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Beyond Symptom Control: Continued Advances in Targeting Gastroenteropancreatic Neuroendocrine Tumors

A Review of a Satellite Symposium of the 2014 European Society for Medical Oncology Congress

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Target Audience

This activity has been designed to meet the educational needs of medical oncologists, endocrinologists, gastroenterologists, pathologists, and nurses involved and/or interested in the management of patients with gastroenteropancreatic neuroendocrine tumors.

Statement of Need/Program Overview

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a group of heterogeneous neoplasms that present with a broad spectrum of clinical manifestations. They can differ in terms of hormone release, tumor growth rate, and related symptoms. Disease staging and grading according to established criteria can differentiate prognostic subgroups. Therapeutic strategies should be selected based on these classification systems. There is no standard of care in the treatment of GEP-NETs, and there are several sets of guidelines. Somatostatin analogs are the cornerstone of therapy for hormone-related symptoms, and these agents recently exhibited an antiproliferative effect in grade 1/low grade 2 enteropancreatic NETs. Increased knowledge of molecular biology has prompted the development of targeted therapies for GEP-NETs, which can be integrated into a treatment plan that might also include somatostatin analogs, chemotherapy, peptide-receptor–targeted radiotherapy, and locoregional therapies. Several targeted agents have already gained approval from the US Food and Drug Administration, and others are in late-stage clinical trials. The traditional watch-and-wait approach for patients with nonprogressing, nonsymptomatic, and nonfunctioning tumors has been challenged by recent phase 3 data.

Educational Objectives

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

- Describe the clinical characteristics and natural history of gastroenteropancreatic neuroendocrine tumors (GEP-NETs)
- Discuss the role of multidisciplinary care in the treatment of GEP-NETs
- Evaluate recent data from clinical trials investigating novel treatment approaches for patients with GEP-NETs
- Employ best practices in treatment selection for patients with GEP-NETs based on current recommendations and emerging data
- Identify appropriate strategies to minimize disease symptoms and treatment-related adverse events to optimize quality of life in patients with GEP-NETs

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This monograph was authored by an independent medical writer, Mindy Tanzola, PhD, based on presentations given at "Beyond Symptom Control: Continued Advances in Targeting Gastroenteropancreatic Neuroendocrine Tumors," a satellite symposium of the 2014 European Society for Medical Oncology Congress, held on September 26, 2014.

Advances in the Treatment of Gastroenteropancreatic Neuroendocrine Tumors

Alexandria T. Phan, MD

Neuroendocrine tumors (NETs) are initially indolent, but they can progress and lead to significant morbidity.[1] Overall survival (OS) and outcomes in pancreatic NET patients have slowly improved throughout the past few decades,[2] largely in response to advances in treatment. In the 1980s, significant improvements were seen with the introduction of somatostatin analogs.[3] In 2011, the US Food and Drug Administration (FDA) approved 2 targeted agents—sunitinib and everolimus—for the treatment of progressive well-differentiated pancreatic NETs in patients with unresectable, locally advanced, or metastatic disease.[4,5] Sunitinib and everolimus were both associated with statistically significant improvements in progression-free survival (PFS) in large, randomized, placebo-controlled clinical trials.[6,7] The current treatment landscape for advanced gastroenteropancreatic neuroendocrine tumors (GEP-NETs) also includes liver-directed therapy, surgical interventions, and peptide receptor radionuclide therapy, which has been used more frequently in Europe than in the United States. Combination chemotherapy remains a reasonable treatment option for patients with pancreatic NETs.[8] Patients who are diagnosed with pancreatic NETs have more treatment options that lead to better prognoses than were expected even 15 years ago.

Emerging Treatment Approaches

The latest option in the treatment of GEP-NETs is the somatostatin analog lanreotide depot/autogel. In the United States, lanreotide depot is approved by the FDA for acromegaly.[9] In the European Union, lanreotide autogel is approved for acromegaly and for NET-associated carcinoid syndrome.[10] The phase 3 CLARINET (Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors) study evaluated the use of lanreotide depot/autogel in patients with grade 1 or 2 GEP-NETs that were nonfunctioning and locally inoperable or metastatic.[11] Among the 204 patients enrolled, 91 had pancreatic NETs, 73 had midgut NETs, and 14 had hindgut NETs.

In the CLARINET trial, treatment with lanreotide depot/autogel resulted in a statistically significant improvement in PFS compared with placebo.[11] The median PFS was not reached with lanreotide depot/autogel vs 18.0 months with placebo. At 2 years, the estimated PFS rate was 65% with lanreotide depot/autogel and 33% with placebo. It is expected that these results will expand the FDA-approved indication for lanreotide depot/autogel to include advanced GEP-NET patients. The anticancer effect of lanreotide depot/autogel was further confirmed

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by a study of another somatostatin analog, octreotide depot. The 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 evaluated treatment with octreotide depot in 85 patients with advanced midgut NETs.[12] The median PFS was 14.3 months with octreotide depot and 6.0 months with placebo. The PROMID study, however, was insufficiently powered to provide convincing evidence for an antitumor effect of octreotide depot in midgut NETs.

Areas of Research

Optimal use of the currently available treatments for pancreatic NETs remains uncertain. One as-yet undefined variable is when to start therapy with a somatostatin analog in GEP-NETs. In addition, because there are more treatment options available in pancreatic NETs, the optimal sequence of systemic therapy (chemotherapy, targeted therapy, or a somatostatin analog) requires further evaluation in prospective clinical trials. The most promising ongoing research to identify novel targeted therapy in pancreatic NETs is focusing on the vascular endothelial growth factor, PI3K/AKT/mammalian target of rapamycin, and cyclin-dependent kinase pathways.[13]

Because treatment options for cancer control are lacking, the intense research in midgut, well-differentiated NETs (or carcinoid tumors) has provided the most exciting findings relating to somatostatin analogs.[14] In the United States, no therapy is FDA-approved for disease control in well-differentiated midgut NETs. Based on the results of the CLARINET trial, lanreotide depot/autogel may become the first agent approved by the FDA for disease control in patients with advanced, well-differentiated midgut NETs. Additionally, results from the RADIANT-4 (RAD001 in Advanced Neuroendocrine Tumors, Fourth Trial) study will elucidate the efficacy of everolimus for this population.[15] Midgut NETs are more indolent than pancreatic NETs. For indolent malignancies, a reasonable therapeutic goal is to achieve cytostatic disease control while maintaining quality of life.

Lanreotide depot has been shown to be effective at controlling symptoms in neuroendocrine tumors. In a recent global, randomized, phase 3 trial, lanreotide depot at 120 mg significantly reduced the need for rescue medication relative to placebo in patients with carcinoid syndrome.[16]

Presentations at the 2014 ESMO Congress

There were several abstracts presented at the 2014 ESMO congress that offered insight into the management of pancreatic NETs. Dr James C. Yao discussed updated OS data for RADIANT-3 (RAD001 in Advanced Neuroendocrine Tumors, Third Trial), the pivotal phase 3 study randomizing patients with pancreatic NETs to either everolimus or placebo.[17] The primary outcome—PFS—was reported in 2011; PFS more than doubled with everolimus (11.0 months vs 4.6 months).[18] Crossover was permitted, and 87% of the placebo arm went on to receive treatment with everolimus.[17] Three years later, almost all enrolled patients met the criteria for survival assessment. Among the patients with progressive pancreatic NETs, OS was 44 months among those initially randomized to everolimus, the longest OS reported in these patients. Among those initially randomized to placebo, the survival was 37.7 months. The log-rank *P* value was .30. The difference failed to meet predetermined statistical significance most likely because of the high rate of crossover patients, which essentially condensed the 2 treatment arms into 1 arm. Although the data suggest a benefit in OS from everolimus over placebo, the study design precludes a direct comparison or final conclusion about OS. What can be reasonably concluded is that patients with advanced pancreatic NETs will benefit from everolimus whether it is given earlier or later in the course of treatment.

Dr Riccardo Marconcini and colleagues presented the results of a single-center, retrospective analysis of 137 patients with advanced, well-differentiated GEP-NETs treated upfront with octreotide depot 30 mg or lanreotide depot/autogel 120 mg every 28 days until disease progression.[19] The analysis showed comparable efficacy between the 2 somatostatin analogs in terms of PFS, regardless of the patients' disease state (pancreatic NETs vs GI NETs) or level of Ki-67. These results are interesting, but difficult to translate into clinical practice. The study is limited because it was a retrospective assessment, it lacked a clearly defined status of disease progression at the time of initiation of therapy, and a case-controlled evaluation was not used.

The 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 was an observational trial involving 273 patients with NETs and carcinoid syndrome in 8 countries who received treatment with lanreotide depot/autogel.[20] Dr Philippe B. Ruszniewski and coworkers presented the results of the patient-reported health-related quality of life (HRQoL).[20] Overall, patients who responded had good control of the symptoms of carcinoid syndrome with lanreotide depot/autogel, translating to high levels of HRQoL.

The GEPNET Registry, which enrolled GEP-NET patients in Turkey and South Africa, as well as countries from the Asian Pacific and Middle Eastern regions, was established in 2009. Epidemiologic findings from this international registry of GEP-NETs were presented for

the first time.[21] They show a different pattern from that reported in the Surveillance, Epidemiology, and End Results analysis by Yao and coworkers in 2004.[22] The registry provides very important findings, representing a tour de force for collaborative efforts. However, the differences from the SEER data do not suggest alternate biologic behaviors, but rather variable referral practices and clinical management patterns.

Disclosure

Dr Phan has served as an advisor or consultant for Novartis and Ipsen Biopharmaceuticals, Inc. She has served as a speaker or a member of a speakers' bureau for Novartis, Celgene Corporation, Genentech, and Lilly. She has performed contracted research for Sanofi and Incyte.

References

1. Strosberg JR, Nasir A, Hodul P, Kvols L. Biology and treatment of metastatic gastrointestinal neuroendocrine tumors. *Gastrointest Cancer Res.* 2008;2(3):113-125.
2. Halfdanarson TR, Rabe KG, Rubin J, Petersen M. Pancreatic endocrine tumors (PETs): incidence and recent trend toward improved survival [ASCO abstract 4584]. *J Clin Oncol*. 2007;25(18 suppl).
3. Wolin EM. The expanding role of somatostatin analogs in the management of neuroendocrine tumors. *Gastrointest Cancer Res*. 2012;5(5):161-168.
4. FDA approval for sunitinib malate. FDA.gov. http://www.cancer.gov/cancertopics/druginfo/fda-sunitinib-malate. Updated May 24, 2011. Accessed October 29, 2014.
5. FDA approval for everolimus. FDA.gov. http://www.cancer.gov/cancertopics/druginfo/fda-everolimus#Anchor-PNET. Updated July 3, 2013. Accessed October 29, 2014.
6. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364(6):501-513.
7. Yao JC, Shah MH, Ito T, et al; the RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364(6):514-523.
8. Fine RL, Gulati AP, Krantz BA, et al. Capecitabine and temozolomide (CAPTEM) for metastatic, well-differentiated neuroendocrine cancers: The Pancreas Center at Columbia University experience. *Cancer Chemother Pharmacol*. 2013;71(3):663-670.
9. Somatuline Depot Injection [package insert]. Boulogne Billancourt Cedex, France: Ipsen Pharma; 2012.
10. European Medicines Agency decision. EMA.europa.eu. http://www.ema.europa.eu/docs/en_GB/document_library/PIP_decision/WC500159588.pdf. Updated November 29, 2013. Accessed October 29, 2014.
11. Caplin ME, Pavel M, Ćwikła JB, et al; CLARINET Investigators. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med*. 2014;371(3):224-233.
12. Rinke A, Müller HH, Schade-Brittinger C, et al; PROMID Study Group. 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: a report from the PROMID Study Group. *J Clin Oncol*. 2009;27(28):4656-4663.
13. Lairmore TC, Quinn CE, Martinez MJ. Neuroendocrine tumors of the pancreas: molecular pathogenesis and current surgical management. *Transl Gastrointest Cancer*. 2014;3(1). doi:10.3978/j.issn.2224-4778.2013.04.03.
14. ClinicalTrials.gov. An efficacy and safety study of somatuline depot (lanreotide) injection to treat carcinoid syndrome (ELECT). https://www.clinicaltrials.gov/ct2/show/NCT00774930?term=Carcinoid+tumors&rank=4. Identifier: NCT00774930. Accessed October 29, 2014.
15. ClinicalTrials.gov. Everolimus plus best supportive care vs placebo plus best supportive care in the treatment of patients with advanced neuroendocrine tumors (GI or lung origin) (RADIANT-4). http://clinicaltrials.gov/show/NCT01524783. Accessed October 17, 2014.
16. Vinik A, Wolin EW, Audry HA, Gomez-Panzani EL; ELECT Study Group. ELECT: A phase 3 study of efficacy and safety of lanreotide autogel/depot (LAN) treatment for carcinoid syndrome in patients with neuroendocrine tumors (NETs) (ASCO abstract 268). *J Clin Oncol*. 2014;32:5(suppl).
17. Yao JC, Pavel M, Lombard-Bohas C, et al. Everolimus (EVE) for the treatment of advanced pancreatic neuroendocrine tumors: final overall survival (OS) results of a randomized, double-blind, placebo (PBO)-controlled, multicenter phase III trial (RADIANT-3) [ESMO abstract 1132O]. *Ann Oncol*. 2014;25(suppl 4).
18. Yao JC, Shah MH, Ito T, et al; RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364(6):514-523.
19. Marconcini R, Ricci S, Vasile E, et al. Efficacy of somatostatin analogs (SSA) in gastroenteropancreatic neuroendocrine tumors (GEP-NET) according to ki67 index: a single centre experience [ESMO abstract 1145P]. *Ann Oncol*. 2014;25(suppl 4).
20. Ruszniewski P, Caplin M, Valle JW, et al. Treatment satisfaction, symptom control, and quality of life (QoL) with lanreotide autogel (LAN) in neuroendocrine tumour (NET) patients with carcinoid syndrome (CS): results from the SymNET study [ESMO abstract 1134PD]. *Ann Oncol*. 2014;25(suppl 4).
21. Yalcin S, Glasber S, Abali H, et al. Gastroenteropancreatic Neuroendocrine Tumors (GEPNET) registry: update from an international collaboration [ESMO abstract 1141PD]. *Ann Oncol*. 2014;25(suppl 4).
22. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol.* 2008;26(18):3063-3072.

