

The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Medical Management of Midgut Neuroendocrine Tumors

Jonathan R. Strosberg, MD,* Thorvardur R. Halfdanarson, MD,† Andrew M. Bellizzi, MD,‡
 Jennifer A. Chan, MD,§ Joseph S. Dillon, MD,|| Anthony P. Heaney, MD,¶ Pamela L. Kunz, MD,#
 Thomas M. O’Dorisio, MD,|| Riad Salem, MD,** Eva Segelov, MBBS, PhD, FRACP,†† James R. Howe, MD,‡‡
 Rodney F. Pommier, MD,§§ Kari Brendtro,|||| Mohammad A. Bashir, MD,¶¶ Simron Singh, MD,###
 Michael C. Soulen, MD,*** Laura Tang, MD,††† Jerome S. Zacks, MD,‡‡‡
 James C. Yao, MD,§§§ and Emily K. Bergsland, MD|||||

Abstract: There have been significant developments in diagnostic and therapeutic options for patients with neuroendocrine tumors (NETs). Key phase 3 studies include the CLARINET trial, which evaluated lanreotide in patients with nonfunctioning enteropancreatic NETs; the RADIANT-2 and RADIANT-4 studies, which evaluated everolimus in functioning and nonfunctioning NETs of the gastrointestinal tract and lungs; the TELESTAR study, which evaluated telotristat ethyl in patients with refractory carcinoid syndrome; and the NETTER-1 trial, which evaluated ¹⁷⁷Lu-DOTATATE in NETs of the small intestine and proximal colon

(midgut). Based on these and other advances, the North American Neuroendocrine Tumor Society convened a multidisciplinary panel of experts with the goal of updating consensus-based guidelines for evaluation and treatment of midgut NETs. The medical aspects of these guidelines (focusing on systemic treatment, nonsurgical liver-directed therapy, and post-operative surveillance) are summarized in this article. Surgical guidelines are described in a companion article.

Key Words: NANETS, medical management, neuroendocrine tumor, midgut NETs

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From the *Department of GI Oncology, H. Lee Moffitt Cancer Center, Tampa FL; †Division of Medical Oncology, Mayo Clinic, Rochester, MN; ‡Department of Pathology, University of Iowa, Iowa City, IA; §Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; ||Department of Medicine, University of Iowa, Iowa City, IA; ¶Departments of Medicine and Neurosurgery, University of California Los Angeles, Los Angeles; #Department of Medicine, Division of Oncology, Stanford University School of Medicine, Stanford, CA; **Department of Radiology, Northwestern University, Chicago IL; ††Department of Oncology, Monash University and Monash Health, Melbourne, Victoria, Australia; ‡‡Department of Surgery, University of Iowa Carver College of Medicine, Iowa City, IA; §§Oregon Health & Science University and |||North American Neuroendocrine Tumor Society, Portland, OR; ¶¶Division of Cardiothoracic Surgery, Department of Surgery, University of Iowa Carver College of Medicine, Iowa City, IA; ###Sunnybrook Hospital, Toronto, Canada; ***Department of Radiology, University of Pennsylvania, Philadelphia, PA; †††Memorial Sloan Kettering University and ‡‡‡Division of Cardiology, Mount Sinai Hospital, New York, NY; §§§Department of Gastrointestinal Medical Oncology, MD Anderson Cancer Center, Houston TX; and ||||Department of Medicine, University of California San Francisco, San Francisco, CA.

Address correspondence to: Jonathan R. Strosberg, MD, H. Lee Moffitt Cancer Center, Faculty Office Building, 2nd Floor, Tampa, FL 33606 (e-mail: jonathan.strosberg@moffitt.org).

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During the past several years, we have witnessed significant advances in diagnostic and therapeutic options for patients with advanced neuroendocrine tumors (NETs). Two studies established the role of somatostatin analogs (SSAs) as antiproliferative agents in patients with well-differentiated NETs. In the early-line treatment setting, the phase 3 PROMID study randomized patients with metastatic midgut NETs to receive octreotide long-acting repeatable (LAR) 30 mg versus placebo. Time to progression was significantly improved with treatment.¹ The phase 3 CLARINET study compared lanreotide to placebo in a more heterogeneous population of patients with gastroenteropancreatic NETs, also demonstrating a clinically and statistically significant improvement in progression-free survival (PFS).²

Other recent phase 3 studies have investigated new drugs in patients with progressive disease. In the RADIANT-4 study, everolimus was compared with placebo in nonfunctional NETs of the gastrointestinal tract and lung, demonstrating a significant improvement in PFS.³ More recently, patients with progressive midgut NETs were randomized to receive the radiolabeled SSA ¹⁷⁷Lu-DOTATATE (investigational arm) or high-dose octreotide LAR at 60 mg monthly (control arm) in the NETTER-1 trial.⁴ A substantial improvement in PFS was documented with the investigational agent. For symptom control, the phase 3 TELESTAR study compared 2 doses of an oral serotonin synthesis inhibitor, telotristat ethyl, to placebo in carcinoid syndrome patients with refractory diarrhea. Telotristat ethyl treatment was associated with a significant reduction in daily bowel movements corresponding to decline in urine 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of serotonin.⁵

