Management of Diarrhea in Patients With Carcinoid Syndrome

Boris G. Naraev, MD, PhD,* Magnus Halland, MD,† Daniel M. Halperin, MD,‡ Amy J. Purvis, MSN, ACNP§ Thomas M. O’Dorisio, MD,|| and Thorvardur R. Halfdanarson, MD¶

Abstract: Neuroendocrine tumors (NETs) arise from enterochromaffin cells found in neuroendocrine tissues, with most occurring in the gastrointestinal tract. The global incidence of NETs has increased in the past 15 years, likely due to better diagnostic methods. Small-bowel NETs are frequently associated with carcinoid syndrome (CS). Carcinoid syndrome diarrhea occurs in 80% of CS patients and poses a substantial symptomatic and economic burden. Patients with CS diarrhea frequently suffer from diarrhea and flushing and report corresponding impairment in quality of life, requiring substantial changes in daily activities and lifestyle. Treatment paradigms range from surgical debulking to liver-directed therapies to treatment with somatostatin analogs, nonspecific anti-diarrheal agents, and a tryptophan hydroxylase inhibitor. Other causes of diarrhea, including steatorrhea, short bowel syndrome, and bile acid malabsorption, should be considered in NET patients with refractory diarrhea. More therapeutic options are needed for symptomatic management of patients with NETs, and better understanding of the pathophysiology can empower clinicians with improved patient care.

Key Words: neuroendocrine tumors, diarrhea, somatostatin analogs, telotristat, carcinoid syndrome, carcinoid tumors

Abbreviations: 5-HIAA - 5-hydroxyindoleacetic acid, 5-HP - 5-hydroxytryptophan, CS - carcinoid syndrome, FDA - US Food and Drug Administration, GI - gastrointestinal, NET - neuroendocrine tumors, QoL - quality of life, SSA - selective somatostatin analogue

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From the *Banner MD Anderson Cancer Center, Gilbert, AZ; †Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN; ‡Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; §University of Arizona Cancer Center (UACC), Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, 2946 E Banner Gateway Drive, Gilbert, AZ 85234 (e-mail: Boris.Naraev@bannerhealth.com).

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N euroendocrine tumors (NETs) are a heterogeneous group of tumors that arise from enterochromaffin cells with traits of both nervous system and hormone-producing cells. Neuroendocrine tumors are principally characterized by originating site, grade, and stage, as well as functional status. Most (70%) are found in the gastrointestinal (GI) tract, but NETs may occur in other sites, including the lungs.12 Within the GI tract, the most common sites are the small bowel, rectum, and colon, followed by the pancreas, stomach, and appendix.3

Nomenclature, Classification, and Staging

Well-differentiated NETs were previously referred to as “carcinoid tumors.” Although the use of this term is now discouraged, it remains in common use by clinicians and patients.2 The World Health Organization classification system was developed to unify various approaches to tumor characterization and staging, thus enabling greater worldwide consistency in reporting.5 World Health Organization nomenclature, which does not recognize “carcinoid tumor,” describes grades 1 and 2 NETs as having well-differentiated histology (low mitotic count and Ki-67 labeling index), whereas grade 3 NETs include tumors with both well-differentiated and poorly differentiated morphology. Staging of NETs is adapted from the American Joint Committee on Cancer staging of more common cancers with the same site of origin, but other staging systems are also in use, including one proposed by the European Neuroendocrine Tumor Society.6

Neuroendocrine tumors can be functional or nonfunctional, with each having a distinct clinical profile. Functional NETs are characterized by symptoms caused by the biologically active compounds they secrete. Functional, non-pancreatic NETs release vasoactive peptides and amines, such as serotonin and tachykinins, resulting in carcinoid syndrome (CS). The most common symptoms of CS are diarrhea, flushing, and, less commonly, bronchoospasm and telangiectasia.2 Carcinoid heart disease, a potentially serious complication of CS, was observed in up to 50% of patients with CS in the past, but the prevalence has decreased in recent years,8,9 and may now be 20% or less.10 Carcinoid heart disease results from cardiac valve damage from fibrosis, predominantly involving the right-side valves, and is thought to be mostly secondary to serotonin production.11

Nonfunctioning NETs are not associated with abnormal hormonal secretion, can be difficult to detect, and often present at an advanced stage with secondary nonspecific symptoms.12 Up to 50% to 75% of patients with nonfunctioning small-bowel NETs present with metastatic disease at diagnosis.13,14 The proportion of patients presenting with metastatic disease has declined over time, suggesting a positive impact of earlier detection.12