Abstract Summaries From the 2014 European Society for Medical Oncology Congress

Abstract 1132O Everolimus for the Treatment of Advanced Pancreatic Neuroendocrine Tumors: Final Overall Survival Results of a Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase III Trial (RADIANT-3)

J.C. Yao, M. Pavel, C. Lombard-Bohas, E. van Cutsem, D. Lam, T. Kunz, U. Brandt, J. Capdevila, E.G.E. De Vries, T. Hobday, P. Tomassetti, and R. Pommier

RADIANT-3 (RAD001 in Advanced Neuroendocrine Tumors, Third Trial) is a placebo-controlled, phase 3 study that enrolled 410 patients from 18 countries. Patients had well-differentiated histology, documented radiologic progression within 12 months of randomization, and a World Health Organization performance status of 0, 1, or 2. They were randomized to receive everolimus (n=207) or placebo (n=203). The primary endpoint, progression-free survival, was reported in 2011 (*N Engl J Med*. 2011;364[6]:514-523). In the everolimus group, median progression-free survival was prolonged by 6.4 months, a 2.4-fold increase from 4.6 months to 11 months. At the 2014 European Society for Medical Oncology (ESMO) congress, Dr James C. Yao presented results of the final overall survival and safety update for RADIANT-3.

Everolimus was associated with a nonsignificant improvement in median overall survival of 6.3 months. In the placebo arm, 85% of patients crossed over to everolimus upon disease progression or completion of the core blinded phase of the study. The high crossover rate essentially meant that the main comparison was between early treatment vs late treatment after an additional progression cycle. Among the population of patients with progressive pancreatic neuroendocrine tumors, survival from study entry was 44 months among those initially randomized to everolimus and 37.7 months among those initially randomized to placebo. The log-rank *P* value was .30 and did not achieve statistical significance. An analysis of rank-preserving structural failure time (RPSFT) adjusting for crossover bias showed a survival benefit with everolimus over the RPSFT-corrected placebo arm. The survival rates were 82.6% vs 74.9%, respectively, at 12 months and 67.7% vs 55.6% respectively, at 24 months.

The safety profile of everolimus observed during the open-label extension phase was similar to the known safety profile of everolimus and to that observed during the double-blind phase. The most common adverse event was stomatitis with aphthous ulceration, which occurred among 54% of patients receiving everolimus during the double-blind phase vs 13% of the patients receiving placebo.

Abstract 1134 PD Treatment Satisfaction, Symptom Control and Quality of Life With Lanreotide Autogel in Neuroendocrine Tumour Patients With Carcinoid Syndrome: Results From the SymNET Study

P. Ruszniewski, M. Caplin, J.W. Valle, C. Lombard-Bohas, G. Poston, P. Perros, L. Holubec, G. Delle Fave, D. Smith, P. Niccoli, P. Maisonobe, and P. Atlan, on behalf of the SymNET Study Group

Carcinoid syndrome is the most common hormone hypersecretion syndrome in patients with NETs. It is associated with symptoms such as flushing, diarrhea, abdominal cramps, and cardiac complications. The 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 was an observational trial of 273 patients with NETs and carcinoid syndrome who received treatment with the long-acting somatostatin analog lanreotide depot/autogel. The primary tumor was located in the small bowel in most patients (66%). Most patients (66%) had undergone surgery. The median time from diagnosis was 4.4 years. Health-related quality-of-life data were presented at the 2014 ESMO congress.

After treatment, 76% of patients were completely satisfied and 73% were rather satisfied with the primary endpoint, diarrhea control. A similar percentage of patients, 73%, were completely or rather satisfied with flushing control. Cognitive and sexual functioning improved in 80.2% and 68.9%, respectively. Most patients reported improved social functioning and global health status/quality of life. Smaller proportions of patients experienced worse symptoms after treatment, notably fatigue

(35.0%), diarrhea (34.0%), insomnia (30.7%), muscle/bone pain (29.4%), gastrointestinal symptoms (23.0%), and dyspnea (20.4%). Disease-related worries were worse after treatment in 45.5%.

This analysis also included data by physicians gathered at an assessment visit. After treatment, mean daily stool frequency was significantly reduced to 2.1 (95% CI, 1.7-2.5). There were decreases in the percentages of patients reporting stool urgency (from 73% to 41%), stool leakage (from 21% to 9%), associated pain (from 37% to 14%), and flushing (from 61% to 33%).

1141PD Gastroenteropancreatic Neuroendocrine Tumors (GEPNET) Registry: Update From an International Collaboration

S. Yalcin, S. Glasber, H. Abali, F. Aykan, L. Bai, J. Kattan, H.Y. Lim, Y.S. Park, H. Raef, J. Ramos, K. Rau, S. Saglam, S. Serdengecti, A. Sevinc, Y. Shan, Y. Shyr, V. Sriuranpong, S.N. Turhal, K. Yeh, and T. Hwang

The GEPNET registry is collecting data on the prevalence, incidence, regional trends in diagnosis, and clinical management of GEP-NET in areas outside of the United States. Enrolled patients are from Turkey and South Africa, as well as the Asian-Pacific and Middle Eastern regions. Patients were enrolled in the registry from July 2009 through December 2012. Results from an interim analysis were presented at the 2014 ESMO congress. The registry enrolled essentially equal numbers of men (49%) and women (51%). The median age of diagnosis was 54 years (range, 12-87 years). The most common primary disease sites were the pancreas (42%) and the stomach (17%). Well-differentiated tumors were found in 80% of patients. Most patients had undergone immunostaining for synaptophysin (77%) and chromogranin A (82%). Fewer patients had undergone analysis for proliferative indices, such as the mitotic index (17%) and Ki-67 (50%). Tests used less often included serum chromogranin A testing at diagnosis (11%) and 24-hour urine 5-hydroxyindoleacetic acid (5-HIAA) tests (7%). Computed tomography scanning was the most common technique used for disease evaluation (44%). Nearly all patients (97%) had received at least 1 initial treatment. The most common initial treatment was surgery (64%), followed by somatostatin analogs (17%). The median progression-free survival was 57.3 months. The most frequently reported symptoms included abdominal pain and weight loss.

Abstract 1145P Efficacy of Somatostatin Analogs (SSA) in Gastroenteropancreatic Neuroendocrine Tumors (GEP-NET) According to Ki67 Index: A Single Centre Experience

R. Marconcini, S. Ricci, E. Vasile, L. Galli, A. Antonuzzo, L. Derosa, A. Farnesi, E. Biasco, E. Bracco, R. Vaglialoro, A. Sbrana, and A. Falcone

At the 2014 ESMO congress, Dr Riccardo Marconcini and colleagues presented results from a retrospective analysis of 137 patients with advanced GEP-NETs that stratified data according to the Ki-67 index. The patients received upfront treatment with octreotide long-acting release (LAR) or lanreotide LAR until disease progression. There were 87 gastrointestinal NET patients and 50 pancreatic NET patients. Ki-67 information was available for 89 patients; this level was less than 3% in 38 patients, 3% to 5% in 15 patients, 5% to 10% in 15 patients, and more than 10% in 21 patients.

The median time between the diagnosis of NET and initiation of treatment was 5.2 months. Twelve patients (9%) achieved a partial response, and 112 patients (81%) had stable disease. Thirteen patients (10%) had progressive disease. The authors analyzed the progression-free survival data in several different ways. Median progression-free survival varied according to the Ki-67 index; it was 27.15 months at less than 2%, 34.77 months at 2% to 5%, 28.3 months at 5% to 10%, and 20 months at greater than 10%. The median progression-free survival was 24.6 months in patients receiving octreotide and 21.83 months in patients receiving lanreotide. Median progression-free survival was 24.73 months in pancreatic NET patients and 21.73 in gastrointestinal NET patients. The authors concluded that octreotide LAR and lanreotide LAR showed comparable efficacy in terms of progression-free survival in both gastrointestinal and pancreatic NETs, and among all Ki-67 index groups.

Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs): A Closer Look at the Characteristics of These Diverse Tumors

Ulrich-Frank Pape, MD

Neuroendocrine neoplasias are a heterogeneous group of tumors that can develop in cells throughout the diffuse endocrine system, causing a wide spectrum of clinical manifestations and sequelae. The gastrointestinal tract, as the largest endocrine organ in the body, is a common site for the development of neuroendocrine tumors (NETs). Neoplasms occur in cells that exert effects on digestion and metabolic processes throughout the gastrointestinal system.[1]

Approximately 40% of NETs are "functional" tumors that secrete hormones, causing hormone hypersecretion syndromes.[2] The remaining tumors are "nonfunctional" and do not cause hormonal symptoms; they must be diagnosed through other methods. Hormone hypersecretion syndromes lead to a broad spectrum of clinical manifestations.[3] The most common hormone hypersecretion syndrome is carcinoid syndrome, which can cause flushing, diarrhea, and edema. The next most common syndromes are insulinoma and gastrinoma, which is associated with peptic ulcer disease and secondary diarrhea (Figure 1).[2] More rare syndromes include glucagonoma, Verner-Morrison syndrome, and Cushing syndrome.[2] The diverse clinical manifestations of NETs require a variety of treatment approaches.

The first classification system for NETs, published in 1963, categorized carcinoid tumors according to their location within the embryonic gastrointestinal tract—the foregut (the thymus, lung, esophagus, stomach duodenum, and pancreas), the midgut (the jejunum, ileum, cecum, and ascending and transverse colon), or the hindgut (the descending and sigmoid colon and rectum).[4] This classification system is no longer used today, and it does not provide guidance regarding prognosis or treatment stratification. It remains useful, however, for considering likely clinical manifestations and potential treatment responses.

The most common primary tumor sites of gastrointestinal NETs in Western populations are the pancreas (16%), bronchus (15%), stomach (15%), jejunum/ileum (15%), appendix (10%), and rectum (10%).[5] There are geographic differences in the distribution of gastroenteropancreatic NETs (GEP-NETs). In Japan, the most common tumor sites are the rectum (56%), followed by the duodenum (17%) and the stomach (15%).[6] Japanese data include a relatively high incidence of small, early-stage tumors that occur primarily in the rectum but also in the pancreas.

