investigational in the United States. Potential toxicities, including bone marrow suppression, make this approach best suited for patients without other options.

Disclosure

Dr Phan is a member of the speakers bureaus of Ipsen, Novartis, Celgene, Genentech, and Lilly. Dr Phan is currently on the advisory boards of Ipsen and Novartis. She is a past member of the advisory boards of Lexicon and GSK (now Novartis).

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Emerging Treatments for Gastroenteropancreatic Neuroendocrine Tumors: Use in the Clinic

Diane L. Reidy-Lagunes, MD

Management of GEP-NETs poses a significant challenge because of the heterogeneous clinical presentations of the malignancies and their varying degrees of aggressiveness. Moreover, many aspects of GEP-NET treatment remain unclear and controversial. To aid the management of these uncommon diseases, guidelines are available from several expert panels, including the NCCN,[1] ENETS,[2] and NANETS.[3]

Factors Guiding Treatment Selection

Although patients with GEP-NETs benefit from a multidisciplinary approach to management, a medical oncologist often takes the lead in determining when and how to initiate treatment. When selecting a treatment approach, it is important to consider factors such as tumor grade, burden, and disease progression. For example, patients with large-volume, functional tumors may require medical therapies in addition to antitumor treatments to control their symptoms. In contrast, patients with low-volume, non–hormone secreting (ie, nonfunctioning) tumors are often completely asymptomatic and can be followed expectantly for months or even years. An understanding of the patient's symptoms and tumor biology is critical to individualize management of these uncommon tumors. Typical indications for therapy are pain or symptoms caused by tumor bulk, symptoms caused by uncontrolled hormone secretion, or clinically significant tumor burden or disease progression under observation. Grade of tumor (eg, low-grade vs intermediate-grade) can aid in treatment decisions and is important for prognosis, but it currently does not drive therapeutic management.

Treatments for Tumor Control

In those patients in whom all hepatic metastases seem to be resectable, and in whom no extrahepatic disease is observed, resection should be considered. Cure, however, is vanishingly rare, even in the setting of achieving an R0 resection. In addition, the lack of randomized data and selection bias likely confound quantitative interpretation of reported results. Nevertheless, resection should be considered in carefully selected patients, particularly in patients with symptoms that can be improved by debulking.

The efficacy of somatostatin analogs for tumor control has now been confirmed in 2 randomized trials.[4,5] It is important to consider the patient populations enrolled in these trials: the PROMID trial of octreotide LAR depot was limited to patients with advanced midgut carcinoids, whereas the CLARINET study of lanreotide depot/autogel included patients with all types of GEP-NETs.[4,5] As noted above, in patients with progressive or symptomatic disease, treatment is indicated. Although there are no prospective data to guide sequencing of systemic treatments for GEP-NETs, somatostatin analogs are often first-line therapy in patients with unresectable disease. This is in part because of the antiproliferative effect and very safe side effect profile. Objective responses are low.

Although the adverse events associated with other targeted therapies are manageable, they may be more persistent and can require that the patient is optimized before initiating therapy. As noted, sunitinib and everolimus are FDA-approved for progressive pancreatic NETs but not for carcinoid tumors. Selection of optimal therapy requires consideration of the agent's safety profile. Importantly, information regarding the duration of each of their toxicities has not been reported, and this information would be clinically relevant. For example, grade 2 hand-foot syndrome would have a very different impact on a patient if it lasted for 3 days vs 3 weeks. The side effect profiles of sunitinib and everolimus are predictable but can impair quality of life and therefore must be considered. Both agents are usually considered for patients with progressive and, generally, low-volume disease, in whom tumor shrinkage is not necessarily a treatment goal. Among patients with pancreatic NETs who require tumor shrinkage—particularly those with a heavy tumor burden—cytotoxic therapy with temozolomide, 5-fluorouracil, or streptozocin-based regimens could be considered. Several trials have failed to convincingly demonstrate the use of cytotoxic chemotherapy in most carcinoid tumors.