Although these agents were tested in various populations of NETs, all have had an important and specific impact on the management of midgut NETs, defined as NETs originating in the jejunum, ileum, and proximal colon. Midgut NETs are typically slow-growing tumors and are often associated with the carcinoid syndrome when metastatic. Until recently, they were characterized

by resistance to systemic treatments other than SSAs and interferon- α (IFN- α). The introduction of new treatment options for tumor and symptom control offers the potential to improve patient outcomes and quality of life, but also raises many questions. How should new treatments be integrated into the therapeutic algorithm? How should they be sequenced? Do they have activity in settings beyond their labeled indications?

To address these and other aspects of the management of midgut NETs, a panel of experts was convened by the North American Neuroendocrine Tumor Society, with the goal of developing updated consensus-based guidelines for the treatment of midgut NETs. During this meeting, issues regarding surgical and medical treatment of midgut NETs were discussed separately.

MATERIALS AND METHODS

The Medical Management of Midgut NETs panel consisted of 15 participants, including 7 medical oncologists, 3 endocrinologists, 2 pathologists, an interventional radiologist, a cardiologist, and a cardiac surgeon, all with expertise in various aspects of midgut NET management. Institutions represented on the panel included Stanford University, the University of California San Francisco, MD Anderson Cancer Center, Mayo Clinic, Memorial Sloan Kettering Cancer Center, Moffitt Cancer Center, the University of Iowa, the University of California Los Angeles, Sunnybrook Research Institute (Toronto, Canada), St Vincent's Hospital (Sydney, Australia), the University of Pennsylvania, Mount Sinai Hospital, and the Dana-Farber Cancer Institute.

Participants in the medical panel debated various topics through a series of short presentations. Presentations were limited to 5 to 10 minutes and included key literature references, with an emphasis on recent advances in the diagnosis and management of patients with NETs. Topics included postoperative surveillance, management of patients with asymptomatic disease, appropriate use of SSAs, appropriate use of novel treatments including everolimus, ^{177}Lu -DOTATATE and telotristat ethyl, the role of liver-directed embolization therapies, and the management of carcinoid syndrome, including carcinoid heart disease (CaHD). Discussions took place after associated presentations. Subsequently, participants voted on multiple-choice questions designed to address areas of controversy using an electronic audience response system (ARS). Although questions were occasionally rephrased for clarity, there was no attempt to alter questions for the purpose of generating a consensus. Following separate medical and surgical panel meetings, all participants in the guidelines committee met in a joint session to summarize discussions and review ARS polling results.

Guidelines were categorized into a series of topics based on the outcomes of the discussions and ARS polling results. For these guidelines, we defined "consensus" as no more than 1 oppositional vote and "significant majority" as 75% agreement or greater. We identified many areas with lack of consensus, which suggests potential opportunities for clinical research. This article summarizes the medical guidelines pertaining to management of advanced, unresectable, midgut NETs and postoperative surveillance of stages I–III NETs. Operative guidelines pertaining to surgical management of local, locoregional, and advanced NETs are reported in a separate manuscript.

RESULTS

The following topics concerning medical management and surveillance of midgut NETs were discussed:

Surveillance After Resection of Stages I–III Midgut NET: Duration and Frequency of Visits

Patients with localized or locally advanced midgut NETs typically undergo surgical resection consisting either of right hemicolectomy or partial small bowel resection. The majority of resected tumors involve locoregional lymph nodes (stage III). The results of studies assessing outcomes in several databases suggest that long-term recurrence rates are approximately 50%.^{6,7} Because of the slow-growing nature of most midgut NETs, metastatic recurrences can occur many years after surgical resection; prospective studies evaluating surveillance strategies have not been performed. There was consensus among panel members that surveillance should continue beyond 5 years. However, there was lack of consensus over whether surveillance should continue beyond 10 years. We therefore recommend that duration of surveillance be approximately 10 years, with the option of continuing surveillance beyond that interval, especially among younger patients or those considered to be at particularly high risk of recurrence (eg, numerous involved lymph nodes).

Frequent surveillance visits are generally not required. A significant majority of the expert panel members recommended initiating radiographic surveillance at 6-month intervals and transitioning to less frequent intervals (eg, annual surveillance) after 1 year in the absence of recurrence. There was no consensus on whether proliferative activity of the tumor would impact surveillance recommendations. There are limited data on recurrence risk of stage I tumors, but a significant majority of participants stated that they would perform surveillance even on patients with very early-stage tumors.