The incidence of GEP-NETs has increased in recent decades, as reported in both the US Surveillance, Epidemiology, and End Results (SEER) database and in a population-based study in Europe.[7,8] Increases have been reported for nearly all organ manifestations.[7,8] Factors leading to the increased diagnoses include the introduction of statin analogs as a treatment option, which provided an incentive to identify patients; and the use of specific immunohistochemical markers—synaptophysin and chromogranin A—which enabled better detection of these tumors. Synaptophysin is a marker for the small synaptic vesicles that store and secrete biogenic amines, such as serotonin, and chromogranin A is a marker for the large dense-core vesicles that store the peptides or propeptide hormones in endocrine cells.

GEP-NETs predominately affect older adults, but they can also develop in younger people. In one series of patients, the median age at diagnosis was 59 years, but the range spanned from 10 to 99 years.[9] GEP-NETs are also biologically diverse. A prospective study in Austria of all GEP-NETs diagnosed within a 1-year period showed substantial heterogeneity in the biologic characteristics of GEP-NETs according to their location. GEP-NETs in the stomach, appendix, and rectum were classified primarily as benign or uncertain, whereas the majority of GEP-NETs in the small intestine, pancreas, and colon were malignant.[10]

In 1995, Capella and colleagues published a revised classification system for NETs of the lung, pancreas, and gastrointestinal system.[11] The revised system attempted to account for the morphologic, functional, and biologic features of the tumors. The complexity of this classification system has limited its clinical applicability; however, its emphasis on primary tumor localization and extent of disease is notable, as these characteristics—in particular, the presence of metastatic disease—have been shown to have substantial prognostic importance (Figure 2).[9,12-15]

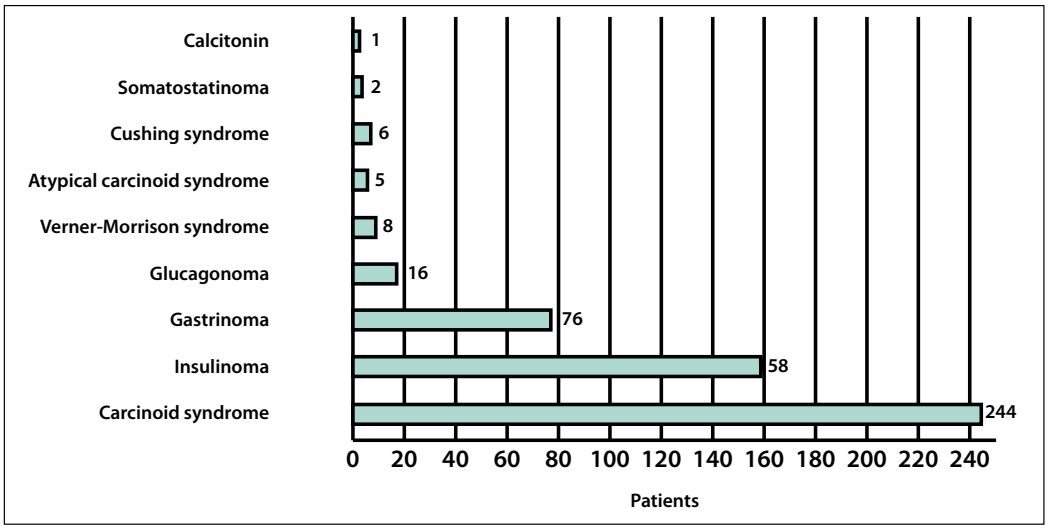

Figure 1. Hormone hypersecretion syndromes in patients with neuroendocrine tumors. Adapted from Begum N et al. *Zentralbl Chir*. 2014;139(3):276-283.[2]

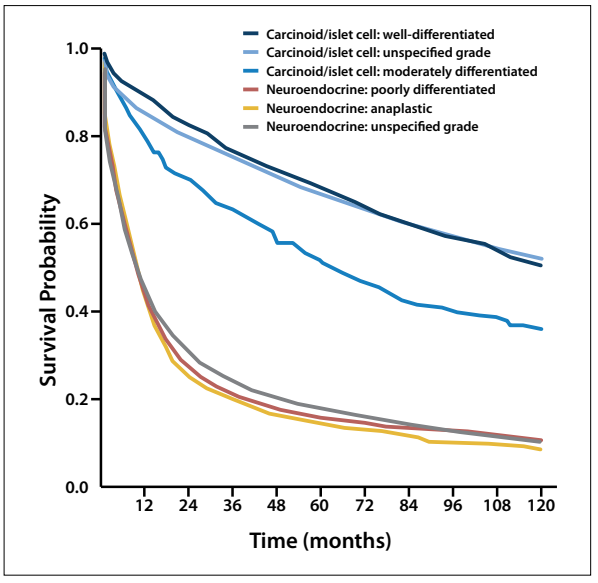

Figure 2. Primary tumor localization and extent of disease have been shown to have prognostic importance. Adapted from Yao JC et al. *J Clin Oncol*. 2008;26(18):3063-3072.[12]

The World Health Organization (WHO) classification criteria for neuroendocrine neoplasms have evolved substantially since their first publication in 1980. Today, they are widely used for the classification of NETs.[16] In 2000, the WHO classified GEP-NETs into 3 categories based on their histologic differentiation.[17] In 2010, the WHO criteria were updated to grade NETs according to their Ki-67 index (using the MIB-1 antibody). Ki-67 has demonstrated significant prognostic value in multiple studies of patients with NETs (Figure 3).[9,15,18-20] German registration data indicate that both disease stage and tumor grade have significant prognostic value in GEP-NETs.[21] Incorporation of Ki-67 into the WHO classification system was an essential update. Ki-67 levels are categorized as follows: 2% or less, grade 1; 3% to 20%, grade 2; higher than 20%, grade 3.[22]

A staging system for GEP-NETs from stage I to stage IV has been developed based on a tumor/lymph node/metastasis (TNM) system specifically defined for each tumor manifestation. First proposed by the European Neuroendocrine Tumor Society (ENETS)[23,24] and later adopted by the American Joint Committee on Cancer/Union for International Cancer Control,[25] the system accounts for differences in growth patterns based on a tumor's primary location. Within each tumor location, tumors are staged from T0 to T4 based on the tumor size and invasion into other tissue, as N0 or N1 based on the presence of regional lymph node metastasis, and as M0 or M1 based on the presence of distant metastasis.

Many of the GEP-NET staging systems have been clinically validated. Analysis of a Berlin cohort of 270 GEP-NETs of midgut and hindgut origin found that classification of tumors using the WHO criteria and the ENETS TNM staging system yielded prognostic significance.[26] Overall, 7% of tumors were stage 1, 8% were stage 2, 19% were stage 3, and 66% were stage 4. Five-year survival rates ranged from 100% for stages 1 and 2 to 83% for stage 4. Based on the WHO criteria, 62% of tumors were grade 1, 32% were grade 2, and 6% were grade 3; 5-year survival rates were 95%, 82%, and 51%, respectively. The prognostic relevance of the classification system has also been validated for foregut NETs,[27] gastric NETs,[28] and pancreatic NETs.[18,29] These studies have confirmed prognostic differences based on the primary tumor location.

Importantly, these outcomes are influenced by the treatments that patients have received. A multicenter analysis of

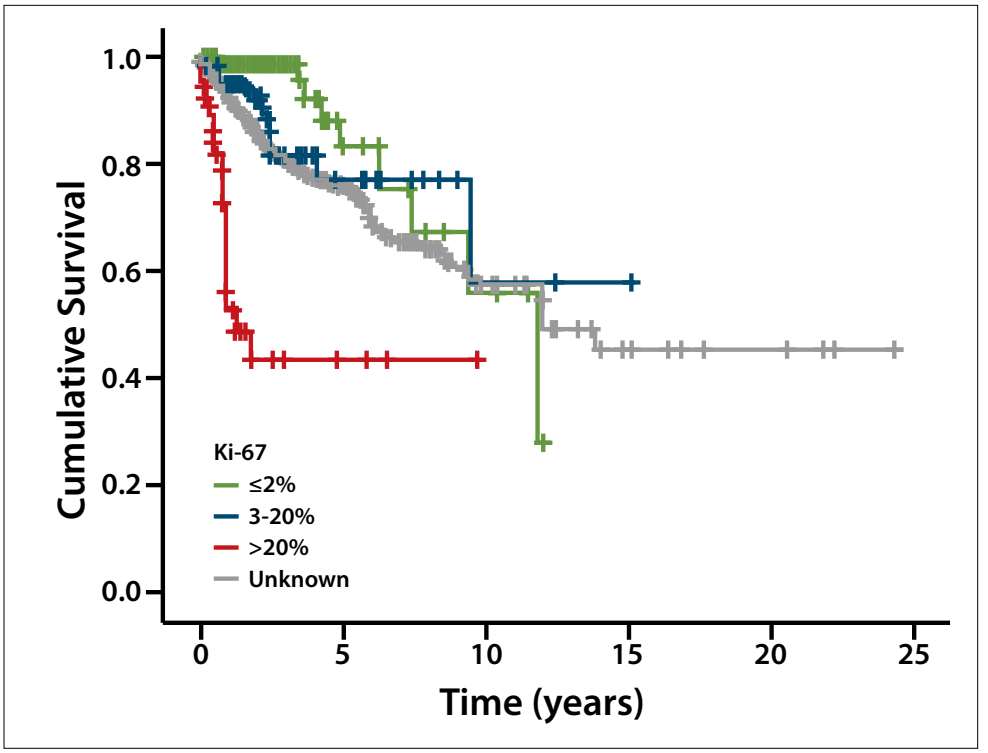

Figure 3. The Ki-67 index has shown significant prognostic value in patients with neuroendocrine tumors. Adapted from Garcia-Carbonero R et al. *Ann Oncol*. 2010;21(9):1794-1803.[9]

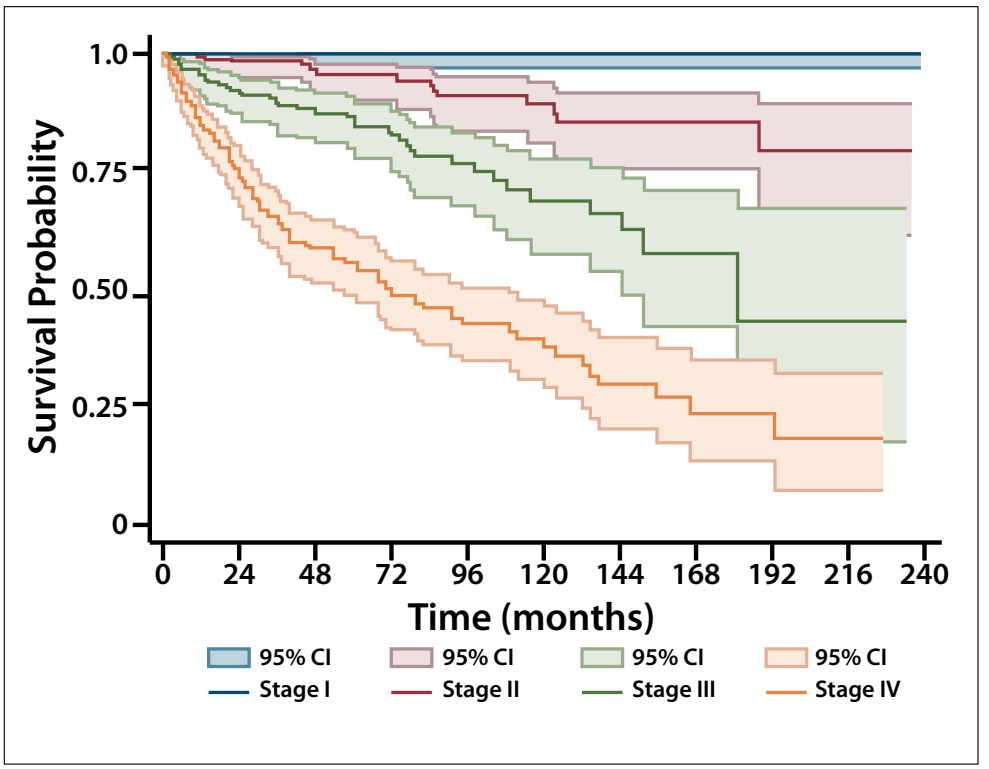

Figure 4. Tumor-related death and ENETS stage in a multicenter analysis of patients who had undergone surgery for pancreatic neuroendocrine tumors. ENETS, European Neuroendocrine Tumor Society. Adapted from Rindi G et al. *J Natl Cancer Inst*. 2012;104(10):764-777.[30]

1072 patients who had undergone surgery for pancreatic NETs confirmed the prognostic significance of the ENETS TNM staging system (Figure 4) and found that curative surgery was also independently associated with survival.[30] Treatment is an important component of outcome for patients with GEP-NETs, and therapeutic strategies can be guided by the current classification systems.