Treatments for Symptom Control

Liver directed therapies, such as surgical debulking or embolization, will decrease tumor burden and improve tumor symptoms. In addition, somatostatin analogs have revolutionized the treatment of patients with carcinoid

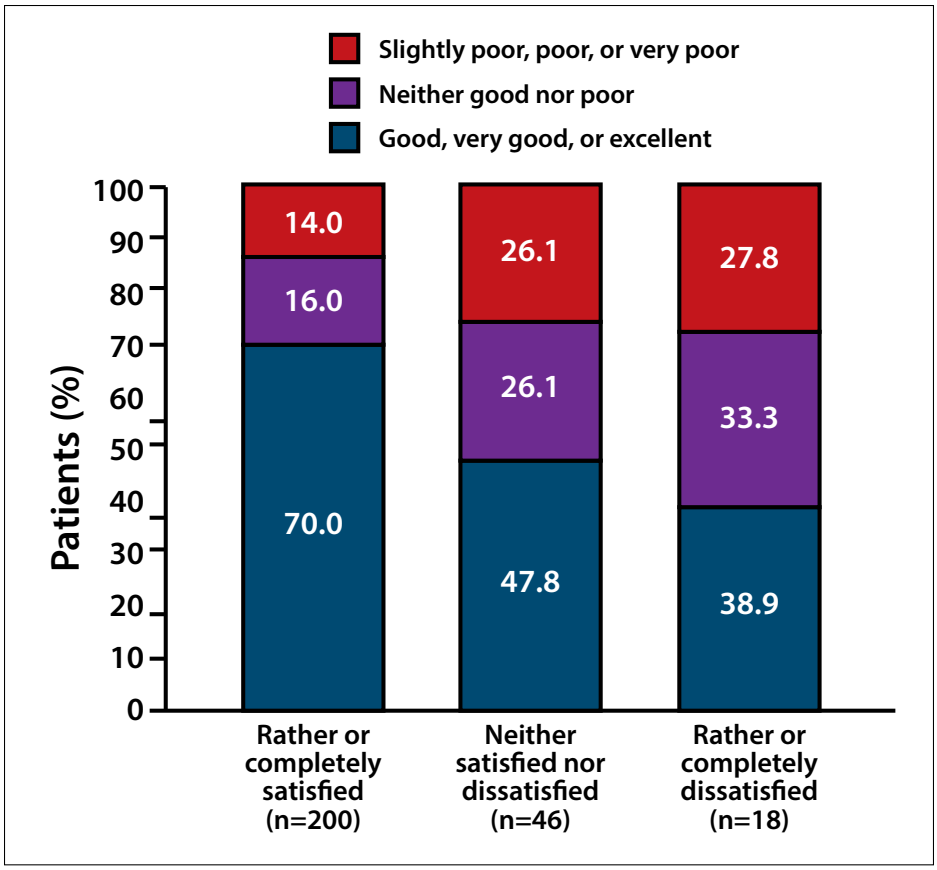

Figure 6. Quality of life based on patient's satisfaction with diarrhea control in the SymNET study. Adapted from Ruszniewski P et al. Treatment satisfaction, symptom control and quality of life with lanreotide autogel in neuroendocrine tumour patients with carcinoid syndrome: results from the SymNET study. Paper presented at: the ESMO Annual Meeting; September 26-30, 2014; Madrid, Spain. Poster 1134 PD.[10]

syndrome; both octreotide and lanreotide depot/autogel can ameliorate the symptoms of carcinoid syndrome. The data for octreotide span several decades, and show that both short-acting and long-acting forms can reduce carcinoid syndrome.[6,7] In a 2010 study by Modlin and colleagues, octreotide LAR depot and lanreotide depot/autogel controlled symptoms of carcinoid syndrome in more than 75% and 65% of patients, respectively.[8] A biochemical response, as defined by chromogranin levels, was observed in approximately half of patients.