In summary, long-term (approximately 10 years) but infrequent (annual) radiographic surveillance is appropriate for most patients with completely resected stages I–III midgut NETs.

Surveillance After Resection of Stages I–III Midgut NET: Imaging Studies and Tumor Markers

Midgut NETs typically metastasize to the liver. Other common sites of metastases include mesenteric and retroperitoneal lymph nodes, peritoneum, and bone. Cross-sectional imaging studies (multiphasic computed tomography scans or magnetic resonance imaging scans focusing on the abdomen/pelvis) are recommended for routine surveillance of patients with resected midgut NETs. A consensus was achieved that somatostatin-receptor nuclear imaging (eg, OctreoScan or ^{68}Ga -DOTATATE scan [Netspot]) should be performed as a baseline preoperative test, but that further somatostatin-receptor imaging is not indicated for routine surveillance unless needed to evaluate symptoms or abnormalities on conventional scans.⁸

Tumor markers including chromogranin A (CgA), pancreastatin, and neuron-specific enolase, among others, can be obtained as part of a surveillance regimen; however, their value in early detection of recurrence is unknown. Chromogranin A is a protein associated with secretory endocrine vesicles and correlates with tumor burden. Elevated CgA levels may be observed months to years before radiographic evidence of recurrence is seen, but the low sensitivity and specificity of CgA limit its use in surveillance. Pancreastatin is a breakdown product of CgA, which may be characterized by improved specificity, particularly among patients using proton pump inhibitors. Neuron-specific enolase is characterized by relatively low sensitivity, particularly in well-differentiated tumors. There was lack of consensus regarding the appropriateness of measuring these tumor markers among patients undergoing radiographic surveillance. Roughly half of panel members indicated that high false-positive and false-negative rates limit their utility.

Management of Patients With Incidentally Detected, Asymptomatic Low-Volume Metastatic Tumors

Increasingly, patients are diagnosed incidentally as having metastatic NETs as they undergo scans and endoscopic evaluations for unrelated conditions. There is significant disagreement among experts over initial management of asymptomatic patients with low-volume, surgically unresectable disease: whether to initiate SSA therapy or to monitor closely until evidence of progression. Two phase 3 studies compared SSAs versus placebo in patients with relatively low-volume, indolent metastatic disease. The PROMID study compared octreotide LAR versus placebo in patients with midgut NETs and absent or mild carcinoid syndrome, whereas the CLARINET study compared depot-lanreotide with placebo in a population of nonfunctional gastroenteropancreatic NETs with predominantly stable disease at baseline.^{1,2} Both studies demonstrated conclusively that SSAs can inhibit tumor growth and delay time to progression. However, neither study showed any evidence of prolongation in overall survival with treatment, likely owing to crossover to the active drug at the time of progression. In the CLARINET study, median PFS on the placebo arm was 18 months, raising multiple questions. Does early versus late use of SSAs in asymptomatic patients impact survival? Should asymptomatic patients be monitored without treatment until progression?

When we presented a clinical vignette describing a newly diagnosed asymptomatic midgut NET patient with low-volume disease, there was no consensus among the expert panel on whether to treat with SSAs or observe the patient, with roughly half respondents selecting “SSA treatment” and half selecting “observation.” We therefore conclude that either observation or initiation of SSA therapy is acceptable in an asymptomatic patient with low-volume disease. In patients in whom observation is selected, a strategy of close observation (eg, scans roughly every 3–4 months initially) should be adopted. Patients with stable disease can subsequently be monitored less frequently (eg, every 6 months). The role of tumor markers in patients with asymptomatic low-volume disease remains unknown.

Pathological Diagnosis of Metastatic Disease: Minimal Requirements and Optional Tests

The pathological diagnosis of metastatic NET is often obtained via needle biopsy and aided by use of immunostaining for synaptophysin and chromogranin. Evaluation of tumor differentiation and grade is critically important for predictive and prognostic purposes. Tumor grade is measured using mitotic rate and/or Ki-67 proliferative index.⁹ There was consensus that both differentiation and grade should be reported. A significant majority of the expert panel indicated that both mitotic rate and Ki-67 index should be measured. Although surgical specimens or core needle biopsies are optimal for accurate assessment of differentiation and grade, a consensus was achieved that fine-needle aspiration can provide adequate information in most cases.

In metastatic NETs where the primary site is uncertain, positive immunostains for CDX2 can point to a midgut primary and should be performed, along with other stains such as TTF1 (suggests lung primary) and ISL-1 (islet-1), which is suggestive of pancreatic primary.