Disclosure

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References

1. Rindi G, Wiedenmann B. Neuroendocrine neoplasms of the gut and pancreas: new insights. *Nat Rev Endocrinol*. 2012;8(1):54-64.
2. Begum N, Maasberg S, Plöckinger U, et al; Weitere Vertreter des deutschen NET-Registers. [Neuroendocrine tumours of the GI tract—data from the German NET Registry]. *Zentralbl Chir*. 2014;139(3):276-283.
3. Maasberg S, Denecke T, Pascher A, Pape UF. [Neuroendocrine neoplasias of the gastroenteropancreatic system]. *Gastroenterology*. 2012;7(2):139-155.
4. Williams ED, Sandler M. The classification of carcinoid tumours. *Lancet*. 1963;1(7275):238-239.
5. Pape UF, Anlauf M, Pavel M. Neuroendokrine neoplasien des gastroenteropankreatischen systems. *Gastroenterolie Up2date*. 2011;7(4):313-339.
6. Ito T, Sasano H, Tanaka M, et al. Epidemiological study of gastroenteropancreatic neuroendocrine tumors in Japan. *J Gastroenterol*. 2010;45(2):234-243.
7. Tsikitis VL, Wertheim BC, Guerrero MA. Trends of incidence and survival of gastrointestinal neuroendocrine tumors in the United States: a seer analysis. *J Cancer*. 2012;3:292-302.
8. Ellis L, Shale MJ, Coleman MP. Carcinoid tumors of the gastrointestinal tract: trends in incidence in England since 1971. *Am J Gastroenterol*. 2010;105(12):2563-2569.
9. Garcia-Carbonero R, Capdevila J, Crespo-Herrero G, et al. Incidence, patterns of care and prognostic factors for outcome of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): results from the National Cancer Registry of Spain (RGETNE). *Ann Oncol*. 2010;21(9):1794-1803.
10. Niederle MB, Hackl M, Kaserer K, Niederle B. Gastroenteropancreatic neuroendocrine tumours: the current incidence and staging based on the WHO and European Neuroendocrine Tumour Society classification: an analysis based on prospectively collected parameters. *Endocr Relat Cancer*. 2010;17(4):909-918.
11. Capella C, Heitz PU, Höfler H, Solcia E, Klöppel G. Revised classification of neuroendocrine tumours of the lung, pancreas and gut. *Virchows Arch*. 1995;425(6):547-560.
12. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol*. 2008;26(18):3063-3072.
13. Weber HC, Venzon DJ, Lin JT, et al. Determinants of metastatic rate and survival in patients with Zollinger-Ellison syndrome: a prospective long-term study. *Gastroenterology*. 1995;108(6):1637-1649.
14. Madeira I, Terris B, Voss M, et al. Prognostic factors in patients with endocrine tumours of the duodenopancreatic area. *Gut*. 1998;43(3):422-427.
15. Pape UF, Berndt U, Müller-Nordhorn J, et al. Prognostic factors of long-term outcome in gastroenteropancreatic neuroendocrine tumours. *Endocr Relat Cancer*. 2008;15(4):1083-1097.
16. Klöppel G. Classification and pathology of gastroenteropancreatic neuroendocrine neoplasms. *Endocr Relat Cancer*. 2011;18(suppl 1):S1-S16.
17. Solcia E, Klöppel G, Sobin LH. Histological typing of endocrine tumours. In: *WHO International Histological Classification of Tumours*. 2nd ed. Berlin, Germany: Springer; 2000.
18. Ekeblad S, Skogseid B, Dunder K, Oberg K, Eriksson B. Prognostic factors and survival in 324 patients with pancreatic endocrine tumor treated at a single institution. *Clin Cancer Res*. 2008;14(23):7798-7803.
19. Vilar E, Salazar R, Pérez-García J, Cortes J, Oberg K, Tabernero J. Chemotherapy and role of the proliferation marker Ki-67 in digestive neuroendocrine tumors. *Endocr Relat Cancer*. 2007;14(2):221-232.
20. Scarpa A, Mantovani W, Capelli P, et al. Pancreatic endocrine tumors: improved TNM staging and histopathological grading permit a clinically efficient prognostic stratification of patients. *Mod Pathol*. 2010;23(6):824-833.
21. NET Register. Herzlich willkommen beim Deutschen Register Neuroendokrine Gastrointestinale Tumore (NET-Register). http://www.net-register.org/index.php?navanchor=1010000. Accessed October 22, 2014.
22. Bosman FT, Carneiro F, Hruban R, Theise N. *WHO Classification of Tumours of the Digestive System*. 4th ed. Lyon, France: International Agency for Research on Cancer (IARC); 2010.
23. Rindi G, Klöppel G, Alhman H, et al; all other Frascati Consensus Conference participants; European Neuroendocrine Tumor Society (ENETS). TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Arch*. 2006;449(4):395-401.
24. Rindi G, Klöppel G, Couvelard A, et al. TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. *Virchows Arch*. 2007;451(4):757-762.
25. Klöppel G, Rindi G, Perren A, Komminoth P, Klimstra DS. The ENETS and AJCC/UICC TNM classifications of the neuroendocrine tumors of the gastrointestinal tract and the pancreas: a statement. *Virchows Arch*. 2010;456(6):595-597.
26. Jann H, Roll S, Couvelard A, et al. Neuroendocrine tumors of midgut and hindgut origin: tumor-node-metastasis classification determines clinical outcome. *Cancer*. 2011;117(15):3332-3341.
27. Pape UF, Jann H, Müller-Nordhorn J, et al. Prognostic relevance of a novel TNM classification system for upper gastroenteropancreatic neuroendocrine tumors. *Cancer*. 2008;113(2):256-265.
28. La Rosa S, Inzani F, Vanoli A, et al. Histologic characterization and improved prognostic evaluation of 209 gastric neuroendocrine neoplasms. *Hum Pathol*. 2011;42(10):1373-1384.
29. La Rosa S, Klersy C, Uccella S, et al. Improved histologic and clinicopathologic criteria for prognostic evaluation of pancreatic endocrine tumors. *Hum Pathol*. 2009;40(1):30-40.
30. Rindi G, Falconi M, Klersy C, et al. TNM staging of neoplasms of the endocrine pancreas: results from a large international cohort study. *J Natl Cancer Inst*. 2012;104(10):764-777.

New Directions in the Treatment of Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs): Shifting From Symptom Management to Targeting Tumors

Matthias Weber, MD

Therapy for patients with NETs is based on 3 main therapeutic principles. The first principle is that surgical therapy is the only curative option for NETs; it is also used for debulking and to treat and prevent complications. The second principle is that symptomatic therapy can be used to control the hormonal symptoms associated with functioning NETs. The third principle is that antiproliferative therapy can be used to control tumor growth and possibly improve survival.

Surgical Therapy

Surgical resection is the only curative option for patients with differentiated (grade 1 or grade 2) GEP-NETs. Curative surgery of liver metastasis should also be considered when R0 or R1 resection is feasible.[1] Surgery may also be undertaken to treat or prevent complications. For example, removal of the primary tumor is recommended in patients with metastatic midgut NETs, as even small tumors in this region can have severe complications. Debulking surgery should be considered when removal of more than 90% of the tumor mass can be achieved, particularly for hormonally active NETs. This approach will likely lead to improved survival, but it is not supported by evidence owing to selection bias.

Local ablative therapies may also have a role in patients with advanced NETs and liver metastases. Techniques include transarterial chemoembolization, radioembolization, and selective internal radiation therapy.[1,2] These approaches provide symptomatic improvement in the majority of patients with highly vascularized, unresectable metastases, and they may also induce a morphologic response. Percutaneous radiofrequency ablation and cryoablation may be considered as cytoreductive therapy for patients with limited numbers (3-4) of smaller (<3-5 cm) liver metastases. These procedures can supplement surgical resection of liver metastases and provide symptomatic improvement in the majority of patients.

Symptomatic Therapy

The gold-standard, first-line approach for symptomatic treatment of functionally active NETs is targeted therapy with somatostatin analogs. Most NETs express somatostatin receptors.[3] The somatostatin receptor subtype 2, the most prevalent in GEP-NETs, exerts an inhibitory effect on hormone secretion and proliferation.[4,5] Treatment with somatostatin can effectively control hormonal symptoms associated with GEP-NETs. Clinical use of somatostatin is limited, however, by its short half-life.[4]

Synthetic derivatives of somatostatin have been developed to overcome the short half-life of the native protein. The development of these agents was a significant advance in the treatment of patients with NETs. The somatostatin analog octreotide is administered by subcutaneous injection 2 to 3 times daily. Long-acting formulations have been developed for both octreotide and lanreotide depot/autogel. The octreotide long-acting release (LAR) formulation is administered once monthly via deep intramuscular injection, and lanreotide depot/autogel is administered once monthly via deep subcutaneous injection.[6] Both octreotide and lanreotide depot/autogel show high affinity for the somatostatin subtype receptor 2 and are approved for antisecretory treatment in NETs.

Symptomatic responses were observed in approximately 65% to 75% of patients receiving lanreotide depot/autogel and octreotide LAR, and biochemical responses were observed in approximately 50% of patients.[1,4] The symptomatic effect of lanreotide depot/autogel in patients with NETs was further evaluated in the multinational 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 included 273 patients with NET and a history of diarrhea associated with carcinoid syndrome.[7] Patients had received lanreotide depot/autogel for at least 3 months. The majority of patients reported improvements in all symptoms, 76% reported satisfaction with diarrhea control, and 73% were satisfied with flushing control. Patients also reported favorable health-related quality-of-life outcomes, with a high level of ability to conduct activities and low symptom scores. Moreover, patient-reported outcomes were consistent

with the investigators' observations. The SymNET study confirmed in a real-world setting the symptomatic effects of lanreotide depot/autogel in patients with functionally active GEP-NETs.

Overview of Antiproliferative Therapy

Antiproliferative therapy for GEP-NETs aims to control tumor growth and ultimately improve survival. It is important to consider the potential antiproliferative effects of therapy in the context of the natural history of GEP-NETs. These tumors generally grow slowly, and patients may demonstrate long phases of apparently stable disease followed by slowly progressing disease. Moreover, spontaneous remissions have been observed in patients with highly differentiated grade 1 or 2 NETs. Rapidly progressing disease is rare and typically observed only in highly aggressive grade 3 neuroendocrine carcinomas.

The typically slow course of NETs has led to the proposal of a fourth treatment principle, which involves watchful waiting for patients with apparently stable tumors who have no hormonal symptoms or clinical sequelae. Antiproliferative therapy is initiated upon disease progression. This strategy, however, has been challenged by recent findings indicating that somatostatin analogs exert an antiproliferative effect in addition to their symptomatic effect.[6] This development may shift the therapeutic algorithm from one based on symptom management by somatostatin analogs in functionally active tumors toward a more integrative approach in which the tumor is targeted to control both hormone secretion and tumor growth.

Several mechanisms have been proposed to explain the antiproliferative activity of somatostatin analogs.[6] Direct antitumor effects mediated through targeting of the somatostatin receptors on tumor cells may include inhibition of cell growth or cell cycle progression and induction of apoptosis.[6] Indirect outcomes may include lowering of growth factors, in particular, insulin-like growth factor 1; inhibition of angiogenesis; and modulation of the immune system.

The PROMID Study

The ability of somatostatin analogs to control tumor growth was demonstrated in small studies but remained under debate until publication of the placebo-controlled, double-blind, prospective, 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) study, which evaluated the effect of octreotide LAR in the control of tumor growth in 85 patients with advanced midgut NETs.[8] This randomized,

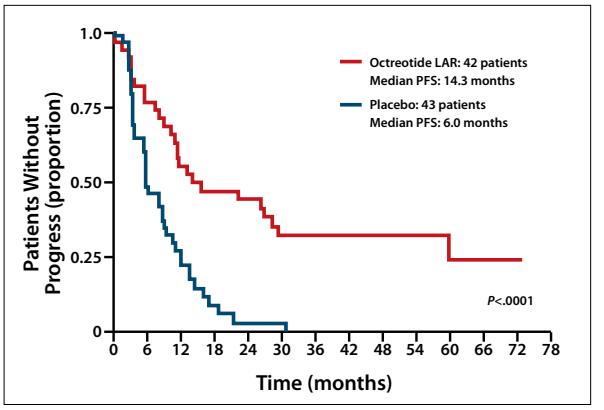

Figure 5. Progression-free survival in the PROMID trial among patients with advanced midgut neuroendocrine tumors. LAR, long-acting release; PFS, progression-free survival; PROMID, Placebo Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors. Adapted from Rinke A et al. *J Clin Oncol.* 2009;27(28):4656-4663.[8]

placebo-controlled trial was the first conducted in a well-defined population of patients with NETs. Notably, 41% of patients in the octreotide arm and 37% in the placebo arm had carcinoid syndrome at baseline. Approximately 75% of patients had a hepatic tumor load of less than 10% at baseline. More than 90% of patients had a Ki-67 level of 2% or less.