Epidemiology

A population-based study using nationally representative data from the United States Surveillance, Epidemiology, and End Results program evaluated 64,971 patients with NETs from 1973 to 2012, and determined annual age-adjusted incidence, limited-duration prevalence, and 5-year overall survival rates.
Table 1. Known Products of Well-Differentiated NETs

| Amines | Polypeptides | Prostaglandins |
|--------|--------------|----------------|
| Serotonin | Kallikrein | Prostaglandins E and F |
| 5-HTP | Pancreatic polypeptide | |
| Norepinephrine | Bradykinin | |
| Dopamine | Motilin | |
| Histamine | Somatostatin | |
| | Vasoactive intestinal peptide | |
| | Neuropeptide K | |
| | Substance P | |
| | Neurokinin A and B | |

Source: 26,27

Clinical Presentation

Neuroendocrine tumors produce peptides and hormones that are responsible for the characteristic symptoms (Table 1). The most common symptoms of CS are cutaneous flushing (45%–96%), diarrhea (58%–100%), wheezing from bronchospasm (3%–18%), valvular heart disease due to thickening and restricted mobility of predominantly right-sided heart valves, and hyperkeratosis and pigmentation.28–30 Even among patients with classic CS, the phenotypic expression and severity of various symptoms vary.

Although less common, patients with extra-GI NETs, such as the bronchopulmonary system, can present clinically with CS in the absence of liver metastases. These non-classic CS presentations may be gastric carcinoid- or bronchial carcinoid-variant syndrome.31 Depending on location, NETs may cause symptoms similar to those of common conditions, such as irritable bowel syndrome, Crohn disease, peptic ulcer disease, gastritis, other digestive disorders, asthma, or pneumonia.32 For these reasons, NETs are often initially diagnosed at an advanced stage12 and are commonly misdiagnosed. Diagnosis is based on histopathology, imaging, and circulating biomarkers. Initial diagnosis must include histological examination by an expert pathologist.33

To establish a diagnosis, patients should have abdominal and pelvic imaging and chest imaging in select cases, a biopsy to confirm the diagnosis and assign a tumor grade, somatostatin receptor-based imaging, and biochemical evaluation.34 Standard imaging procedures consist of contrast-enhanced computed tomography or magnetic resonance imaging (MRI), frequently in conjunction with somatostatin receptor–based imaging. Gallium 68 DOTATATE positron emission tomography (PET) or PET/MRI somatostatin receptor–based imaging is preferred over somatostatin receptor scintigraphy (OctreoScan, Curium US LLC, Maryland Heights, Mo), given the superior sensitivity of PET imaging.35–37

Biochemical assessment is essential in patients with clinical evidence of hormone hypersecretion. Testing of amine markers (eg, serotonin, histamine), as well as neuro peptide biomarkers such as chromogranin A, pancreastatin, gastrin, glucagon, and vasoactive intestinal peptide should be considered based on the presentation. The production of serotonin is best assessed by measuring the serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA), either in a fasting plasma sample or a timed urine collection.27,33,36 Plasma 5-HIAA levels correlate well with 24-hour urine levels and are more convenient. Serotonin measurement is generally not needed. Chromogranin A remains the most commonly used marker but suffers from a lack in both sensitivity and specificity and the results rarely change the management.38 Pancreastatin has been suggested as a marker for tumor burden in both pancreatic NETs and small-bowel NET, but awaits further validation.39

CS DIARRHEA

Patients with CS diarrhea experience watery, loose stools multiple times a day—sometimes associated with considerable urgency—and the management can be very challenging.40,41 In addition to CS, patients with NETs can have other causes of diarrhea, discussed in detail below. Broad consideration of this differential diagnosis is required to optimize management.42

Because the symptoms of CS are often nonspecific, a delay in diagnosis is common.43 Detected early, NETs can often be cured with surgery; unfortunately, many will eventually recur, often more than 5 to 10 years after surgery.44,45 Most NETs are diagnosed as advanced metastatic disease, however, at which point surgical cure is not possible and treatment is focused on symptom management.

Quality of Life

Increased frequency of bowel movements, diarrhea, fecal incontinence, and cutaneous flushing correlate with decreased

The age-adjusted incidence rate of NETs increased 6.4-fold, from 1.09 per 100,000 in 1973 to 6.98 per 100,000 in 2014 across all sites, stages, and grades of disease. The highest incidence rates were 3.56 per 100,000 in gastroenteropancreatic sites (including 1.05/100,000 in the small intestine, 1.04/100,000 in the rectum, and 0.48/100,000 in the pancreas). The estimated 20-year limited-duration prevalence of NETs in the United States on January 1, 2014, was 171,321. There was a considerable variation in median 5-year overall survival rates for all NETs by stage, grade, age at diagnosis, primary site, and time period of diagnosis. From 2000–2004 to the 2009–2014 period, overall survival improved (hazard ratio [HR], 0.79; 95% confidence interval [CI], 0.73–0.85). Even larger increases in overall survival were noted in distant-stage GI NETs (HR, 0.71; 95% CI, 0.62–0.81) and distant-stage pancreatic NETs (HR, 0.56; 95% CI, 0.44–0.70).4 Sim- liar increase in NET incidence has been observed in Western Europe, Norway, and Japan.13,15–17 The observed rise in incidence may in part be due to earlier detection.12