The benefits of lanreotide depot/autogel in carcinoid syndrome were explored in the multinational, cross-sectional, observational SymNET (A Study to Assess Neuroendocrine Tumour [NET] Patients Currently Treated by Somatuline Autogel for History of Carcinoid Syndrome Associated With Episodes of Diarrhea) study, which assessed patient-reported outcomes in 273 GEP-NET patients with diarrhea related to carcinoid syndrome.[9] Patients had received lanreotide depot/autogel for at least 3 months. After a median of 22 months of treatment, 76% of patients reported being "completely" or "rather" satisfied with their diarrhea control, and 79% of patients reported an overall improvement in diarrhea. A subsequent analysis of the SymNET study showed that higher levels of patient satisfaction based on diarrhea control corresponded to better overall health-related quality of life and better scores for most symptom-related health-related quality of life measures (Figure 6).[10]

The efficacy of lanreotide depot/autogel in the treatment of patients with carcinoid syndrome was also evaluated in the randomized, double-blind, placebo-controlled phase 3 trial known as ELECT (A Double-Blind, Randomized Placebo-Controlled Clinical Trial Investigating the Efficacy and Safety of Somatuline Depot [Lanreotide] Injection in the Treatment of Carcinoid Syndrome).[11] The trial enrolled 115 patients with confirmed NETs and carcinoid syndrome; symptoms had persisted for at least a year in 72% of patients. Nearly half of patients (44%) were somatostatin analog–naive, and the remaining 56% of patients had previously responded to conventional doses of octreotide (short-acting or LAR).[11] Patients were randomly assigned to lanreotide depot/autogel or placebo