First-Line Management of Symptomatic Patients With Tumor-Related Symptoms or Carcinoid Syndrome

Somatostatin analogs (octreotide LAR and lanreotide) are appropriate initial therapy in most patients with unresectable

metastatic midgut NETs for control of carcinoid syndrome and inhibition of tumor growth. The antiproliferative effects of SSAs were established in the PROMID and CLARINET trials, and their antisecretory effects have been described in numerous single-arm studies, retrospective series, and a randomized study.^{1,2,10–14} In general, SSAs are associated with major improvements in flushing and diarrhea in roughly 75% of patients with carcinoid syndrome. Because of their relatively benign side effect profile, SSAs are typically selected as first-line systemic therapy.

Selection of Octreotide LAR Versus Lanreotide

Currently, 2 long-acting SSAs are commercially available: octreotide LAR and lanreotide. Octreotide LAR is administered every 4 weeks as an intramuscular injection, whereas lanreotide is administered in the same schedule as a deep subcutaneous injection. Both drugs have similar somatostatin receptor subtype-binding profiles, with particular affinity for somatostatin receptor subtype 2. Both have shown evidence of antisecretory and antiproliferative effects in clinical trials. Indeed, the hazard ratio for time to progression on the PROMID study (0.35) was similar to the hazard ratio for PFS in the CLARINET study midgut NET subgroup.^{1,2} However, in the United States, octreotide is approved by the Food and Drug Administration (FDA) for palliation of carcinoid syndrome, whereas lanreotide is approved for control of tumor growth. When asked whether the 2 drugs can be used interchangeably or whether they should be prescribed according to label (octreotide for control of syndrome and lanreotide for control of tumor growth), roughly half of the experts selected the former, and half selected the latter. We therefore conclude that no definitive statements can be made regarding selection between octreotide LAR and lanreotide in patients with midgut NETs regardless of the presence of carcinoid syndrome.

Management of Patients With Negative Somatostatin-Receptor Imaging

The large majority of midgut NETs express high levels of somatostatin receptors that are targeted by SSAs and can be visualized by somatostatin-receptor imaging. Traditionally, somatostatin-receptor scintigraphy (OctreoScan) has been used to assess somatostatin-receptor expression. More recently, a variety of novel radiopeptides for positron emission photography (PET) imaging of the somatostatin receptor have been developed (eg, ⁶⁸Ga-DOTA-Tyr³-octreotide, ⁶⁸Ga-DOTATOC and ⁶⁸Ga-DOTA-Tyr³-octeotate, ⁶⁸Ga-DOTATATE).¹⁵ These radiopeptides vary in their affinity for the different somatostatin receptor subtypes 1 to 5, but the resultant PET imaging has been shown to have higher sensitivity for NETs, particularly for imaging small lesions.^{8,15} Historically available in the United States only as a research tool, the ⁶⁸Ga-DOTATATE PET scan recently received FDA approval. As such, use of somatostatin-receptor PET imaging is becoming routine in the clinical setting and should be considered instead of traditional somatostatin-receptor scintigraphy and/or when a patient with advanced disease has a negative OctreoScan. When asked whether SSAs should be used in patients with carcinoid syndrome who lack evidence of somatostatin-receptor expression based on somatostatin imaging, there was a consensus that SSAs should be tried regardless of somatostatin receptor imaging results.

Treatment After Radiographic Progression on First-Line SSA

There are several new and emerging systemic treatment options for patients with midgut NETs progressing radiographically

on SSA therapy. Everolimus was recently approved by the FDA for treatment of nonfunctional NETs based on the RADIANT-4 study, a randomized, placebo-controlled study of patients with progressive, nonfunctional NETs of the gastrointestinal tract and lung.³ Median PFS improved from 3.9 to 11 months ($P < 0.00001$). An earlier study, the RADIANT-2 trial, randomized patients with progressive NETs and a history of carcinoid syndrome to receive everolimus plus octreotide LAR versus placebo plus octreotide LAR.¹⁶ This study, in which a majority of patients had NETs of midgut origin, fell narrowly short of statistical significance for its primary end point of PFS improvement.

In the NETTER-1 trial, patients with progressive midgut NETs were randomized to receive ¹⁷⁷Lu-DOTATATE versus high-dose octreotide (60 mg every 4 weeks).⁴ ¹⁷⁷Lu-DOTATATE is a radiolabeled SSA, a form of treatment also known as peptide receptor radiotherapy (PRRT). The primary end point was PFS by central, blinded radiology review. In this study, median PFS was 8 months on the high-dose octreotide arm and was not yet reached on the ¹⁷⁷Lu-DOTATATE arm, translating to a 79% improvement in PFS ($P < 0.00001$).