Neuroendocrine Tumors and CS

Small-bowel NETs associated with CS are most commonly identified in the terminal ileum. Carcinoid syndrome has also been reported in patients with more proximal and appendiceal NETs.4 Patients with CS have liver metastases at the time of the emergence of CS symptoms.14,18 Localized small-bowel NETs can produce biologically active substances, but symptoms are usually absent as these substances are inactivated in the liver. Substances produced in the liver are released into the systemic circulation, with some inactivation taking place in the lungs. Pelvic NETs (primary or metastatic), as well as NETs metastatic to lymph nodes and bones, can result in CS in the absence of liver metastases.19 Thoracic NETs and foregut NETs (bronchus, stomach, and duodenum) are less likely to cause CS, although a recent study suggested a higher prevalence of CS among patients with lung NETs than previously reported.20 Recent studies have suggested that pancreatic NETs may occasionally produce serotonin, resulting in CS.21,22

In an analysis of the proportion of patients 65 years or older with NETs and CS and associated clinical factors between April 2000 and December 2011 from the United States Surveillance, Epidemiology, and End Results and Medicare databases, 9512 patients with NETs and CS were identified in the terminal ileum. Carcinoid syndrome has also been reported in patients with more proximal and appendiceal NETs.4 Patients with CS have liver metastases at the time of the emergence of CS symptoms.14,18 Localized small-bowel NETs can produce biologically active substances, but symptoms are usually absent as these substances are inactivated in the liver. Substances produced in the liver are released into the systemic circulation, with some inactivation taking place in the lungs. Pelvic NETs (primary or metastatic), as well as NETs metastatic to lymph nodes and bones, can result in CS in the absence of liver metastases.19 Thoracic NETs and foregut NETs (bronchus, stomach, and duodenum) are less likely to cause CS, although a recent study suggested a higher prevalence of CS among patients with lung NETs than previously reported.20 Recent studies have suggested that pancreatic NETs may occasionally produce serotonin, resulting in CS.21,22

In an analysis of the proportion of patients 65 years or older with NETs and CS and associated clinical factors between April 2000 and December 2011 from the United States Surveillance, Epidemiology, and End Results and Medicare databases, 9512 patients with NETs, of whom 1786 (19%) had CS. The proportion of patients with NETs and CS increased from 11% of 465 patients in 2000 to 19% of 854 patients in 2011 (P < 0.0001). Patients with CS were more likely to be female (61%, P = 0.0003) and non-Hispanic white (84% P < 0.0001). Carcinoid syndrome was associated with inferior survival.24
quality of life (QoL). When compared to non-NET cancer populations and population norms, patients with NETs have high rates of depression and cognitive impairment, decreases in overall physical function, impairment in sleep, fatigue, and anxiety.

Diarrhea has a particularly prominent adverse impact on physical, emotional, and social well-being. Interventions to improve individual daily activities and productivity can improve health-related QoL and reduce stress in patients with NETs. In a longitudinal study of 59 patients, fatigue and dyspnea were identified as the worst aspects of physical distress and depression as the worst aspect of emotional distress.

Economic Burden
Diarrhea has a significant medical and economic impact. Carcinoid syndrome diarrhea accounts for 1.5-fold higher total healthcare spending and almost a 2-fold higher risk of CS-related hospitalizations compared to when diarrhea is not present. A substantial financial burden has been demonstrated in NET patients in the United States, particularly in the first year after receipt of the diagnosis and regardless of whether patients received surgery or medical therapy. Reduction in CS diarrhea-related healthcare expenditures may be achievable through preventive treatment and appropriate management of diarrhea.

A study evaluating the economic burden of illness in patients with malignant GI NETs concluded that the mean annual cost was over $70,000 US dollars (USD; based on 2012 USD), higher than the national average of approximately $38,000 USD for all cancers. A separate study of 625 patients with NETs undergoing medical or surgical therapy concluded that the significant costs may be associated with the slow progression of the disease and that there is an unmet need for GI NET patients for additional effective therapies targeting improvement in outcomes, leading to lower healthcare resource use and cost utilization.

Morbidity and Mortality
Patients with NETs have significantly higher rates of mortality and hepatic and GI morbidities compared to patients without NETs or other cancers matched by age, sex, and year of diagnosis. Weight loss and malnutrition in patients with malignant tumors are linked to unfavorable outcomes, including excess mortality and morbidity and higher treatment costs.

Pathophysiology of CS Diarrhea
Carcinoid syndrome diarrhea is largely a consequence of tumoral secretion of serotonin (Fig. 1). In a healthy individual, serotonin is primarily (95%) found in the GI tract with most secreted by enterochromaffin cells, the cellular source of NETs. Circulating serotonin is exclusively derived from the GI tract and is an important component of normal gut function. Excess serotonin increases peristalsis, which results in reduced absorption of water and electrolytes, leading to diarrhea. Patients with CS present with a significant increase in serotonin plasma levels and, consequently, in the levels of soluble urinary metabolite 5-HIAA. Reduction in serotonin production, reflected in lower levels of 5-HIAA, is associated with improvement in CS diarrhea.