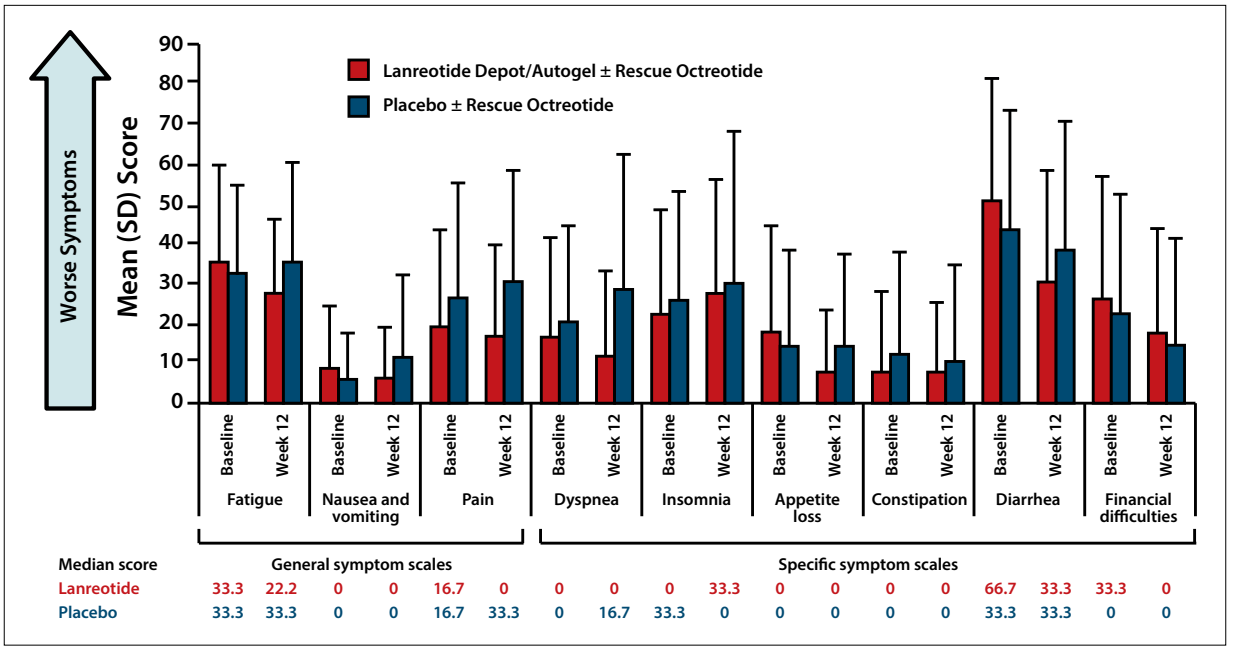

Figure 7. Health-related quality of life analysis in the ELECT trial. Adapted from Gomez-Panzani E et al. Quality of life with lanreotide autogel treatment for carcinoid syndrome in gastroenteropancreatic neuroendocrine tumor patients: results of the ELECT study. Paper presented at: the ESMO Annual Meeting; September 26-30, 2014; Madrid, Spain. Poster 1135 PD.[12]

for 16 weeks, followed by a 32-week open-label extension of lanreotide depot/autogel. The primary objective of the trial was the proportion of days patients required rescue octreotide during the double-blind phase. This proportion was significantly lower with lanreotide depot/autogel vs placebo (34% vs 49%; *P*=.02), however, the predefined absolute treatment difference was not met. A health-related quality of life analysis of the ELECT trial showed that treatment with lanreotide depot/autogel was not associated with a decrease in quality of life (Figure 7).[12] As a result of these findings, the NCCN guidelines include the use of lanreotide depot/autogel for symptom control.

Routes of Administration of Somatostatin Analogs

Octreotide LAR depot and lanreotide depot/autogel differ in their routes of administration. Octreotide LAR depot is administered intramuscularly, and lanreotide depot/autogel is administered via deep subcutaneous injection. In patients with NETs, both agents are administered every 28 days. Octreotide LAR depot is reconstituted prior to administration.[13] Lanreotide depot/autogel is supplied in a prefilled syringe that does not require reconstitution.[13] In a survey of 77 nurses in the United States and Europe, respondents preferred the lanreotide device over that of octreotide LAR depot.[13] However, the results of this survey should be interpreted with caution due to the open-label (nonblinded) design.

Guidelines for Key Controversial Topics

In the PROMID study, octreotide LAR depot demonstrated antitumor efficacy in well-differentiated, metastatic midgut NETs.[4] Lanreotide depot/autogel demonstrated antitumor efficacy among patients with pancreatic NETs and midgut NET/carcinoid tumors in the CLARINET trial.[5] Therefore, both lanreotide depot/autogel and octreotide LAR depot are considered for cytostatic control in the clinic. Anecdotal evidence suggests that increasing the dose could result in better tumor control. The NANETS committee is the only one to recommend consideration of this approach. There are no randomized or prospective data to suggest that such an approach is effective.

For patients with progressive metastatic pancreatic NETs, the NANETS, ENETS, and NCCN guidelines recommend both sunitinib and everolimus based on the significant PFS improvements demonstrated with these agents.[3] The NANETS guidelines note that there is not sufficient evidence to recommend the routine use of everolimus in patients with carcinoid tumors.[3]

ENETS guidelines state that given the limited treatment options for antiproliferative therapy in NET, everolimus may be considered a treatment option in progressive, nonfunctioning NETs.[2] RADIANT-4 data, however, will provide the definitive answer to this question. Data analysis for this trial is ongoing.[14]

The NANETS, ENETS, and NCCN guidelines recommend considering the use of cytotoxic agents, such

as temozolomide, streptozocin, or 5-fluorouracil, for palliative therapy in patients with advanced pancreatic NETs and symptoms caused by heavy tumor burden.[1-3]

Dosing of Somatostatin Analogs for Carcinoid Syndrome and Symptom Control

The guidelines acknowledge that refractory carcinoid syndrome is an unmet medical need. Carcinoid syndrome is caused by the secretion of serotonin and other bioactive amines into the systemic circulation, which manifests as flushing and diarrhea, fibrosis of the right-sided heart valves, and intestinal mesentery. Over time, however, patients with carcinoid syndrome may become refractory to somatostatin analogs. For this reason, physicians often increase the dose and/or frequency of somatostatin analogs in an attempt to control refractory carcinoid syndrome. Such an approach has anecdotally improved symptoms, although it has never been tested in a rigorous or randomized fashion. The NANETS committee recommends that somatostatin analog doses be escalated or the interval shortened in an attempt to control these symptoms, but no prospective data exist. ENETS guidelines state that doses are adapted to individual needs and depend on tumor burden and symptoms. Although this approach has not been formally evaluated, anecdotal reports and a retrospective study[15] suggest that dose escalations may improve symptom control.