Other treatment options that have been traditionally available for progressive midgut NETs include IFN- α (typically in combination with SSA) and hepatic arterial embolization for patients with liver-dominant disease. Interferon- α has been studied in multiple single-arm studies and several randomized but underpowered clinical studies.^{17–19} It has not been approved by the FDA for this indication, but may have cytostatic activity. Hepatic arterial embolization therapies have been predominantly studied in retrospective institutional series. Several strategies are routinely used in clinical practice, including bland embolization, chemoembolization, and selective internal radiation therapy. Treatment is associated with tumor shrinkage and a reduction in hormone-mediated symptoms in more than 50% of patients; however, there are no randomized data regarding the superiority of one modality over another.^{20–22}

When asked about appropriate choice of second-line treatment in patients with somatostatin receptor–positive midgut NETs, a significant majority of the expert panel selected ¹⁷⁷Lu-DOTATATE as the most appropriate option based on the results of the NETTER-1 study. It was noted that the evidence of everolimus efficacy appears stronger in nonmidgut NETs (which represented the majority of patients on the RADIANT-4 study) compared with midgut NETs (which represented the majority of patients on the RADIANT-2 study). Interferon- α was not selected as an option by any members of the panel based on the relatively weak level of evidence supporting its use and its side effect profile, which includes significant fatigue. While liver embolization therapies appear to result in high radiographic response rates, most experts indicated that there was insufficient high-quality evidence to favor embolization as a second-line option for patients with progressive midgut NETs. Most panelists supported its use as a later line of treatment for patients with liver-dominant disease. There was debate about the role of liver-directed therapy in patients with a high burden of liver disease (in part because of the relatively low response rate associated with ¹⁷⁷Lu-DOTATATE therapy).⁴ There was a consensus that randomized prospective clinical trials of liver embolization are needed to test the benefit of embolization in patients with progressive midgut NETs. The risks associated with sequence of therapy also warrant further investigation (ie, PRRT then liver-directed therapy vs liver-directed therapy then PRRT). For patients with liver-predominant disease and suboptimal control of carcinoid syndrome, liver embolization was considered an appropriate second-line treatment option (see “Should Liver Embolization Be Considered as an Early Line of Treatment for Patients With Suboptimal Control of Carcinoid Syndrome?”) based on high rates of symptomatic response associated with this therapy.

Management of Patients With Progressive Midgut NET and Negative Somatostatin-Receptor Imaging

In patients who are not candidates for radiolabeled SSAs (because of weak or absent somatostatin-receptor expression) and have liver-dominant metastases, an equal number of panelists chose everolimus versus liver embolization as treatment options. In patients with extensive extrahepatic metastases and weak/absent somatostatin-receptor expression, everolimus is the appropriate choice of therapy.

Does Tumor Functionality (History of Carcinoid Syndrome) Influence Selection of Everolimus as a Treatment Option?

The labeled indication for everolimus is for treatment of progressive nonfunctional NETs, based on eligibility criteria for the RADIANT-4 study.²³ A large number of metastatic midgut NETs (>50% in some studies) secrete serotonin and are associated with the carcinoid syndrome.²⁴ A trend toward improved PFS with everolimus was demonstrated in the patients with carcinoid syndrome in the RADIANT-2 study; however, the result did not meet the prespecified threshold for statistical significance.¹⁶ When asked whether tumor functionality influences choice of everolimus, half of the respondents indicated that they were less likely to recommend everolimus in a functional tumor, and half indicated that tumor functionality had no impact on their choice. No panelist stated that they would refrain from use of everolimus in functional NETs. Therefore, we recommend that everolimus should be considered an option for patients with progressive midgut NETs, even if there is a history of carcinoid syndrome.

Role of Interferon- α

Several small randomized clinical trials have investigated use of IFN- α in patients with progressive carcinoid tumors.^{17–19} More recently, a randomized phase 3 clinical trial of bevacizumab versus IFN- α showed no evidence of improved PFS with either arm of the study; however, the bevacizumab arm was associated with a higher response rate, longer time on treatment, and fewer clinically significant toxicities.²⁵ When asked about their use of IFN- α , a significant majority of panelists indicated that they never use IFN- α , and the remainder stated that they rarely prescribe the drug. We therefore conclude that in the current treatment landscape IFN- α should generally be considered only if no other option is available for the patient.

Choice of Embolization Therapy

Current transarterial embolic options can be broadly classified into 3 types: bland embolization, chemoembolization, and radioembolization (also known as selective intrahepatic radiotherapy).²² All 3 have been primarily evaluated in institutional series rather than prospective clinical trials. There is currently no standard-of-care embolization modality, and choice of therapy is often based on institutional preferences. There have been no completed randomized clinical trials comparing embolization modalities. One prospective trial comparing bland to chemoembolization in midgut NETs was terminated early because of poor accrual.²⁶ On analysis of 26 patients enrolled, there was no evidence of improvement in PFS with bland versus chemoembolization, nor were there any significant differences in toxicities, although the results were underpowered because of underenrollment.