Octreotide LAR was associated with a significant improvement in progression-free survival (PFS) over placebo. The median PFS was 14.3 months with octreotide LAR and 6.0 months with placebo (Figure 5). The greatest benefit of octreotide LAR was observed in patients with midgut tumors, grade 1 tumors, and a hepatic tumor burden of less than 10%.[8] Octreotide had the greatest effect in patients with minimal liver involvement, but this outcome may reflect tumor mass and disease progression. Octreotide LAR failed to achieve an antiproliferative effect in patients with nonmidgut tumors, higher liver tumor burden, grade 2 tumors, or progressive disease.

The CLARINET Study

The randomized, double-blind, placebo-controlled phase 3 CLARINET (Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors) study was undertaken to evaluate the antiproliferative effect of lanreotide depot/autogel in a larger and more advanced patient population than in the PROMID trial.[8,9] The CLARINET study enrolled 204 patients with grade 1 or 2 GEP-NETs that were well-differentiated or moderately differentiated (Ki-67 <10%), nonfunctioning, and locally inoperable or metastatic.[9] Nearly all patients (96%) had not experienced

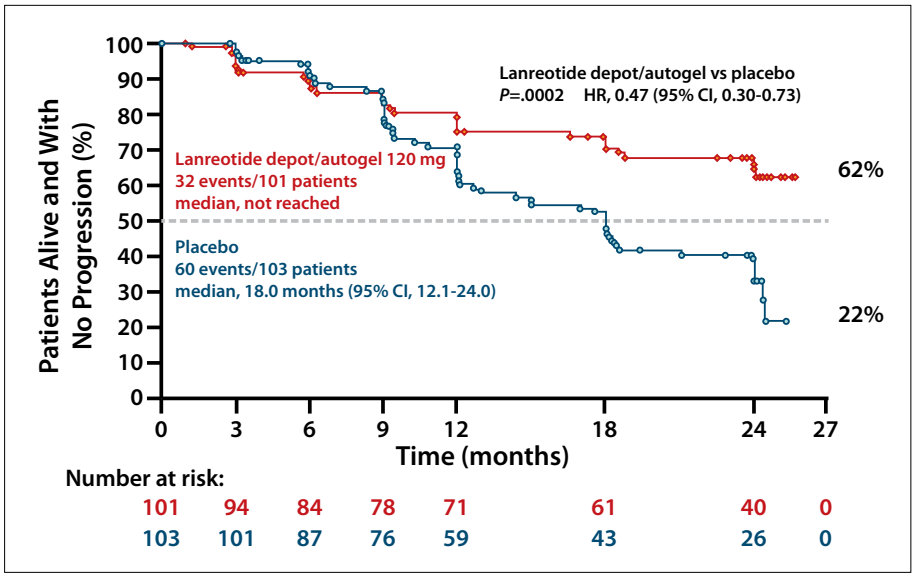

Figure 6. Progression-free survival among the intent-to-treat population in the CLARINET trial in patients with grade 1 or 2 GEP-NETs that were well-differentiated or moderately differentiated, nonfunctioning, and locally inoperable or metastatic. CLARINET, Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors. Adapted from Caplin ME et al. *N Engl J Med*. 2014;371(3):224-233.[9]

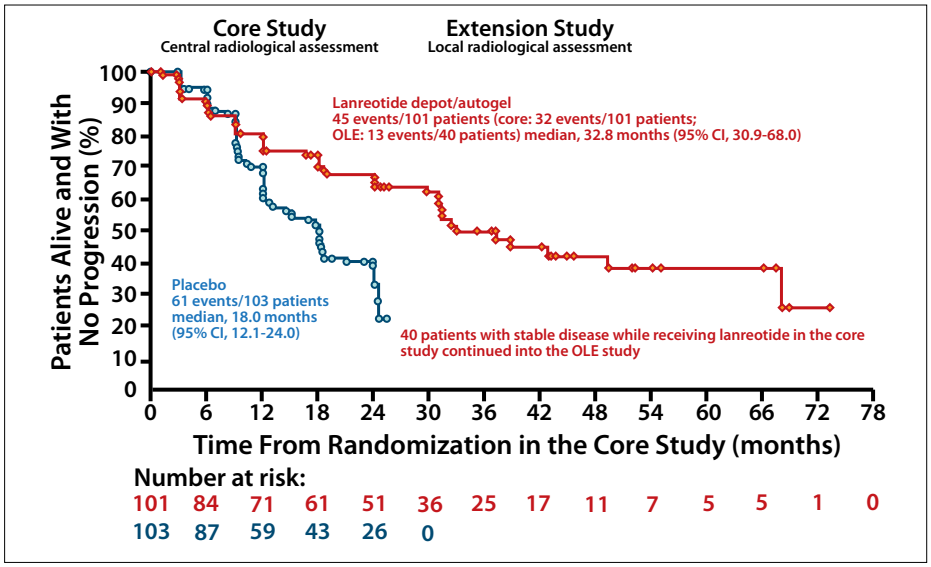

Figure 7. Median progression-free survival in the CLARIENT-OLE trial, which included patients with stable disease who continued on lanreotide and patients in the placebo group with or without progressive disease who received open-label lanreotide. CLARIENT-OLE, Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors Open-Label Extension. Adapted from Caplin ME et al. ASCO abstract 4107^. *J Clin Oncol*. 2014;32:5(suppl).[10]

tumor progression during the 3 to 6 months before randomization. Enrolled patients were randomly assigned to receive subcutaneous lanreotide depot/autogel at 120 mg every 28 days or placebo every 28 days, with treatment continuing until tumor progression or death.

Lanreotide depot/autogel was associated with a significant 53% reduction in the risk of progression or death as compared with placebo. The median PFS was not reached with lanreotide depot/autogel vs 18.0 months with placebo (hazard ratio [HR], 0.47; 95% CI, 0.30-0.73; *P*<.001).[9] At the end of 24 months, the estimated PFS rate was 65% with lanreotide depot/autogel and 33% with placebo (Figure 6). The antiproliferative effect of lanreotide depot/autogel demonstrated in the overall population was maintained during an analysis of predefined subgroups, including grade 1 vs grade 2 tumors and low vs high hepatic tumor load. There was a trend toward improved PFS in patients with midgut and pancreatic

NETs; the difference did not reach statistical significance in the pancreatic NET subgroup, although the CIs were wide owing to the small numbers of patients.

The safety analysis confirmed the good tolerability of somatostatin analogs demonstrated in other studies. The most prominent adverse events were diarrhea (reported in 26% of patients in the lanreotide depot/autogel group and 9% in the placebo group) and abdominal pain (reported in 14% and 2%, respectively).[9] Other adverse events were reported at similar levels with lanreotide depot/autogel and placebo. There were no significant differences in quality of life between the groups.

An open-label extension study evaluated the long-term safety and efficacy of lanreotide depot/autogel for up to 6 years in patients with GEP-NETs.[10] The study included patients with stable disease who continued on lanreotide depot/autogel and patients in the placebo group with or without progressive disease who received open-label lanreotide depot/autogel. The median PFS in the lanreotide depot/autogel group was 32.8 months vs 18.0 months in the placebo group (Figure 7).[10] The core CLARINET trial and the open-label extension phase used different radiologic assessment protocols (local vs central radiologic assessment), and therefore a direct comparison of outcomes is precluded. However, the open-label extension study suggests the extent of PFS improvement that might be attained with lanreotide depot/autogel. Among the patients who initially received placebo and switched to lanreotide depot/autogel after documented radiologic disease progression, the median time to second progression after starting therapy was 14 months.[10]

In summary, the CLARINET study demonstrated that lanreotide depot/autogel was associated with a 53% reduction in the risk of progression or death in patients with metastatic well-differentiated or moderately differentiated GEP-NETs.[9] This antiproliferative effect was observed in patients with grade 1 and grade 2 tumors, in patients with low and high hepatic tumor load, and, in the open-label extension, in patients with progressive disease.[9,10] Lanreotide depot/autogel also showed a good tolerability profile that was consistent with previous studies.[9] Overall, these findings support an important role for lanreotide depot/autogel in the treatment of GEP-NETs.

Other Therapeutic Approaches for Patients With Advanced or Progressive Disease

Several alternative antiproliferative therapies might be considered for systemic treatment in patients with advanced or progressive disease. Chemotherapy is generally ineffective in patients with grade 1 or grade 2 cancers of the midgut, yielding overall response rates of less than 20%.[11-15] However, streptozotocin-based chemotherapy has demonstrated efficacy in patients with grade 1 or

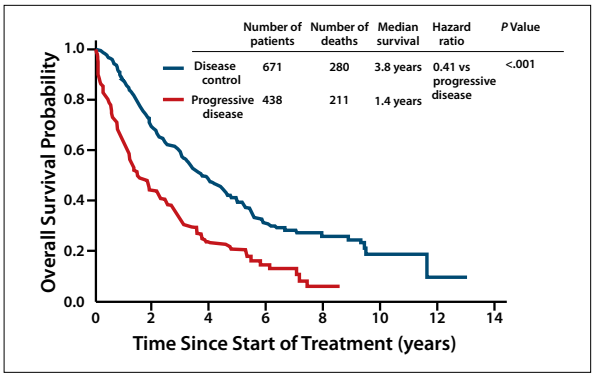

Figure 8. An open-label, phase 2 study suggested a survival benefit with peptide-receptor–targeted radiotherapy in patients responding to therapy. Adapted from Imhof A et al. *J Clin Oncol*. 2011;29(17):2416-2423.[20]

grade 2 pancreatic NETs, yielding objective response rates of 40% to 50% and a stable disease rate of 50%.[16] Based on these outcomes, the ENETS guidelines regard streptozotocin-based chemotherapy as first-line treatment in patients with progressive or advanced pancreatic NETs.[15]

Another setting in which chemotherapy has demonstrated benefit is the group of patients with poorly differentiated (grade 3) NETs, in whom etoposide plus cisplatin has demonstrated objective response rates of 40% to 70%.[15] These responses, however, were generally short, and the median survival was approximately 12 to 18 months.[15]

Peptide-receptor–targeted radiotherapy (PRRT) using radiolabeled somatostatin analogs may be a therapeutic option for some patients with unresectable metastatic somatostatin receptor–positive NETs.[17] The approach has been evaluated primarily in small phase 2 studies and retrospective reports, which have yielded objective response rates of approximately 30% to 40%.[17-19] Moreover, an open-label, phase 2 study suggested a survival benefit with PRRT in patients responding to therapy (Figure 8).[20] Given the limited data available for this approach, including a lack of randomized studies, PRRT is considered a second-line therapy by the ENETS guidelines.[15] Use of PRRT is also limited by safety concerns, including hematologic and renal toxicity, and a lack of widespread commercial availability.