Other mediators secreted by NETs include 5-hydroxytryptophan (5-HTP), prostaglandins, tachykinins, other kinins (eg, bradykinin), and, rarely, histamine.

In a comparative assessment using radiopaque markers, GI transit time is faster in patients with CS diarrhea (n = 7) compared with healthy subjects (n = 15). Overall transit time was 12.5 hours in patients versus 25.1 hours in healthy volunteers, whereas small-intestine transit time was 3.8 hours versus 4.4 hours, respectively. The greatest difference was noted in colonic transit time, which was 5.2 hours in patients versus 18.1 hours in healthy volunteers.

Differential Diagnosis
In assessing a patient with suspected CS diarrhea, it is important to differentiate the GI symptoms of NETs from the diarrhea, abdominal pain, and dyspepsia related to other causes (eg, irritable bowel syndrome) by eliciting a thorough patient history that details age, sleep patterns, and nonspecific symptoms. Unfortunately, the literature on the differential diagnosis of CS diarrhea is limited. Diarrhea in patients with NETs is secretory, typically causing large-volume stools, with no osmotic gap between serum and stool, compared with malabsorptive diarrhea in other GI diseases. It may disturb sleep and is associated with bleeding, fever, weight loss, and persistent severe pain. Other causes of secretory diarrhea (eg, bile acid-induced diarrhea, medications, infections, and metabolic causes, including diabetes mellitus) should be ruled out. Inquiry about ingested laxatives and osmotic agents such as fructose and artificial sweeteners, which are common contributors to diarrhea in general, is important.

Diarrhea associated with CS tends to be watery after the first 1 or 2 movements, and the frequency of bowel movements can range from 2 to 5 in a day to more than 20, which can be extremely debilitating and deleterious to QoL. The presence of watery diarrhea, in association with cutaneous facial flushing (especially when associated with evidence of elevated serotonin blood levels), and radiographic evidence of malignancy is almost always diagnostic of CS diarrhea. Pellagra secondary to niacin depletion has been reported in patients with CS. Although biochemical niacin deficiency is not uncommon, clinical manifestations of pellagra, including diarrhea, are rare but could contribute to CS in some patients.

Ongoing diarrhea after initiation of therapy with selective somatostatin analogues (SSAs) is common and most commonly due to incompletely controlled CS. In such circumstances, the diarrhea retains the characteristics of the diarrhea prior to initiation of therapy but occurs less frequently. Use of SSAs, approved by the US Food and Drug Administration (FDA) for the management and control of CS, may contribute to worsening of diarrhea. One of the more common adverse reactions of chronic use of SSAs is steatorrhea, with frequency of 26% to 65% for lanreotide (dose related), and 36% to 61% for octreotide. Steatorrhea associated with SSAs results from inhibition of meal-stimulated digestive enzymes from the pancreas. Although stool collection for fat content analysis can be helpful for diagnosis, a more practical approach is empiric therapy with pancreatic enzymes. The importance of taking the enzyme supplements with meals and snacks should be stressed and the dose titrated upward until desired effects are achieved. Fecal elastase-1 has been reported as a reliable diagnostic test, especially in symptomatic patients, but is uncommonly used.

Bile acid malabsorption may also cause diarrhea in patients with NETs, particularly among those who have undergone resection of the terminal ileum and/or right colon or cholecystectomy. Identification of bile acid-induced diarrhea is important as specific therapy, such as bile acid-sequestrant therapy is available. Assessing levels of serum 7α-hydroxy-4-cholesten-3-one can help detect bile acid malabsorption, although availability of this test is limited. A quantitative analysis of total and bile acid fraction on 48-hour stool testing can confirm the diagnosis. In practice, empiric therapy with bile acid sequestrants can be tried, and clinical improvement strongly suggests bile acid malabsorption as the cause of the diarrhea.
Patients who have undergone extensive small-bowel resections can have diarrhea secondary to short bowel syndrome. This can lead to significant malabsorption and weight loss, and, in extreme cases, parenteral nutrition is necessary. The onset of such diarrhea can usually be traced back to the time of surgery. Resections of longer segments of the small bowel, especially those >100 cm, may lead to additional steatorrhea, complicating both the diagnosis and therapy.76,77 This form of diarrhea may be suspected when high doses of octreotide, administered subcutaneously, do not improve the diarrheal state.

Management Options

Treatment planning in patients with NETs is a complex and complicated process due to heterogeneity of the tumors and multiple treatment options and approaches available. In patients with NETs and CS managing the symptoms of hormone excess is one of the key considerations during treatment decision making.78 Treatment guidelines, such as those from the National Comprehensive Cancer Network and North American Neuroendocrine Society,25,33 elevate the importance of CS management in addition to tumor control.

