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The North American Neuroendocrine Society (NANETS) Consensus Guidelines for Surveillance and Medical Management of Midgut Neuroendocrine Tumors

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Abstract

There have been significant developments in diagnostic and therapeutic options for patients with neuroendocrine tumors. Key phase III studies include the CLARINET trial which evaluated lanreotide in patients with non-functioning enteropancreatic NETs, the RADIANT 2 and RADIANT 4 studies, which evaluated everolimus in functioning and non-functioning NETs of the GI tract and lungs, the TELESTAR study which evaluated telotristat ethyl in patients with refractory carcinoid syndrome, and the NETTER-1 trial which evaluated ^{177}Lutetium-dotatate in NETs of the small intestine and proximal colon (midgut). Based on these and other advances, the North American Neuroendocrine Tumor Society (NANETS) 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 manuscript. Surgical guidelines are described in a companion manuscript.

INTRODUCTION

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 III 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 III 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 III studies have investigated new drugs in patients with progressive disease. In the RADIANT 4 study, everolimus was compared to placebo in non-functional NETs of the GI tract and lung, demonstrating a significant improvement in PFS.[3] More recently, patients with progressive midgut NETs were randomized to receive the radiolabeled SSA ^{177}Lutetium-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 III TELESTAR study compared two 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-alpha. 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 (NANETS), 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.

METHODS

The ‘Medical Management of Midgut NETs’ panel consisted of fifteen participants, including seven medical oncologists, three endocrinologists, two 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 (UCSF), MD Anderson Cancer Center, Mayo Clinic, Memorial Sloan Kettering Cancer Center, Moffitt Cancer Center, the University of Iowa, the University of California Los Angeles (UCLA), Sunnybrook Research Institute, Toronto, Ontario, 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 5–10 minutes and included key literature references, with an emphasis on recent advances in the diagnosis and management of patients with NETs. Topics included post-operative 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. 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 one oppositional vote, and ‘significant majority’ as ≥75% agreement. We identified many areas of lack of consensus which suggest potential opportunities for clinical research. This manuscript summarizes the medical guidelines pertaining to management of advanced, unresectable, midgut NETs, and post-operative surveillance of stage 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:

1. Surveillance after resection of stage 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] Due to 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 for recurrence (e.g. 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 (e.g. 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 stage I–III midgut NETs.

2. Surveillance after resection of stage 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 CT scans or MRI 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 (e.g. 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 (NSE), among others, can be obtained as part of a surveillance regimen, however their value in early detection of recurrence is unknown. CgA 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 limits 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. NSE 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 negative rates limit their utility.

3. Management of patients with incidentally detected, asymptomatic low-volume metastatic tumors

Increasingly, patients are diagnosed incidentally with 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 III studies compared SSAs versus placebo in patients with relatively low-volume, indolent metastatic disease. The PROMID study compared octreotide LAR vs. placebo in patients with midgut NETs and absent or mild carcinoid syndrome, whereas the CLARINET study compared depot-lanreotide to 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 (OS) with treatment, likely owing to crossover to the active drug at the time of progression. In the CLARINET study, median progression-free survival (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 (e.g. scans roughly every 3–4 months initially) should be adopted. Patients with stable

disease can subsequently be monitored less frequently (e.g. every 6 months). The role of tumor markers in patients with asymptomatic low-volume disease remains unknown.

4. 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 are 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 (FNA) 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.

5. 1st line management of symptomatic patients with tumor-related symptoms or carcinoid syndrome

SSAs (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. Due to their relatively benign side effect profile, SSAs are typically selected as first-line systemic therapy.

6. Selection of octreotide LAR versus lanreotide

Currently, two long-acting somatostatin analogs 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 two 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.

7. Management of patients with negative somatostatin receptor imaging

The large majority of midgut NETs express high levels of somatostatin receptors (SSTR) which are targeted by SSAs and can be visualized by somatostatin receptor imaging. Traditionally, somatostatin receptor scintigraphy (SRS; 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 (e.g. ^{68}Ga-DOTA-Tyr^{3}-octreotide, ^{68}Ga-DOTA-TOC and ^{68}Ga-DOTA-Tyr^{3}-octreotate, ^{68}Ga-DOTA-TATE).[15] These radiopeptides vary in their affinity for the different SSTR subtypes 1–5, but the resultant PET imaging has been shown to have higher sensitivity for NETs, particularly for imaging small lesions.[8,15] Historically only available in the US as a research tool, the ^{68}Ga-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 SRS, 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 upon somatostatin imaging, there was a consensus that SSAs should be tried regardless of somatostatin receptor imaging results.

8. 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 non-functional 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 endpoint of PFS improvement.

In the NETTER-1 trial, patients with progressive midgut NETs were randomized to receive ^{177}Lu-dotatate versus high-dose octreotide (60 mg every 4 weeks).[4] ^{177}Lu-dotatate is a radiolabeled somatostatin analog, a form of treatment also known as peptide receptor radiotherapy (PRRT). The primary endpoint 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 ^{177}Lu-dotatate arm, translating to a 79% improvement in PFS ($p<0.00001$).