The somatostatin analogs are molecularly targeted based on the pathogenesis of NETs. Other molecularly targeted therapies have also been evaluated in the treatment of these tumors, including the multiple tyrosine kinase inhibitor sunitinib and the mammalian target of rapamycin inhibitor everolimus.[21]

Sunitinib was evaluated in a randomized, double-blind, placebo-controlled, phase 3 trial in patients with advanced, well-differentiated pancreatic NETs. In this trial, median PFS doubled with sunitinib vs placebo (11.4 months vs 5.5 months, respectively; HR, 0.418; 95% CI, 0.263-0.662; *P*=.0001).[22] This highly significant

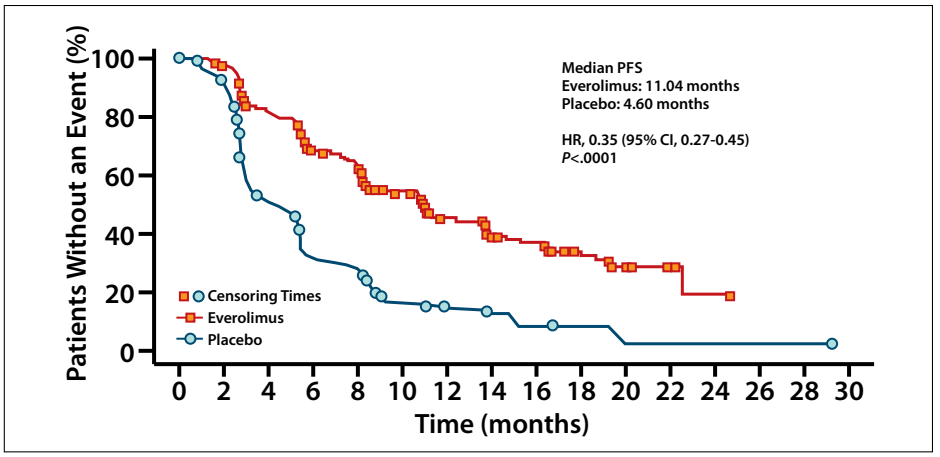

Figure 9. Median progression-free survival in the RADIANT-3 trial, which enrolled patients with advanced low-grade or intermediate-grade pancreatic NETs who had experienced radiographic progression in the previous 12 month. RADIANT-3, RAD001 in Advanced Neuroendocrine Tumors, Third Trial. Adapted from Yao JC et al. *N Engl J Med*. 2011;364(6):514-523.[23]

improvement in PFS led to the approval of sunitinib for the treatment of advanced pancreatic NETs.

Everolimus was evaluated in the randomized, double-blind, placebo-controlled, phase 3 RADIANT-3 (RAD001 in Advanced Neuroendocrine Tumors, Third Trial) study, which enrolled 410 patients with advanced low-grade or intermediate-grade pancreatic NETs who had experienced radiographic progression in the previous 12 months.[23] Median PFS was 11.0 months with everolimus vs 4.6 months with placebo (HR, 0.35; 95% CI, 0.27-0.45; *P*<.0001; Figure 9). Based on these results, everolimus received approval for the treatment of advanced pancreatic NETs.

A combination approach of everolimus plus octreotide LAR has also been evaluated in patients with NETs. The randomized, placebo-controlled, double-blind, phase 3 RADIANT-2 (RAD001 in Advanced Neuroendocrine Tumors, Second Trial) study compared octreotide LAR with everolimus or placebo in patients with advanced, well-differentiated NETs and carcinoid syndrome.[24] Everolimus plus octreotide LAR was associated with a trend toward improved median PFS (16.4 vs 11.3 months) that was clinically meaningful but failed to reach statistical significance.

Conclusion

The optimal management of patients with NETs requires a multidisciplinary approach that may involve surgery, localized therapy, somatostatin analogs, targeted therapy, PRRT, and chemotherapy. Given the substantial antisecretory effects of somatostatin analogs, their antiproliferative effects, and their good tolerability profile, these agents should play an important role in the therapeutic armamentarium of NETs.

Although a survival benefit for somatostatin analogs has not been directly demonstrated, data from the SEER program registries indicate that survival has improved in the era of somatostatin analogs, with the median survival increasing from 18 months for patients diagnosed with metastatic NETs from 1973 through 1987 to 38 months for patients diagnosed from 1998 through 2004.[25]

Disclosure

Dr Weber has received consulting fees from Ipsen, Novartis, and Pfizer. He has received fees for non-CME services from Ipsen, Novartis, and Pfizer.

References

1. Pavel M, Baudin E, Couvelard A, et al; Barcelona Consensus Conference participants. ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. *Neuroendocrinology*. 2012;95(2):157-176.
2. Frilling A, Modlin IM, Kidd M, et al. Recommendations for management of patients with neuroendocrine liver metastases. *Lancet Oncol*. 2014;15(1):e8-e21.
3. Basu B, Sirohi B, Corrie P. Systemic therapy for neuroendocrine tumours of gastroenteropancreatic origin. *Endocr Relat Cancer*. 2010;17(1):R75-R90.
4. Modlin IM, Pavel M, Kidd M, Gustafsson BI. Review article: somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine (carcinoid) tumours. *Aliment Pharmacol Ther*. 2010;31(2):169-188.
5. Ferrante E, Pellegrini C, Bondioni S, et al. Octreotide promotes apoptosis in human somatotroph tumor cells by activating somatostatin receptor type 2. *Endocr Relat Cancer*. 2006;13(3):955-962.
6. Susini C, Buscail L. Rationale for the use of somatostatin analogs as antitumor agents. *Ann Oncol*. 2006;17(12):1733-1742.
7. Ruszniewski PB, Caplin ME, Valle JW, et al. Lanreotide autogel/depot (LAN) treatment for carcinoid syndrome (CS) symptoms: patient-reported outcomes (PROs) from the SYMNET study [ASCO abstract 4111^]. *J Clin Oncol*. 2014;32:5(suppl).
8. Rinke A, Müller HH, Schade-Brittinger C, et al; PROMID Study Group. 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: a report from the PROMID Study Group. *J Clin Oncol*. 2009;27(28):4656-4663.
9. Caplin ME, Pavel M, Ćwikła JB, et al; CLARINET Investigators. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med*. 2014;371(3):224-233.
10. Caplin ME, Ruszniewski PB, Pavel ME, et al. Progression-free survival with lanreotide autogel/depot in enteropancreatic neuroendocrine tumor patients: the CLARINET extension study [ASCO abstract 4107^]. *J Clin Oncol*. 2014;32:5(suppl).
11. Moertel CG, Hanley JA. Combination chemotherapy trials in metastatic carcinoid tumor and the malignant carcinoid syndrome. *Cancer Clin Trials*. 1979;2(4):327-334.
12. Engstrom PF, Lavin PT, Moertel CG, Folsch E, Douglass HO Jr. Streptozocin

plus fluorouracil versus doxorubicin therapy for metastatic carcinoid tumor. *J Clin Oncol*. 1984;2(11):1255-1259.
13. Bukowski RM, Johnson KG, Peterson RF, et al. A phase II trial of combination chemotherapy in patients with metastatic carcinoid tumors. A Southwest Oncology Group Study. *Cancer*. 1987;60(12):2891-2895.
14. Sun W, Lipsitz S, Catalano P, Mailliard JA, Haller DG; Eastern Cooperative Oncology Group. Phase II/III study of doxorubicin with fluorouracil compared with streptozocin with fluorouracil or dacarbazine in the treatment of advanced carcinoid tumors: Eastern Cooperative Oncology Group Study E1281. *J Clin Oncol*. 2005;23(22):4897-4904.
15. Öberg K, Akerström G, Rindi G, Jelic S; ESMO Guidelines Working Group. Neuroendocrine gastroenteropancreatic tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2010;21(suppl 5):v223-v227.
16. Kouvaraki MA, Ajani JA, Hoff P, et al. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. *J Clin Oncol*. 2004;22(23):4762-4771.
17. van Essen M, Krenning EP, Kam BL, de Jong M, Valkema R, Kwekkeboom DJ. Peptide-receptor radionuclide therapy for endocrine tumors. *Nat Rev Endocrinol*. 2009;5(7):382-393.
18. Kwekkeboom DJ, de Herder WW, Kam BL, et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. *J Clin Oncol*. 2008;26(13):2124-2130.
19. Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol*. 2008;9(1):61-72.
20. Imhof A, Brunner P, Marincek N, et al. Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [90Y-DOTA]-TOC in metastasized neuroendocrine cancers. *J Clin Oncol*. 2011;29(17):2416-2423.
21. Pavel M. Translation of molecular pathways into clinical trials of neuroendocrine tumors. *Neuroendocrinology*. 2013;97(1):99-112.
22. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364(6):501-513.
23. Yao JC, Shah MH, Ito T, et al; RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364(6):514-523.
24. Pavel ME, Hainsworth JD, Baudin E, et al; RADIANT-2 Study Group. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2011;378(9808):2005-2012.
25. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol*. 2008;26(18):3063-3072.

Clinical Scenario 1: Advanced, Grade 2, Neuroendocrine Tumor in the Midgut

Jaume Capdevila, MD

Case Description

In July 2004, a 40-year-old otherwise healthy man with no relevant family history underwent an abdominal computed tomography (CT) scan following an accident. The CT scan showed no traumatic organ damage, but it revealed a 2-cm mass in the terminal ilium with 3 liver lesions suspicious for metastases. Endoscopic biopsy of the ileum mass showed a grade 2 NET with a Ki-67 of 4% and 3 mitoses per 10 high-power fields. Somatostatin receptor scintigraphy showed an uptake in liver lesions. The patient's 5-hydroxyindoleacetic acid (5-HIAA) levels and neuron-specific enolase levels were within the normal range. The patient underwent radical resection, had a full recovery, and remained disease-free 5 years after the resection. He was then lost to follow-up.

In 2014, the patient presented with renal colic. An abdominal ultrasound showed multiple liver metastases, and a body CT scan revealed bilobar liver metastases with involvement of mesenteric lymph nodes. Somatostatin receptor scintigraphy showed high uptake in the liver and lymph nodes (Krenning scale, 4). The patient was asymptomatic with no carcinoid syndrome. Laboratory tests were within the normal range, except for an elevated chromogranin A (1450 U/L). The decision was made to start medical treatment with a somatostatin analog.

Criteria for Treatment Decisions in GEP-NETs

Several parameters should be weighed when considering treatment decisions in patients with NETs. First is the histologic assessment, based on the WHO 2010 grading system[1] and/or the differentiation status (which is more commonly used in the United States). Second is the presence of hormonal release, which can lead to potentially significant or even fatal complications (eg, carcinoid syndrome, insulinoma, and gastrinoma) that require treatment.[2] Third is the primary tumor site; currently, the important distinction is to identify pancreatic vs intestinal carcinomas. Other factors to consider include results of somatostatin receptor imaging tests and the degree of tumor burden—in particular, the presence of extrahepatic disease.

Currently, radical surgery of the primary tumor and metastases is recommended if an R0 resection can be achieved. There are no data regarding the use of adjuvant therapy in this setting. However, locoregional liver therapies could be options depending on the tumor size, anatomic location, number of metastases, and presence of extrahepatic disease.

Clinical Guidelines for NETs

Currently, there are 3 major clinical guidelines that address the treatment of NETs: the European Society for

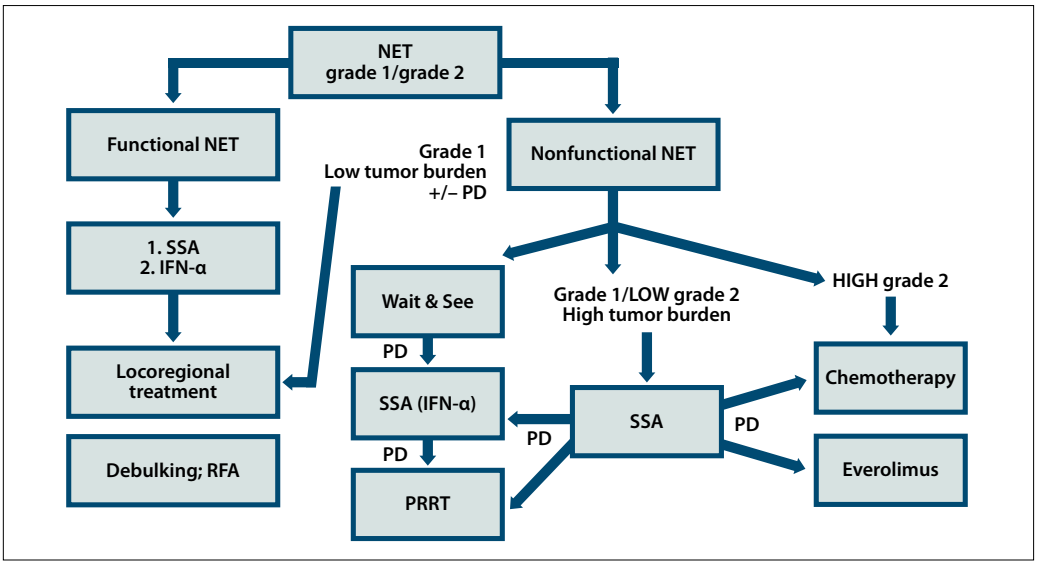

Figure 10. The ENET guidelines stratify the treatment approach based on 2 general categories of functional vs nonfunctional neuroendocrine tumors. ENET, European Neuroendocrine Tumor Society; IFN-α, interferon-α; PD, progressive disease; PRRT, Peptide receptor radionuclide therapy; RFA, radiofrequency ablation; SSA, somatostatin analog. Adapted from Pavel M et al. *Neuroendocrinology*. 2012;95(2):157-176.[4]