Dietary Modification

Although dietary modifications for management of specific GI symptoms for NET patients are recommended through patient websites and healthcare provider interviews, there is no clear evidence to be found within the literature that would scientifically attest to their efficacy and neither of the major treatment guidelines provides dietary advice.25,33 However, anecdotal evidence for symptom improvement in NET patients has been observed by the authors in their clinical practice with recommendation for frequent small meals and avoidance of aged cheeses and fermented foods with high amine content by patients with secretory diarrhea. A retrospective chart review of 69 patients with gastric NETs and...
diarrhea who received an amino acid-based glucose-free medical diet with electrolytes reported 80% of patients had subjective improvement of diarrheal symptoms and 51% reported >50% reduction in diarrhea frequency.79

Surgical Cytoreduction
Resection of liver metastases can quickly decrease tumor bulk, especially in patients with completely resectable or mostly resectable liver metastases. More than 80% to 90% tumor volume debulking can promptly resolve symptoms of diarrhea and flushing and may translate to improved survival.80

Liver-Directed Therapies
Use of liver-directed therapies, such as transarterial chemoembolization, transarterial embolization, radioembolization (selective internal radiation therapy), or radiofrequency ablation, may contribute to reducing tumor burden and hormone release and increase response to medical therapy to control the symptoms of NET-related hormone-excess states in patients with refractory disease.81,82 Liver-directed therapy can effectively control symptoms in patients with liver-dominant metastases. Of the available modalities, none has emerged as being superior, and toxicities differ among the available modalities. Small, retrospective studies and 1 very small prospective trial have suggested similar efficacy of the different

| TABLE 2. Practical Considerations for Noninfectious Chronic Diarrhea in Patients with Neuroendocrine Tumors |
|---|---|---|---|
| Types of Diarrhea | Causes | Symptoms | Symptomatic treatment |
| CS Diarrhea | Increased production of serotonin | watery stools | Dietary adjustments: use complex carbohydrates, fat consumption restriction, increased fiber consumption |
| Short GI Transit Time | Increased production of vasoactive intestinal polypeptide | large stool volume (>1 L/day) | Fluid consumption adjustment: restriction of hypertonic (eg, fruit juices, soda) and hypotonic (eg, water, alcohol, coffee, tea) fluids, use of oral rehydration therapy (eg, electrolytes with glucose) |
| Steatorrhea | Resection of the small bowel | not affected by fasting | Histamine-2 blockers or proton pump inhibitors |
| Bile Acid Diarrhea | Loss of the ileocecal valve | happens daytime and nighttime | Loperamide |
| | Exocrine pancreatic insufficiency after surgical resection of the pancreas | stool frequency ranging from 2 to >20/day | Codeine sulfate |
| | Decreased production of secretin and/or cholecystokinin-pancreozymin after gastric and/or duodenal resection | bowel movements occur soon after meals | Diphenoxylate/atropine |
| | Pancreatic insufficiency secondary to treatment with SSAs | undigested or partially digested food in the stool | Octreotide |
| | Inactivation of pancreatic enzymes by high levels of gastric acid in patients with gastrinoma | diarrhea without flatulence | Deodorized tincture of opium |
| | Excessive volume of bile acids in the colon after cholecystectomy or due to dysmotility of the gallbladder | stool is yellow in color | Paregoric (camphorated tincture of opium) |
| | Resection of the terminal ileum resulting in decreased bile acids resorption | frequent and urgent bowel movements | Clonidine |
| | Burning sensation with bowel movements | wet stool | Exenatidine |
| | | unusual stool color | Teduglutide |

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hepatic arterial interventions. There are concerns about excessive cumulative hepatic radiotoxicity in patients who receive both selective internal radiation therapy and peptide receptor radionuclide therapy, and even in patients who receive selective internal radiation therapy alone.

Peptide Receptor Radionuclide Therapy

Peptide receptor radionuclide therapy provides a means of delivering targeted radiation to tumors, such as NETs, that express somatostatin receptors. Strosberg et al. reported results from the randomized phase 3 NETTER-1 clinical trial showing that DOTATATE lutetium-Lu-177 significantly increased progression-free survival with a trend toward improved overall survival versus long-acting octreotide. NETTER-1 also confirmed that DOTATATE lutetium-Lu-177 was superior to high-dose octreotide LAR in maintaining or delaying worsening of QoL, role functioning, and diarrhea and suggested improved CS diarrhea. A small retrospective study suggested symptomatic benefit of peptide receptor radionuclide therapy in patients with refractory CS diarrhea and flushing.