Other treatment options which have been traditionally available for progressive midgut NETs include Interferon-alpha (typically in combination with SSA), and hepatic arterial embolization for patients with liver-dominant disease. Interferon-alpha 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 (SIRT). Treatment

is associated with tumor shrinkage and a reduction in hormone-mediated symptoms in >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 2nd-line treatment in patients with somatostatin-receptor positive midgut NETs, a significant majority of the expert panel selected ^{177}Lu-dotatate as the most appropriate option based on results of the NETTER-1 study. It was noted that the evidence of everolimus efficacy appears stronger in non-midgut NETs (which represented the majority of patients on the RADIANT 4 study) compared to midgut NETs (which represented the majority of patients on the RADIANT 2 study). Interferon-alpha 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 2nd 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 ^{177}Lu-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 (i.e. PRRT then liver-directed therapy versus liver-directed therapy then PRRT). For patients with liver predominant disease and suboptimal control of carcinoid syndrome, liver embolization was considered an appropriate 2nd line treatment option (see section 14) based on high rates of symptomatic response associated with this therapy.

9. Management of patients with progressive midgut NET and negative somatostatin receptor imaging

In patients who are not candidates for radiolabeled SSAs (due to 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.

10. 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 non-functional NETs, based on eligibility criteria for the RADIANT 4 study.[23] A large number of metastatic midgut NETs (over 50% in some studies) secrete serotonin and are associated with the carcinoid syndrome.[24] A trend towards 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.

11. Role of interferon-alpha

Several small randomized clinical trials have investigated use of interferon-alpha in patients with progressive carcinoid tumors. [17–19] More recently, a randomized phase III clinical trial of bevacizumab versus interferon-alpha 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 interferon-alpha, a significant majority of panelists indicated that they never use interferon-alpha and the remainder stated that they rarely prescribe the drug. We therefore conclude that in the current treatment landscape, interferon-alpha should generally be considered only if no other option is available for the patient.

12. Choice of embolization therapy

Current transarterial embolic options can be broadly classified into three types: bland embolization, chemoembolization, and radioembolization (also known as Selective Intrahepatic Radiotherapy; SIRT).[22] All three 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 terminated early due to 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 due to under-enrollment.

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 both for evidence of benefit as well as toxicity.

13. 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 currently available treatment options (e.g. liver-directed therapy of all types and ^{177}Lu-dotatate) presents a significant challenge. As outcomes improve in this patient population, the significance of long-term toxicities could become more profound.[28]

14. 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.

15. 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 one 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.

16. 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 (e.g. PRRT).

17. 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. SSAs 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, diphenoxelate-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 (TPH) 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 III, placebo-controlled TELESTAR trial at two doses, 250 mg and 500 mg three times daily.[5] Eligible patients had carcinoid syndrome and at least 4 bowel movements per day. The primary endpoint of the study was reduction in number of daily bowel movements, averaged over a 12-week period. A key secondary endpoint 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 tid 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 hrs in patients receiving the 500 mg dose and 40 mg/24 hrs with the 250 mg dose; mean urinary 5-HIAA levels increased in the placebo group by 11 mg/24 hrs at week 12. Side 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, use of nonspecific antidiarrheal, or antitumor therapy. However, in a circumstance where increase in flushing and/or diarrhea occurs only towards 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.

18. 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.

19. Carcinoid heart disease: screening and surveillance

Carcinoid heart disease (CaHD) is characterized by fibrosis of the 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 carcinoid heart disease 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 carcinoid heart disease prior to onset of right heart failure is important to optimize post-operative 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 (NT-proBNP) 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, NT-BNP, are 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 (e.g. >5x 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. Healthcare providers should have a low threshold to obtain an echocardiogram in any patient with midgut NET exhibiting signs or symptoms of CaHD.

20. Use of telotristat ethyl for prevention of carcinoid heart disease

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 carcinoid heart disease. However, to date there is 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 due to the rarity of the condition and difficulty in establishing validated endpoints.

When presented with a vignette describing a patient with symptomatically controlled carcinoid syndrome, highly elevated levels of urine 5-HIAA (>5 x ULN) but no evidence of CaHD on echocardiogram, a small minority of the expert panel recommended initiation of telotristat for carcinoid heart disease prevention. When presented with a vignette describing a similar patient with early evidence of carcinoid heart disease, 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.

21. Valve replacement for carcinoid heart disease

Surgical valve replacement is generally the recommended treatment for patients with moderate to severe CaHD who otherwise have a life expectancy exceeding one year.[33] There was a consensus among the expert panel that both tricuspid and pulmonic 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 towards 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.

22. 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.

23. Monitoring of nonhormonal tumor markers in patients with advanced midgut NETs

CgA 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] CgA 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 only assist in patient management 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, PCR based NETest report higher rates of sensitivity, specificity and accuracy, compared to conventional monoanalyte tumor markers.[41] Validation studies are currently ongoing.

DISCUSSION

In the past 8 years, the treatment landscape for midgut NETs has changed significantly. Five positive phase III clinical trials have transformed a field that was previously characterized by absence of high quality, randomized prospective trials. The updated NANETS guidelines for medical management of midgut NETs discuss the appropriate use of new diagnostic and therapeutic agents. These include ^{177}Lu-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 ^{68}Ga-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 carcinoid heart disease; 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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