Alternative Strategies for Symptom Control

Other therapies, in addition to somatostatin analogs, have been evaluated for their ability to control symptoms of carcinoid syndrome. The investigational somatostatin analog pasireotide was evaluated in a multicenter, randomized, blinded phase 3 trial in patients with metastatic NETs who had carcinoid syndrome that was inadequately controlled by somatostatin analogs.[16] A total of 110 patients were randomly assigned to pasireotide LAR or octreotide LAR depot. The 2 arms showed similar effects in regard to symptom control, and the study was stopped for futility. The safety profiles were also similar, except for a higher rate of hyperglycemia with pasireotide vs octreotide LAR depot (11% vs 0%).

Telotristat etiprate, an oral serotonin synthesis inhibitor, has also been tested in patients with diarrhea associated with carcinoid syndrome. In one prospective, randomized study, patients with evidence of carcinoid tumor and at least 4 bowel movements per day despite stable-dose octreotide LAR depot therapy were enrolled in sequential, escalating cohorts.[17] Among the evaluable patients treated with telotristat etiprate, 5 of 18 (28%) experienced a 30% or greater reduction in bowel movement frequency for at least 2 weeks, 9 of 16 (56%) experienced biochemical response (≥50% reduction or normalization in 24-hour urinary 5-HIAA) at week 2 or 4, and 10 of 18 (56%) reported adequate relief during at least 1 of the first 4 weeks of treatment. Similar activity was not observed in placebo-treated patients. Further studies are ongoing to confirm these findings. The treatment of patients with somatostatin analog–refractory carcinoid syndrome remains an unmet medical need.

Disclosure

Dr Reidy-Lagunes is a member of the advisory boards of Novartis, Ipsen, and Pfizer. She has received research funds from Novartis.

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New and Emerging Treatment Options for Gastroenteropancreatic Neuroendocrine Tumors: Q&A Discussion

Alexandria T. Phan, MD, and Pamela L. Kunz, MD

H&O Which patients are most likely to benefit from emerging treatments for GEP-NETs?

Alexandria T. Phan, MD Historically, the only group of patients with no FDA-approved therapies for cancer control has been those with midgut NETs. With the demonstrated antiproliferative effect of lanreotide depot/autogel in the CLARINET trial, there is now an FDA-approved therapy for patients with midgut NETs. The other group that may benefit from lanreotide depot/autogel is patients with pancreatic NETs. Lanreotide depot/autogel is the first therapy approved by the FDA for the frontline treatment of pancreatic NETs, and it is associated with less toxicity than other approaches, such as everolimus, sunitinib, or chemotherapy.

H&O What is known about the proper sequencing of agents?

Pamela L. Kunz, MD The optimal sequence of systemic therapies is currently unknown, but a subject of ongoing and future clinical trials. For now, selection of therapies is based on a combination of patient and treatment characteristics.

H&O What are some areas of future research?

Alexandria T. Phan, MD Many new targeted therapies are being studied, and patients should be encouraged to enroll in clinical trials. The concept of a task force has been proposed to consolidate efforts in order to more quickly answer the most pressing research questions. An important goal of current research is to gain a better understanding of the natural history of disease at the molecular level. Currently, there is some information on natural history based on histologic distinctions, but designations that are based on differentiation status or tumor grade are inaccurate and heterogeneous, varying among pathologists and within the tumor itself.

It is necessary to move toward a molecular understanding of the tissues (at the primary site and beyond) to obtain biologic or genetic signatures that would help inform the appropriate treatment strategy. Many research centers are working toward this goal.