CS-Specific Therapies

Somatostatin Analogs

Somatostatin inhibits secretion of hormones and growth of NETs. Consequently, metabolically stable SSAs are the cornerstone of treatment for patients with NETs due to their inhibition of secretion of multiple hormones and reduction in the rate of disease progression. Guidelines recommend use of an SSA (octreotide or lanreotide) as the initial first-line treatment in patients with CS, with
evidence that both long- and short-acting SSAs effectively control symptoms. Among patients with severe symptoms, the initial concurrent use of short-acting octreotide may be necessary until the effects of the long-acting formulation become fully effective.25,33

There are currently 3 SSAs available. The first-generation SSAs, octreotide and lanreotide, are indicated and widely used for the management of NETs. Octreotide, first approved in the United States in 1988, has been a cornerstone of therapy for management of diarrhea in patients with CS. Use of lanreotide was associated with improvements in symptoms as well as a range of patient-reported outcomes in patients with NETs and CS.93 Lanreotide is also indicated for use in CS patients.72 The increased understanding of somatostatin receptor pharmacology provides new opportunities to design more sophisticated analogs to aid future development of SSAs with improved efficacy (Fig. 2).94 The second-generation SSA, pasireotide, is not FDA-approved for treatment of NETs.

Uncontrolled CS Diarrhea—Treatment Strategies

Despite use of SSAs, patients may become refractory to treatment and experience symptom progression. Treatment options used in clinical practice for refractory CS include SSA dose escalation, interferon, and surgical, embolic, and radiation therapies. A retrospective analysis reported that among 239 patients with symptomatic NETs 62% had symptom progression while on octreotide LAR 30 mg, 81% [of the 239] had limited improvement in flushing, and 79% [of the 239] had improvement in diarrhea after the first-dose escalation to either 40 or 60 mg.95 Dose escalation can be considered for patients with suboptimal symptom control on standard doses and can be done by either increasing the long-acting dose, shortening the interval between doses, or using concomitant subcutaneously administered octreotide. If patient symptoms worsen the week immediately prior to the next scheduled dose, shortening of the dosing interval may be an appropriate course of action. For patients who do not have their symptoms under control at any time during each treatment cycle, a trial of increasing the dose may be a better strategy.96

Switching SSAs is another treatment approach; however, there are limited data from small studies and case reports to support this approach. In a small phase 2 trial of 15 patients with progressive metastatic NETs (7 of which were of midgut origin) while receiving lanreotide 30 mg biweekly, the switch to octreotide LAR 30 mg led to overall biochemical and symptomatic response of 41% and 82%, respectively.97 Currently, there is very limited evidence to suggest that a switch from one SSA to another will result in improved control of CS symptoms or tumor growth; this practice cannot be routinely recommended based on the available data. Furthermore, despite these treatment strategies, patients are likely to continue to experience progression of CS diarrhea symptoms and continue to have 4 or more daily bowel movements.98

Tryptophan Hydroxylase Inhibitors—Telotristat

Telotristat ethyl inhibits tryptophan hydroxylase, the rate-limiting enzyme in the synthesis of serotonin.99–101 By inhibiting serotonin synthesis, the specific activity in targeting the underlying pathophysiology of serotonin overproduction in CS is addressed and, as a result, many of the symptoms of CS may theoretically be controlled. Telotristat ethyl is approved by the FDA to address refractory CS diarrhea in combination with SSA therapy for adult patients (Fig. 3).102,103 The National Comprehensive Cancer Center guidelines recommend telotristat as second-line therapy in patients with progression of CS.33

Two pivotal phase 3, randomized, placebo-controlled trials, TELESTAR and TELECAST, investigated the efficacy and safety of telotristat ethyl 250 mg and 500 mg administered 3 times a day in patients with CS refractory to SSA therapy for 3 times a day in patients with CS refractory to SSA therapy. Both studies included a 12-week double-blind treatment period followed by a 36-week open-label extension period.104 Both doses of telotristat ethyl provided significant reduction in bowel movement frequency compared with placebo in both studies. The reductions in bowel movements noted in the double-blind period were generally sustained during the open-label extension period (Fig. 4). Understanding the time to onset of sustained improvement in bowel movement frequency is important when considering the use of telotristat ethyl in patients with CS diarrhea. Dillon et al reported further analyses of data from TELESTAR and TELECAST showing a median time to sustained improvement of 4 to 5 weeks, which

FIGURE 3. Mechanism of action of telotristat ethyl in NETs. Editor’s note: A color image accompanies the online version of this article.
should be considered when patients are started on telotristat ethyl therapy. The TELESTAR study also showed significant improvement in QoL based on the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ)-C30 diarrhea subscale score (Fig. 5). Other subscales, such as nausea and vomiting and global health status, did not show significant differences; however, the response in the diarrhea subscale specifically suggests a greater sensitivity to the CS diarrhea patient population in comparison to the other EORTC QLQ-C30 subscales.

Telotristat ethyl was generally well tolerated, with nausea and headache being the most commonly reported adverse events. Long-term follow-up for up to 6 years has shown no new safety concerns and positive impact on relief of CS symptoms is maintained.