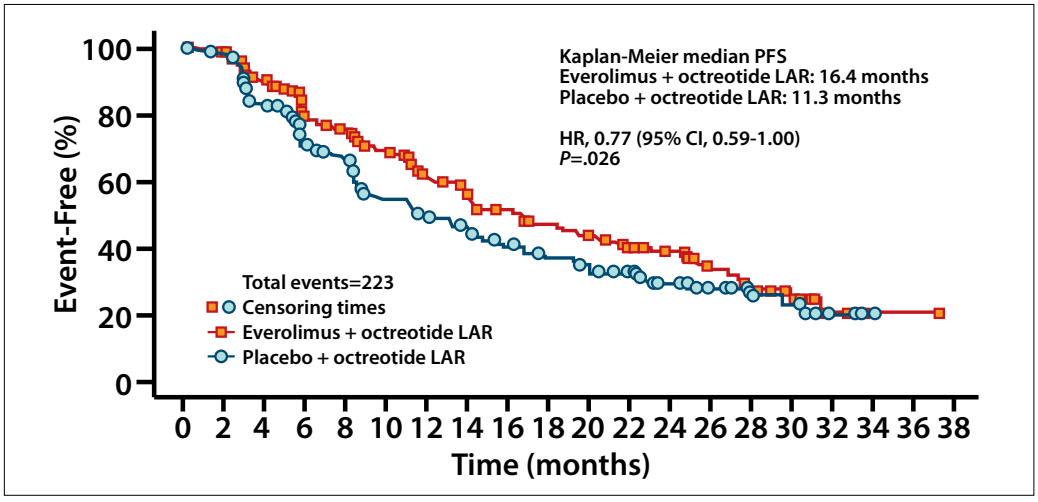

Figure 11. Median PFS in the RADIANT-2 trial in patients with advanced neuroendocrine tumors and a history of secretory symptoms with radiologic progression in the previous 12 months. LAR, long-acting release; PFS, progression-free survival; RADIANT-4, RAD001 in Advanced Neuroendocrine Tumors, Fourth Trial. Adapted from Pavel ME et al. *Lancet*. 2011;378(9808):2005-2012.[6]

Medical Oncology (ESMO) guidelines, updated in 2012[2]; the National Comprehensive Cancer Network (NCCN) guidelines, updated in December 2013[3]; and the ENETS consensus guidelines, updated in 2012.[4]

The ESMO guidelines recommend a variety of approaches based on the tumor location (pancreas vs small intestine), resectability, functionality, and tumor grade.[2] Recommended treatments include somatostatin analogs, interferon, everolimus, sunitinib, chemotherapy, and PRRT.

The NCCN guidelines categorize treatment approaches based on the tumor burden and extent of symptoms.[3] Although the recommendations are similar to those in the ESMO guidelines, the NCCN guidelines also offer watchful waiting as an option for asymptomatic patients with a low tumor burden.[3]

The ENETs guidelines require an update, but they are perhaps the most complete treatment guidelines for NETs.[4] The guidelines stratify the treatment approach based on 2 general categories of functional vs nonfunctional NETs (Figure 10). Therapies for functional NETs include somatostatin analogs or interferon; locoregional treatment and debulking surgery may be used to reduce tumor mass and

improve hormone release. For patients with nonfunctional NETs, management approaches vary based on the grade and tumor burden and include observation, somatostatin analogs, PRRT, chemotherapy, and everolimus.

Systemic Approaches in NET Therapy

In general, chemotherapy has a limited role in enteric NETs, with overall response rates typically below 20%.[5] Everolimus, an inhibitor of the mammalian target of rapamycin, demonstrated near-positive results in the phase 3 RADIANT-2 trial in patients with advanced NET and a history of secretory symptoms with radiologic progression in the previous 12 months (Figure 11).[6] In most countries, everolimus is not approved for use in extrapancreatic NETs.

A likely factor contributing to the lack of statistical significance in the RADIANT-2 trial was the inclusion of octreotide in the control arm, as somatostatin analogs have demonstrated antiproliferative effects in this patient population.[7] Ongoing phase 3 trials will help clarify the role of everolimus and other targeted therapies in patients with extrapancreatic NETs. The RADIANT-4 (RAD001 in Advanced Neuroendocrine Tumors, Fourth Trial) study is comparing everolimus vs placebo in patients with nonfunctioning grade 1/2 gastrointestinal or lung NETs with documented disease progression.[8] The Southwestern Oncology Group trial 0518 is comparing octreotide plus bevacizumab vs octreotide plus interferon-α in patients with grade 2 small intestine NETs with prior disease progression.[9] The NETTER-1 (A Study Comparing Treatment With 177Lu-DOTA0-Tyr3-Octreotate to Octreotide LAR in Patients With Inoperable, Progressive, Somatostatin Receptor Positive Midgut Carcinoid Tumours) trial is comparing lutetium plus octreotide vs octreotide alone in patients with grade 1/2 small intestine NETs with progression after a somatostatin analog.[10]

Several phase 3 trials have demonstrated the ability of somatostatin analogs to induce an antiproliferative effect. In the phase 3 PROMID study, octreotide LAR was associated with a significant PFS benefit over placebo in patients with well-differentiated functioning or nonfunctioning small-intestine NETs.[11] In the phase 3 CLARINET study, lanreotide depot/autogel was associated with a significant PFS benefit over placebo in patients with nonfunctional, nonprogressive, enteropancreatic grade 1/2 NETs.[12] Subgroup analyses showed similar efficacy with lanreotide depot/autogel regardless of tumor origin, grade, or hepatic tumor volume.

When considering the optimal treatment approach for NETs based on the evidence, it appears that radical surgery for the primary tumor and for all metastatic sites increases survival. Another point to consider is that assessment of disease progression status is not always easy or feasible. Moreover, phase 3 trials with targeted agents include populations with documented disease progression. Finally, the results of the CLARINET study challenge the conventional "wait-and-see" approach.

Disclosure

Dr Capdevila has received consulting fees from Ipsen, Novartis, and Pfizer. He has performed contracted research for Ipsen, Novartis, and Pfizer. He has received fees for non-CME services from Ipsen, Novartis, and Pfizer.

References

1. Klöppel G. Classification and pathology of gastroenteropancreatic neuroendocrine neoplasms. *Endocr Relat Cancer*. 2011;18(suppl 1):S1-S16.
2. Öberg K, Akerström G, Rindi G, Jelic S; ESMO Guidelines Working Group. Neuroendocrine gastroenteropancreatic tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2010;21(suppl 5):v223-v227.
3. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: neuroendocrine tumors. Version 2.2014. Updated December 11, 2013. http://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf. Accessed October 17, 2014.
4. Pavel M, Baudin E, Couvelard A, et al; Barcelona Consensus Conference participants. ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. *Neuroendocrinology*. 2012;95(2):157-176.
5. Grande E, Díez JJ, Pachón V, Carrato A. Advances in the therapy of gastroenteropancreatic-neuroendocrine tumours (GEP-NETs). *Clin Transl Oncol*. 2010;12(7):481-492.
6. Pavel ME, Hainsworth JD, Baudin E, et al; RADIANT-2 Study Group. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2011;378(9808):2005-2012.
7. Susini C, Buscail L. Rationale for the use of somatostatin analogs as antitumor agents. *Ann Oncol*. 2006;17(12):1733-1742.
8. ClinicalTrials.gov. Everolimus plus best supportive care vs placebo plus best supportive care in the treatment of patients with advanced neuroendocrine tumors (GI or lung origin) (RADIANT-4). http://clinicaltrials.gov/show/NCT01524783. Accessed October 17, 2014.
9. ClinicalTrials.gov. Octreotide acetate and recombinant interferon alfa-2b or bevacizumab in treating patients with metastatic or locally advanced, high-risk neuroendocrine tumor. http://clinicaltrials.gov/ct2/show/NCT00569127. Identifier: NCT00569127. Accessed October 17, 2014.
10. ClinicalTrials.gov. A study comparing treatment with 177Lu-DOTA0-Tyr3-octreotate to octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive midgut carcinoid tumours (NETTER-1). http://clinicaltrials.gov/ct2/show/NCT01578239. Identifier: NCT01578239. Accessed October 17, 2014.
11. Rinke A, Müller HH, Schade-Brittinger C, et al; PROMID Study Group. 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: a report from the PROMID Study Group. *J Clin Oncol*. 2009;27(28):4656-4663.
12. Caplin ME, Pavel M, Ćwikła JB, et al; CLARINET Investigators. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med*. 2014;371(3):224-233.

Clinical Scenario 2: Exploring Treatment Options for Patients With Symptomatic, Progressive GEP-NETs

Ulrich-Frank Pape, MD

Case Description: Part 1

In March 2009, a 48-year-old teacher presented with a 6-month history of increasingly troublesome diarrhea and dizzy spells. During the investigations, she developed signs of intestinal obstruction, including abdominal pain and vomiting. Her CT scan was abnormal, revealing small intestinal loops and a tumor mass within the mesentery. The findings suggested an NET with lymph node metastasis. Her urinary 5-HIAA was elevated (120 mg/24 hours), and her chromogranin A was 350 U/L.

The patient underwent laparotomy for impending obstruction and bowel resection, with excision of the tumor mass and involved regional mesenteric lymph nodes. It revealed a 4-cm carcinoid tumor with involved external margin; 4 of 12 nodes contained metastases (stage 3 tumor). Her Ki-67 level was 20%, which indicated a grade 2 tumor.

There was possible residual disease noted on the retroperitoneum. Postoperative somatostatin receptor scintigraphy and 24-hour urinary 5-HIAA were normal. The patient was monitored every 3 to 6 months with urinary 5-HIAA measurements.

In November 2012, she reported symptoms of flushing and diarrhea causing occasional incontinence. At that time, her urinary 5-HIAA level was marginally elevated (20 mg/24 hours). A CT scan revealed 15 to 20 small metastases throughout both liver lobes. Treatment with a somatostatin analog was initiated.

Considerations Regarding the Use of Somatostatin Analog Therapy in NETs

The ENETS guidelines state that the use of somatostatin analogs is standard for patients with functioning NETs, as these agents have demonstrated significant efficacy in treating carcinoid syndrome or other syndromes related to hormone hypersecretion.[1] When considering the use of somatostatin analogs, the indication for using these agents may be antisecretory treatment, proliferation control, or both (as in the current patient).

Upon disease progression, the patient developed carcinoid syndrome despite having marginally elevated 5-HIAA. It is likely that liver metastases bypassed the intrahepatic circulation, resulting in direct release of the hormone into the hepatic veins, which caused systemic effects. If the patient had nonsymptomatic disease rather than carcinoid syndrome, a somatostatin analog would still be the appropriate choice, given the demonstrated efficacy of these agents for controlling tumor proliferation. However, one caveat to consider is that this patient does not reflect the majority of clinical trial participants. The PROMID trial of octreotide enrolled treatment-naive patients,[2] and the CLARINET trial of lanreotide depot/autogel primarily enrolled patients who had stable disease for 3 to 6 months before randomization.[3]

Moreover, in 2012, when the patient's disease progression was detected, there was not yet evidence supporting the efficacy of somatostatin analogs for highly proliferative grade 2 NETs (as seen in this patient, based on her Ki-67 level of 20%). In 2014, subset analyses from the CLARINET trial supported the use of lanreotide depot/autogel in these patients (Figure 12).[3] It appears that if somatostatin receptors are present on the tumor cell surface, somatostatin analogs are likely to be effective.

One caveat concerning somatostatin analog therapy is that overall survival is difficult to assess. Many patients receive multiple subsequent therapies, and therefore overall survival reflects the total sequential therapeutic strategy. The use of multiple therapies, combined with the slow-growing biology of these tumors, makes survival analyses challenging. Although an overall survival analysis from the PROMID cohort showed a trend toward a survival benefit with octreotide in patients with low hepatic load, the difference did not reach statistical significance.[4] The study, however, was underpowered to detect differences in this subgroup.