Although radioembolization is generally associated with fewer short-term toxicities than bland or chemoembolization, there has been increased recognition that some patients may develop chronic radioembolization-induced liver disease that mimics

cirrhosis in its radiographic appearance and results in hyperbilirubinemia and portal hypertension.^{27,28} After discussion of risks/benefits associated with different embolization modalities, the panel members were unable to reach consensus on a preferred type of embolization. We therefore conclude that any of the embolization modalities can be considered appropriate and that patients should be informed of the risks and benefits of each approach. There was consensus that prospective randomized clinical trials with long-term follow-up, such as the ongoing Randomized Embolization Trial in Neuroendocrine Tumors (RETNET, ClinicalTrials.gov NCT02724540), are needed to compare embolization modalities for evidence of both benefit and toxicity.

Does Potential Availability of PRRT Affect Use of Radioembolization?

There are few data indicating whether the addition of systemic radiotherapy (via PRRT) to patients who have undergone intrahepatic radiation (through radioembolization) increases the risk of radiation-induced liver damage. However, based on this theoretical concern, there was consensus among panel members that availability of PRRT would reduce their propensity to recommend radioembolization treatments. There was consensus that the question of cumulative liver radiation needs to be studied more closely. The lack of data regarding optimal sequence and long-term toxicity for current treatment options (eg, liver-directed therapy of all types and ¹⁷⁷Lu-DOTATATE) presents a significant challenge. As outcomes improve in this patient population, the significance of long-term toxicities could become more profound.²⁸

Should Liver Embolization Be Considered as an Early Line of Treatment for Patients With Suboptimal Control of Carcinoid Syndrome?

In most series, hepatic arterial embolization treatments are associated with high rates of symptom improvement, particularly in patients with hormonal syndromes.²² When presented with a clinical vignette of a patient with inoperable liver metastases and suboptimal control of carcinoid syndrome on SSA therapy, there was consensus that liver embolization was an appropriate palliative treatment modality. However, some panel members indicated that systemic treatment options such as everolimus or PRRT could also be added to SSAs to achieve improved symptom control. Higher-quality data are needed to compare symptom control using various treatment modalities.

Should SSAs Be Continued Beyond Progression?

In patients with carcinoid syndrome, SSAs are generally continued across multiple lines of therapy to palliate symptoms. However, in patients with nonfunctioning tumors, it is unclear whether SSAs should be continued across lines of treatment. When presented with a clinical vignette describing a nonfunctional midgut NET with slow progression of disease on SSA treatment (10% growth over 1 year), roughly half the panelists recommended continuation of SSA together with next line of therapy versus discontinuation of the drug. When presented with a similar scenario but rapid disease progression, a significant majority advocated stopping SSA treatment. Our findings suggest a need for a clinical trial to address the question of continuation of SSA treatment beyond progression.

Can Liver Embolization Therapies Be Repeated in Patients Who Have Progressed After Earlier Embolizations?

There was consensus agreement that embolizations can be repeated among patients who responded to prior hepatic arterial embolizations. However, there was also agreement that multiple liver-directed therapies can eventually result in cumulative liver toxicity. Furthermore, the risks and benefits of repeat embolizations must be considered carefully in the context of other approved and emerging therapies for midgut NETs (eg, PRRT).

Management of Refractory Carcinoid Syndrome and Role of Telotristat Ethyl

Carcinoid syndrome frequently develops in patients with metastatic midgut NETs. Serotonin is the primary hormone associated with carcinoid syndrome, and particularly with diarrhea, whereas flushing appears to be multifactorial. Somatostatin analogs are highly effective at palliating the carcinoid syndrome; however, many patients have suboptimal control or become somewhat refractory to SSAs over time.^{29,30} Strategies for management of refractory carcinoid syndrome have included increasing dose or frequency of SSAs, addition of short acting octreotide for breakthrough symptoms, and initiation of antidiarrheal therapies with loperamide, diphenoxylate-atropine, or other nonspecific medications.³¹ It is also important to rule out competing causes of diarrhea such as pancreatic insufficiency from SSA use, short gut syndrome, or biliary salt malabsorption related to intestinal surgery. Pancreatic enzymes can be prescribed empirically if fat malabsorption is suspected. Bile acid sequestrants (such as cholestyramine and colestipol) are recommended to treat bile acid malabsorption.

Recently, the oral serotonin inhibitor telotristat ethyl has been developed for management of refractory diarrhea in the setting of carcinoid syndrome.³² Telotristat inhibits the enzyme tryptophan hydroxylase, which mediates the rate-limiting step in the serotonin biosynthesis. With minimal activity in the central nervous system, it appears to have little effect on the role of serotonin as a neurotransmitter.