**Bile Acid Sequestrants**

In confirmed cases of bile acid-induced diarrhea or, in the right clinical scenario, an empiric trial of bile acid sequestrants (such as cholestyramine, colestipol, or colesevelam), is reasonable. Therapy typically is started at a low dose and titrated to response.

**Antidiarrheals**

Although therapy with nonspecific antidiarrheals, such as loperamide or diphenoxylate, may improve the diarrhea, evidence from prospective trials is lacking and there can be substantial side effects, especially with the use of anticholinergic drugs in the elderly. It is important to note that antidiarrheals do not address the underlying changes in motor function associated with CS diarrhea, nor to do they reduce circulating serotonin.

**Other Options**

Ondansetron has been reported to have some activity in patients with CS diarrhea in small retrospective studies, but no prospective studies have compared it with other interventions. A small retrospective study of 13 patients with treatment-refractory CS diarrhea reported that 85% of patients experienced a decrease in the frequency of bowel movements. In 4 patients, the diarrhea recurred after initial improvement, but 7 patients had ongoing benefit. These findings should be confirmed in a larger prospective trial. The role of serotonin receptor antagonists in the management of diarrhea needs to be further evaluated before it can be routinely recommended.

Cyproheptadine has been reported be effective in the management of CS diarrhea. Cyproheptadine can have substantial side effects, however, and is thus rarely used for CS diarrhea given safer and more effective treatment options. Based on the authors' clinical experience, the combination of cyproheptadine with octreotide can also be effective in controlling refractory CS diarrhea.

A treatment algorithm of CS diarrhea is provided (Fig. 6). Although initial management can be conducted with preliminary steps such as dietary modification, more directed approaches,
such as surgical cytoreduction and liver-directed therapies, may be necessary to make specific impact. Pharmacological treatment approaches with SSAs have shown modest improvement, but telotristat ethyl is the only agent that is specifically indicated to address CS diarrhea in combination with SSA therapy.

FUTURE DIRECTIONS

Carcinoid syndrome diarrhea remains a very significant clinical problem with substantial symptom burden resulting in reduced QoL and negative financial impact in patients with metastatic NETs. Although tumor-directed therapy, especially SSAs, remains active, diarrhea may become refractory to conventional therapy. It is important to rule out and treat common morbidities that may mimic CS diarrhea, especially steatorrhea, short gut, dysmotility, and bile acid malabsorption. Telotristat ethyl is a novel agent inhibiting the tryptophan hydroxylase, the rate-limiting step in the production of serotonin by NETs, which is the main driver of CS diarrhea. It has demonstrated statistically significant reductions in bowel movement frequency. However, many patients receiving concurrent SSAs and telotristat ethyl continue to suffer from diarrhea. Peptide receptor radionuclide therapy with DOTATATE lutetium-Lu-177 can alleviate diarrhea in some patients, but better treatments are still needed for patients with poorly controlled symptoms. With a better understanding of the symptomatology and pathophysiology of NET symptom burden, our hope is that standard and novel therapies can be deployed for optimal patient benefit.

REFERENCES

1. Choti MA, Bobiak S, Strosberg JR, et al. Prevalence of functional tumors in neuroendocrine carcinoma: an analysis from the NCCN NET database. J Clin Oncol. 2012;30(15 suppl):4126.abstract.
2. Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol. 2017;3:1335–1342.
3. Lawrence B, Gustafsson BI, Chan A, et al. The epidemiology of gastroenteropancreatic neuroendocrine tumors. Endocrinol Metab Clin North Am. 2011;40(1):1–18.

4. Bosman FT, Carneiro F, Hruban RH, et al., eds. WHO Classification of Tumours of the Digestive System. 4th ed. Lyon, France: International Agency for Research on Cancer; 2010.

5. Kim JY, Hong SM. Recent updates on neuroendocrine tumors from the gastrointestinal and pancreaticobiliary tract. Arch Pathol Lab Med. 2016;140:437–448.

6. Luo G, Javed A, Strosberg JR, et al. Modified staging classification for pancreatic neuroendocrine tumors on the basis of the American Joint Committee on Cancer and European Neuroendocrine Tumor Society systems. J Clin Oncol. 2017;35:274–280.

7. Öberg KE. Gastrointestinal neuroendocrine tumors. Ann Oncol. 2010;21 Suppl 7:vii72–vii80.

8. Hayes AR, Davar J, Caplin ME. Carcinoid heart disease: a review. Endocrinol Metab Clin North Am. 2018;47:671–682.

9. Bhattacharyya S, ToupOpaque K, Burke M, et al. Features of carcinoid heart disease identified by 2- and 3-dimensional echocardiography and cardiac MRI. Circ Cardiovasc Imaging. 2010;3:103–111.

10. Møller JE, Pellikka PA, Bernheim AM, et al. Prognosis of carcinoid heart disease: analysis of 200 cases over two decades. Circulation. 2005;112:3320–3327.