For the current patient, somatostatin analog therapy had the potential to extend PFS and control symptoms. A disadvantage of octreotate, as shown in the PROMID trial, was the occurrence of progressive disease after a median of 40 months.[5] In the ENETS guidelines, somatostatin analogs are recommended as first-line agents for antiproliferative treatment in patients with nonfunctioning, progressive, small intestinal grade 1 NETs.[1] This recommendation will likely need to be revised. ESMO guidelines are less specific but also recommend somatostatin analogs as a first-line treatment in patients with nonfunctioning and functioning progressive grade 1/2

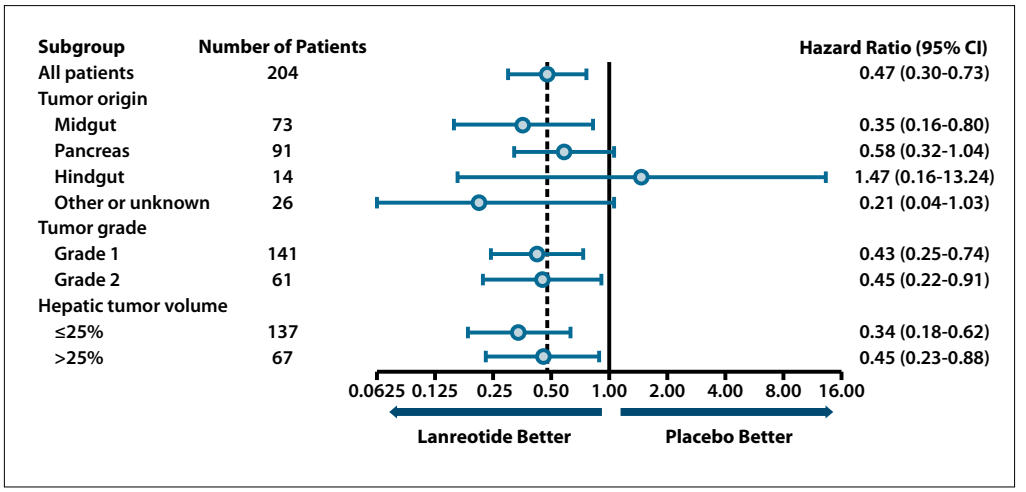

Figure 12. Subset analyses from the CLARINET trial supported the use of somatostatin analogs in several patient groups. CLARINET, Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors. Adapted from Caplin ME et al. *N Engl J Med.* 2014;371(3):224-233.[3]

NETs.[6] The North American Neuroendocrine Tumor Society guidelines recommend considering a somatostatin analog as an option for tumor stabilization.[7]

Case Description: Part 2

The patient began treatment with lanreotide depot/autogel. Her symptoms improved, and her 5-HIAA level normalized. Follow-up CT scans showed stable disease by the Response Evaluation Criteria In Solid Tumors (RECIST) criteria, with necrosis of some metastases. The treatment benefits lasted for 18 months, at which time the patient's symptoms returned, and a CT scan showed progression of liver metastases.

Options After Somatostatin Analog Therapy

Lanreotide depot/autogel provided a benefit that persisted for 18 months. Although this duration is fairly aligned with results from the PROMID trial, in which octreotide was associated with a median PFS of 14.3 months,[2] it was inferior to the average results reported in the CLARINET trial of lanreotide depot/autogel, in which the median PFS had not been reached in the overall cohort but was 18 months with placebo.[3] Considering that the patient had a grade 2 tumor, this result can be considered reasonable.

There are several options for second-line therapy after a first-line somatostatin analog. One approach is to continue the somatostatin analog and add everolimus or sunitinib, although the RADIANT-2 trial missed its primary endpoint of extending PFS.[8] A more aggressive approach, such as PRRT, might be appropriate if the tumor has sufficient somatostatin receptor expression. Other options include interferon-α, chemotherapy, or best supportive care, depending on the circumstances.

Influence of the Primary Tumor Site

The primary tumor site can influence the treatment approach. For patients with pancreatic NETs, multiple options are available, including chemotherapy and targeted agents, such as everolimus and sunitinib. The treatment decision may be influenced by the management goals, which can include induction of remission, reduction in tumor mass, and control of proliferation.

Tumor grade must also be a consideration for pancreatic NETs, as it will influence the treatment approach. Importantly, tumor grade may change, and therefore rebiopsy may be necessary. There may be a role for somatostatin analogs to control proliferation of the most slowly progressing pancreatic NETs, although this approach is not yet supported by evidence. Clearly, additional trials are needed to further elucidate the optimal treatment strategy and sequence for these patients.

Disclosure

Dr Pape has performed contracted research from Novartis Pharma. He has received fees for non-CME services from Ipsen Pharma, Novartis Pharma, and Pfizer Pharma.

References

1. Pavel M, Baudin E, Couvelard A, et al; Barcelona Consensus Conference participants. ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. *Neuroendocrinology*. 2012;95(2):157-176.
http://clinicaltrials.gov/ct2/show/NCT01578239. Accessed October 17, 2014.
2. Rinke A, Müller HH, Schade-Brittinger C, et al; PROMID Study Group. 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: a report from the PROMID Study Group. *J Clin Oncol*. 2009;27(28):4656-4663.
3. Caplin ME, Pavel M, Ćwikła JB, et al; CLARINET Investigators. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med*. 2014;371(3):224-233.
4. Arnold R, Wittenberg M, Rinke A, et al. Placebo controlled, double blind, prospec-

tive, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors (PROMID): results on long-term survival [ASCO abstract 4030]. *J Clin Oncol*. 2013;31(15 suppl).
5. Kwekkeboom DJ, de Herder WW, Kam BL, et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. *J Clin Oncol*. 2008;26(13):2124-2130.
6. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: neuroendocrine tumors. Version 2.2014. Updated December 11, 2013. http://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf. Accessed October 17, 2014.
7. Boudreaux JP, Klimstra DS, Hassan MM, et al; North American Neuroendocrine Tumor Society (NANETS). The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the Jejunum, Ileum, Appendix, and Cecum. *Pancreas*. 2010;39(6):753-766.
8. Pavel ME, Hainsworth JD, Baudin E, et al; RADIANT-2 Study Group. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2011;378(9808):2005-2012.

Continued Advances in Targeting Gastroenteropancreatic Neuroendocrine Tumors: General Discussion

Jaume Capdevila, MD, Matthias Weber, MD, and Ulrich-Frank Pape, MD

Jaume Capdevila, MD Do you recommend removing the wait-and-see option from the guidelines?

Matthias Weber, MD I would consider use of somatostatin analog therapy within the wait-and-watch strategy.

Ulrich-Frank Pape, MD It would be easy to move toward the early use of somatostatin analogs in patients who match clinical trial populations. In other patients, we may still consider careful observation, as they will likely soon meet these criteria. Somatostatin analogs may have a broader role in the future. Moreover, given their tolerability, these agents will likely gain wider use. In the field of endocrinology, there is a rather low threshold for long-term use of somatostatin analogs, which is likely a result of experience with other conditions that express somatostatin receptors. In other areas, such as oncology or gastroenterology, the threshold may be higher.

Matthias Weber, MD One challenge is the lack of overall survival data for these agents. Such data may never be available, given the slow-growing nature of these tumors. The clinical relevance of PFS prolongation in these patients is unclear. However, evidence from the SEER database suggests an overall survival benefit with octreotide.[1]

Jaume Capdevila, MD From a medical oncologist's perspective, it seems strange to *not* use a treatment that can produce a 40% difference in the PFS rate at 2 years (62% with lanreotide depot/autogel vs 22% with placebo).[2] However, other specialists within the multidisciplinary team may have a different perspective of the role of chemotherapy in the treatment of NETs. If the decision is made to delay therapy until disease progression, the option will be there at that point. NETs are slow-growing tumors. Despite the lack of overall survival data, however, many physicians would probably agree that a wait-and-see would not be appropriate for patients with liver metastasis.

In conclusion, neuroendocrine neoplasms are heterogeneous tumors that vary in their hormone functionality, tumor growth rate, and associated symptoms related to hormone release and tumor growth. The classification of these tumors is complicated by the use of the ENETS TNM grading system.

Somatostatin analogs are the cornerstone of therapy based on their symptomatic effects. Results from the phase 3 PROMID and CLARINET studies indicate that these agents also have an antiproliferative effect.[2,3] Ongoing studies are continuing to investigate the role of other targeted agents in the treatment of NETs. It will be important to appropriately integrate the various treatment approaches, including targeted therapy, chemotherapy, PRRT, and liver-directed therapies, to attain the best outcomes for patients with NETs.

Disclosures

Dr Capdevila has received consulting fees from Ipsen, Novartis, and Pfizer. He has performed contracted research for Ipsen, Novartis, and Pfizer. He has received fees for non-CME services from Ipsen, Novartis, and Pfizer. Dr Weber has received consulting fees from Ipsen, Novartis, and Pfizer. He has received fees for non-CME services from Ipsen, Novartis, and Pfizer. Dr Pape has performed contracted research from Novartis Pharma. He has received fees for non-CME services from Ipsen Pharma, Novartis Pharma, and Pfizer Pharma.

References

1. Tsikitis VL, Wertheim BC, Guerrero MA. Trends of incidence and survival of gastrointestinal neuroendocrine tumors in the United States: a seer analysis. *J Cancer*. 2012;3:292-302.
2. Caplin ME, Pavel M, Ćwikła JB, et al; CLARINET Investigators. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med*. 2014;371(3):224-233.
3. Rinke A, Müller HH, Schade-Brittinger C, et al; PROMID Study Group. 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: a report from the PROMID Study Group. *J Clin Oncol*. 2009;27(28):4656-4663.

Beyond Symptom Control: Continued Advances in Targeting Gastroenteropancreatic Neuroendocrine Tumors

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

1. What percentage of neuroendocrine tumors (NETs) are "functional" tumors that secrete hormones, causing hormone hypersecretion syndromes?

   a. Approximately 40%
   b. Approximately 50%
   c. Approximately 60%
   d. Approximately 70%

2. Which organ is the least common primary tumor site of gastrointestinal NETs in Western populations?

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

3. What is the most common hormone hypersecretion syndrome in NET patients?

   a. Carcinoid syndrome
   b. Cushing syndrome
   c. Glucagonoma
   d. Verner-Morrison syndrome

4. Which of the following is a marker for the small synaptic vesicles that store and secrete biogenic amines?

   a. Chromogranin A
   b. 5-HIAA
   c. Ki-67
   d. Synaptophysin

5. In the observational SymNET study of lanreotide depot/autogel in NET patients, satisfaction with diarrhea control was reported by ___.

   a. 56%
   b. 64%
   c. 76%
   d. 81%

6. In the PROMID trial, octreotide long-acting release formulation was associated with a median progression-free survival of:

   a. 8.1 months
   b. 11.5 months
   c. 14.3 months
   d. 16.2 months

7. In the CLARINET study, lanreotide depot/autogel was associated with a ___ reduction in the risk of progression or death as compared with placebo.

   a. 29%
   b. 33%
   c. 41%
   d. 53%

8. In the RADIANT-3 trial, everolimus plus octreotide long-acting release formulation was associated with a median progression-free survival of:

   a. 16.4 months
   b. 19.2 months
   c. 21.6 months
   d. 24.7 months

9. What is the response rate of chemotherapy in enteric NETs?

   a. Below 5%
   b. Below 10%
   c. Below 15%
   d. Below 20%

10. Which guidelines stratify the treatment approach based on 2 general categories of functional vs nonfunctional NETs?

    a. ENETs
    b. ESMO
    c. NANETS
    d. NCCN

Project ID: 10395

Evaluation Form: Beyond Symptom Control: Continued Advances in Targeting 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 10395**. Upon successfully registering/logging in and 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 with 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 (GEP-NETs)

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

Discuss the role of multidisciplinary care in the treatment of GEP-NETs

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

Evaluate recent data from clinical trials investigating novel treatment approaches for patients with GEP-NETs

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

Employ best practices in treatment selection for patients with GEP-NETs based on current recommendations and emerging data

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

Identify appropriate strategies to minimize disease symptoms and treatment-related adverse events to optimize quality of life in patients with GEP-NETs

❒ 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)

Name* _____

Degree* _____

Organization _____

Specialty* _____

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Telephone _____ Fax _____

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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: **10395**