Telotristat was studied in the phase 3, placebo-controlled TELESTAR trial at 2 doses, 250 and 500 mg, 3 times daily.⁵ Eligible patients had carcinoid syndrome and at least 4 bowel movements per day. The primary end point of the study was reduction in the number of daily bowel movements, averaged over a 12-week period. A key secondary end point was reduction in levels of urine 5-HIAA. The trial showed a statistically significant 35% improvement in mean daily bowel movements associated with the 500-mg thrice-daily dose at week 12 compared with baseline. Moreover, levels of urine 5-HIAA improved significantly in both treatment groups versus the placebo group: at week 12, mean urine 5-HIAA decreased by 58 mg/24 hours in patients receiving the 500-mg dose and 40 mg/24 hours with the 250-mg dose; mean urinary 5-HIAA levels increased in the placebo group by 11 mg/24 hours at week 12. Adverse effects were generally mild.

A consensus was reached that in a patient with stable radiographic disease and refractory carcinoid syndrome characterized by suboptimal control of diarrhea, telotristat ethyl was the appropriate drug of choice. Under these circumstances, telotristat was considered a more appropriate choice than an increase in SSA dose, use of short-acting octreotide, or use of nonspecific anti-diarrheal or antitumor therapy. However, in a circumstance where increase in flushing and/or diarrhea occurs only toward the end of a 4-week SSA cycle, the majority of participants advocated increase in frequency of SSA (to every 3 weeks) as the preferred intervention. In the setting of refractory carcinoid syndrome

stemming from tumor progression, antitumor therapy should be considered.

Use of Telotristat Ethyl in a Patient With Normal Urine 5-HIAA

In the TELESTAR study, patients with normal urine 5-HIAA, a serotonin metabolite, represented roughly 25% of the enrolled population and appeared to derive similar benefit from the drug.⁵ However, the mechanism of benefit is uncertain. When asked whether they would consider use of telotristat in a patient with normal levels of urine 5-HIAA but suboptimal control of diarrhea, roughly half the respondents stated that they would consider use of telotristat.

Carcinoid Heart Disease: Screening and Surveillance

Carcinoid heart disease is characterized by fibrosis of right-sided cardiac valves (tricuspid/pulmonic) and endocardium and eventually leads to right heart failure.³³ It is usually associated with highly elevated levels of circulating serotonin. Indeed, serotonin is generally considered to be the primary etiologic factor. Estimates of the incidence of CaHD among patients with metastatic midgut carcinoid tumors vary widely; past reports indicated an occurrence rate of approximately 50%; however, more recent reports point to a decline in the condition, possibly associated with use of SSAs.³⁴

Definitive treatment for CaHD consists of valve replacement, typically involving both the tricuspid and pulmonary valves. Identification of CaHD prior to onset of right heart failure is important to optimize postoperative outcomes. Another possible advantage of early detection is the ability to institute more aggressive medical therapy to reduce serotonin output, thereby potentially impacting the progression of CaHD.

Echocardiographic imaging is the most common and accurate evaluation method for CaHD.³³ Serum N-terminal pro-brain natriuretic peptide (BNP) is another method of assessing for evidence of heart failure, with a high negative predictive value.³³

There are limited data to guide selection of patients who are most appropriate for CaHD surveillance. Among the expert panel, some advocated baseline echocardiogram in all midgut NET patients with advanced disease, whereas others recommended baseline echocardiogram only in patients with significant elevations in levels of serotonin, or its metabolite 5-HIAA. Regular echocardiographic evaluation was recommended for all patients at risk, but there was no consensus on how this population should be defined and/or how often echocardiograms should be performed. There was agreement that in patients with evidence of mild CaHD echocardiographic evaluation should be performed at least once a year. There was no consensus as to whether serum BNP, or its pro-factor, N-terminal pro-BNP, is of any additional diagnostic benefit among patients undergoing echocardiographic surveillance.

As a result of these discussions, we recommend that at a minimum all patients with significant elevations in serotonin or 5-HIAA levels (eg, $>5\times$ upper limit of normal) undergo annual echocardiography. Screening of patients with less prominent elevations of serotonin levels can be likewise considered. Patients with evidence of early CaHD should be monitored more closely. Health care providers should have a low threshold to obtain an echocardiogram in any patient with midgut NET exhibiting signs or symptoms of CaHD.

Use of Telotristat Ethyl for Prevention of CaHD

Because CaHD is associated with significant elevations in serum serotonin, reductions in levels of circulating serotonin should, in theory, reduce the risk of development or progression of CaHD. However, to date, there are no data to suggest that telotristat ethyl, a serotonin inhibitor, can inhibit development or progression of CaHD. Studies to test the potential effects of telotristat on CaHD are anticipated to be logistically challenging because of the rarity of the condition and difficulty in establishing validated end points.