The use of a checkpoint inhibitor in NETs appears to be promising. Studies of combination therapy, either with everolimus or a vascular endothelial growth factor therapy, would also be of value.

Pamela L. Kunz, MD Key issues in the field include selecting first-line treatments, determining the optimal sequence of therapies, and defining the best cytotoxic chemotherapy. I am also excited about the possible application of immunotherapies in NETs. Although NETs are not classically considered immunosensitive tumors, combination immunotherapies may make this issue irrelevant.

Disclosures

Dr Phan is a member of the speakers bureaus of Ipsen, Novartis, Celgene, Genentech, and Lilly. Dr Phan is currently on the advisory boards of Ipsen and Novartis. She is a past member of the advisory boards of Lexicon and GSK (now Novartis).Dr Kunz has performed contracted research for Lexicon, Genentech, Merck, Advanced Accelerator Applications, and Oxigene. She is a member of the advisory boards of Ipsen and Novartis.

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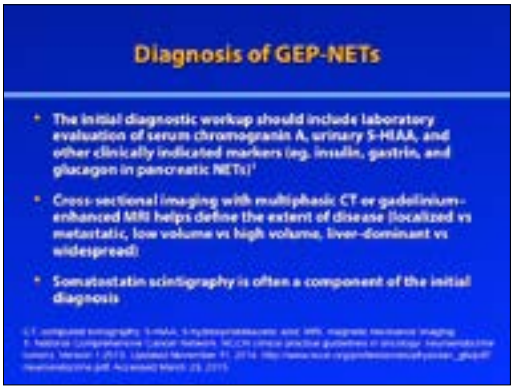

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New and Emerging Treatment Options for Gastroenteropancreatic Neuroendocrine Tumors

CME Post-Test: *Circle the correct answer for each question below.*

1. Which area has the highest incidence rate of GEP-NETs?

   a. Colon
   b. Pancreas
   c. Rectum
   d. Stomach

2. Median overall survival for patients with pancreatic NETs is reported to be:

   a. 13 months
   b. 27 months
   c. 36 months
   d. 42 months

3. Which ethnic group has the highest rate of neuroendocrine tumors?

   a. African American
   b. American Indian/Alaskan Native
   c. Asian/Pacific Islander
   d. White

4. In the PROMID trial of patients with well-differentiated, metastatic midgut NETs, octreotide LAR depot was associated with a median time to tumor progression of:

   a. 12.9 months
   b. 14.3 months
   c. 16.4 months
   d. 17.8 months

5. In the CLARINET trial of patients with advanced, well-differentiated or moderately differentiated, nonfunctioning grade 1 or 2 GEP-NETs, lanreotide depot/autogel reduced the risk of disease progression or death by a significant ___ vs placebo.

   a. 34%
   b. 49%
   c. 53%
   d. 65%

6. In the RADIANT-2 trial of patients with advanced midgut NETs/carcinoid tumors, what was the median PFS among those receiving everolimus plus octreotide LAR depot?

   a. 12.9 months
   b. 14.3 months
   c. 16.4 months
   d. 17.8 months

7. Which guidelines state that there is not sufficient evidence to recommend the routine use of everolimus in patients with carcinoid tumors?

   a. American Society of Clinical Oncology
   b. European Neuroendocrine Tumor Society
   c. National Comprehensive Cancer Network
   d. North American Neuroendocrine Tumor Society

8. In the A6181111 study of patients with pancreatic NETs, sunitinib was associated with a PFS of:

   a. 11.4 months
   b. 12.1 months
   c. 13.8 months
   d. 14.2 months

9. Control of symptoms requires substantial tumor shrinkage.

   a. True
   b. False

10. Which agent is an oral serotonin synthesis inhibitor?

    a. 5-Fluorouracil
    b. Pasireotide
    c. Telotristat etiprate
    d. Temozolomide

Evaluation Form: New and Emerging Treatment Options for Gastroenteropancreatic Neuroendocrine Tumors

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876. You may also complete the post-test online at www.cmeuniversity.com. On the navigation menu, click on "Find Post-tests by Course" and search by **project ID 10576**. Upon successfully registering/logging in, completing the post-test and evaluation, your certificate will be made available immediately.