When presented with a vignette describing a patient with symptomatically controlled carcinoid syndrome, highly elevated levels of urine 5-HIAA ($>5\times$ upper limit of normal) but no evidence of CaHD on echocardiogram, a small minority of the expert panel recommended initiation of telotristat for CaHD prevention. When presented with a vignette describing a similar patient with early evidence of CaHD, a nonsignificant majority recommended that telotristat therapy should be initiated. We therefore suggest that telotristat can be considered in patients with significantly elevated urine 5-HIAA (or other measures of circulating serotonin) and echocardiographic signs of valvular damage associated with CaHD. However, more evidence is needed before telotristat can be definitively recommended for prevention or management of CaHD. At this time, we do not recommend initiation of telotristat simply for the purpose of reducing serotonin levels in patients lacking evidence of valvular damage.

Valve Replacement for CaHD

Surgical valve replacement is generally the recommended treatment for patients with moderate to severe CaHD who otherwise have a life expectancy exceeding 1 year.³³ There was a consensus among the expert panel that both tricuspid and pulmonary valves should be evaluated carefully for evidence of thickening and insufficiency preoperatively as well as operatively. In most cases, replacement of both valves is performed during the same operation.

There is an increasing tendency for placement of bioprosthetic valves for avoidance of anticoagulation and evidence of improved outcomes and survival. However, the literature also indicates a role for mechanical valves when anticoagulation can be tolerated to avoid early valve degeneration. As evidence matures further, a role for percutaneous valve-in-valve therapy and the protective effects of telotristat on bioprosthetic valves might shift the paradigm further toward bioprosthetic valves. In the meantime, the choice of valve prosthesis should be individualized to each patient. When debating the optimal prosthetic valve type, a significant majority of the panel selected bioprosthetic valves.

Monitoring of Serotonin Levels in Patients With Advanced Midgut NETs

A significant majority of the expert panel indicated that they routinely monitor serotonin output in patients with advanced midgut NETs, typically at the time of radiographic staging. There are multiple methods for measuring serotonin output, including blood serotonin levels, 24-hour urine 5-HIAA measurements, and plasma 5-HIAA measurements.³⁵ There was no consensus regarding the optimal method for measurement of serotonin output. Half of respondents indicated that plasma 5-HIAA measurements were sufficiently validated for routine use as an alternative to 24-hour urine 5-HIAA collections.

Monitoring of Nonhormonal Tumor Markers in Patients With Advanced Midgut NETs

Chromogranin A is the most commonly measured nonspecific tumor marker in patients with midgut NETs; however, there was consensus that high rates of false-positive and false-negative results as well as unexplained fluctuations limit its utility.^{36,37} Chromogranin A has been validated as a prognostic marker in midgut NET in randomized clinical trials.³⁸ Pancreastatin, a breakdown product of CgA, may be more specific in certain contexts, such as patients using proton pump inhibitors (which raise CgA levels).^{39,40}

A significant majority of the expert panel reported that they measure tumor markers such as CgA and/or pancreastatin in routine practice, but a significant majority also indicated that these tumor markers assist in patient management only occasionally or rarely. As a result, no consensus was achieved on whether tumor markers should be routinely measured in patients with advanced midgut NETs. Studies of the relatively novel 51-gene, polymerase chain reaction–based NETest report higher rates of sensitivity, specificity, and accuracy compared with conventional monoanalyte tumor markers.⁴¹ Validation studies are ongoing.

DISCUSSION

In the past 8 years, the treatment landscape for midgut NETs has changed significantly. Five positive phase 3 clinical trials have transformed a field that was previously characterized by absence of high-quality, randomized prospective trials. The updated North American Neuroendocrine Tumor Society guidelines for medical management of midgut NETs discuss the appropriate use of new diagnostic and therapeutic agents. These include ¹⁷⁷Lu-DOTATATE and everolimus in patients with radiographically progressive tumors, telotristat ethyl in patients with suboptimal control of diarrhea in the context of carcinoid syndrome, and ⁶⁸Ga-DOTATATE (Netspot) for identification of somatostatin receptor–expressing tumors.

However, it is important to acknowledge that many questions remain unanswered. Further clinical research will be needed to address key issues pertaining to the management of midgut NETs. We have identified the following high-priority areas for study: randomized trials comparing liver-directed treatments to systemic treatments (including PRRT) in patients with progressive, liver-dominant, midgut NETs; randomized trials comparing radiolabeled SSAs to everolimus in progressive somatostatin receptor–expressive midgut NETs; randomized trials comparing risks/benefits of various transarterial liver embolization modalities; trials evaluating effects of telotristat ethyl on clinical and echocardiographic progression of CaHD; biomarker validation studies comparing sensitivity and specificity of monoanalyte and multianalyte circulating tumor makers; studies testing whether early changes in biomarkers accurately predict subsequent clinical and radiographic changes; and prospective longitudinal studies evaluating risk of recurrence and optimal monitoring after resection of early-stage midgut NETs. Future guidelines will hopefully be able to rely on high-level data to answer key questions pertaining to selection and sequencing of treatments and ensure that diagnostic tests are judiciously performed.

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