1. What degree best describes you?

❒ MD/DO ❒ PA/PA-C ❒ NP ❒ RN ❒ PharmD/RPh ❒ PhD
❒ Other, please specify:

2. What is your area of specialization?

❒ Oncology, Medical ❒ Oncology, Other ❒ Gastroenterology

3. Which of the following best describes your *primary* practice setting?

❒ Solo Practice ❒ Group Practice ❒ Government
❒ University/teaching system ❒ Community Hospital
❒ HMO/managed care ❒ Non-profit/community ❒ I do not actively practice
❒ Other, please specify:

4. How long have you been practicing medicine?

❒ More than 20 years ❒ 11-20 years ❒ 5-10 years ❒ 1-5 years
❒ Less than 1 year ❒ I do not directly provide care

5. Approximately how many patients do you see each week?

❒ Less than 50 ❒ 50-99 ❒ 100-149 ❒ 150-199 ❒ 200+
❒ I do not directly provide care

6. How many patients do you currently see each week who have gastroenteropancreatic neuroendocrine tumors?

❒ Fewer than 5 ❒ 6-15 ❒ 16-25 ❒ 26-35 ❒ 36-45 ❒ 46-55
❒ 56 or more ❒ I do not directly provide care

7. Rate how well the activity supported your achievement of these learning objectives:

Describe the clinical characteristics and natural history of gastroenteropancreatic neuroendocrine tumors

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Identify patients who will benefit from treatment vs a watch-and-wait approach

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Select treatment based on guidelines and disease staging

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Discuss clinical data concerning the use of somatostatin analogs and targeted therapies

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

8. Rate how well the activity achieved the following:

The faculty were effective in presenting the material

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The content was evidence based

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The educational material provided useful information for my practice

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The activity enhanced my current knowledge base

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The activity provided appropriate and effective opportunities for active learning (e.g., case studies, discussion, Q&A, etc.)

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The opportunities provided to assess my own learning were appropriate (e.g., questions before, during or after the activity)

❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

9. Based upon your participation in this activity, do you intend to change your practice behavior? *(choose only one of the following options)*

❒ I do plan to implement changes in my practice based on the information presented

❒ My current practice has been reinforced by the information presented

❒ I need more information before I will change my practice

10. Thinking about how your participation in this activity will influence your patient care, how many of your patients are likely to benefit?

Please use a number (for example, 250):

11. If you plan to change your practice behavior, what type of changes do you plan to implement? *(check all that apply)*

❒ Apply latest guidelines ❒ Choice of treatment/management approach
❒ Change in pharmaceutical therapy ❒ Change in current practice for referral
❒ Change in nonpharmaceutical therapy ❒ Change in differential diagnosis
❒ Change in diagnostic testing ❒ Other, please specify:

12. How confident are you that you will be able to make your intended changes?

❒ Very confident ❒ Somewhat confident ❒ Unsure ❒ Not very confident

13. Which of the following do you anticipate will be the primary barrier to implementing these changes?

❒ Formulary restrictions ❒ Insurance/financial issues ❒ Time constraints
❒ Lack of multidisciplinary support ❒ System constraints
❒ Treatment-related adverse events ❒ Patient adherence/compliance
❒ Other, please specify:

14. Was the content of this activity fair, balanced, objective and free of bias?

❒ Yes ❒ No, please explain:

15. Please list any clinical issues/problems within your scope of practice you would like to see addressed in future educational activities:

Request for Credit (*required fields)

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Degree* _____

Organization _____

Specialty* _____

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Signature* _____ Date* _____

For Physicians Only:

I certify my actual time spent to complete this educational activity to be:

❒ I participated in the entire activity and claim 1.25 credits.
❒ I participated in only part of the activity and claim _____ credits.

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

Project ID: **10576**