11. Davar J, Connolly HM, Caplin ME, et al. Diagnosing and managing carcinoid heart disease in patients with neuroendocrine tumors: an expert statement. J Am Coll Cardiol. 2017;69:1288–1304.

12. Hallet J, Law CHL, Culik M, et al. Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes: Neuroendocrine Tumor Epidemiology. Cancer. 2015;121:589–597.

13. Boyar Cetinkaya R, Aagnes B, Myklebust TA, et al. Survival in neuroendocrine neoplasms in Norway: a report of 16,075 cases from 1993 through 2010. Neuroendocrinology. 2017;104:1–10.

14. Bertani E, Falconi M, Grana C, et al. Small intestinal neuroendocrine tumors with liver metastases and resection of the primary: prognostic factors for decision making. Int J Surg. 2015;20:58–64.

15. Huguet L, Grossman AB, O'Toole D. Changes in the epidemiology of neuroendocrine tumours. Neuroendocrinology. 2017;104:105–111.

16. Boyar Cetinkaya R, Aagnes B, Myklebust TA, et al. Survival in neuroendocrine neoplasms: a report from a large Norwegian population-based study. Int J Cancer. 2018;142:1139–1147.

17. Frenkel M, Kim M, Faggiano A, et al. Incidence of gastroenteropancreatic neuroendocrine tumours: a systematic review of the literature. Endocr Relat Cancer. 2014;21(R153–R163).

18. Shi C, Gonzalez RS, Zhao Z, et al. Liver metastases of small intestine neuroendocrine tumors: Ki67 heterogeneity and WHO grade discordance with primary tumors. Am J Clin Pathol. 2015;143:398–404.

19. Harring TR, Nguyen NT, Goss JA, et al. Treatment of liver metastases in patients with neuroendocrine tumors: a comprehensive review. Int J Hepatol. 2011;2011:54541.

20. Robelin P, Hadoux J, Forestier J, et al. Characterization, prognosis and treatment of patients with metastatic lung carcinoid tumors. J Thorac Oncol. 2019;14:993–1002.

21. Patel ME, Phan AT, Wolin EM, et al. Effect of flarnetide depot/autogel on urinary 5-hydroxyindoleacetic acid and plasma chromogranin A biomarkers in nonfunctional metastatic enteropancreatic neuroendocrine tumors. Oncologist. 2019;24:463–474.

22. Zandee WT, van Adrichem RC, Kamp K, et al. Incidence and prognostic value of serotonin secretion in pancreatic neuroendocrine tumours. Clin Endocrinol (Oxf). 2017;87:165–170.

23. Tsoukalas N, Chatzellis E, Rontogianni D, et al. Pancreatic carcinoids (serotonin-producing pancreatic neuroendocrine neoplasms): report of 5 cases and review of the literature. Medicine (Baltimore). 2017;96:e6201.

24. Halperin DM, Shen C, Dasari A, et al. Frequency of carcinoid syndrome at neuroendocrine tumour diagnosis: a population-based study. Lancet Oncol. 2017;18:525–534.

25. Strosberg JR, Halfdanarson TR, Bellizzi AM, et al. The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Medical Management of Midgut Neuroendocrine Tumors. Pancreas. 2016;47:707–714.

26. Strosberg JR. Clinical characteristics of well-differentiated neuroendocrine (carcinoid) tumors arising in the tubular digestive tract, lung, and genitourinary tract. Tanabe KK, Whitcomb DC, Savarese DM, eds. October 2017. Available at: https://www.uptodate.com/contents/clinical-characteristics-of-well-differentiated-neuroendocrine-carcinoid-tumors- arising-in-the-tubular-digestive-tract-lung-and-genitourinary-tract. Accessed July 18, 2018.

27. Öberg K, Modlin IM, De Herder W, et al. Consensus on biomarkers for neuroendocrine tumour disease. Lancet Oncol. 2015;16:e435–e446.

28. Creutzfeldt W. Carcinoid tumors: development of our knowledge. World J Surg. 1996;20:126–131.

29. Dimitriadis GK, Weickert MO, Randeva HS, et al. Medical management of secretory syndromes related to gastroenteropancreatic neuroendocrine tumours. Endocr Relat Cancer. 2016;23:R423–R436.

30. Ito T, Lee L, Jensen RT. Carcinoid-syndrome: recent advances, current status and controversies. Curr Opin Endocrinol Diabetes Obes. 2018;25:22–35.

31. Zandee WT, Kamp K, van Adrichem RC, et al. Effect of hormone secretory syndromes on neuroendocrine tumor prognosis. Endocr Relat Cancer. 2017;24:R261–R274.

32. International Agency for Research on Cancer. Why are NET cancers so often misdiagnosed? INCA. September 2015. Available at: http://incaalliance.org/why-are-net-cancers-so-often-misdiagnosed/. Accessed May 9, 2018.

33. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) Neuroendocrine and Adrenal Tumors. Version 2.2018. Presented at the: May 4, 2018. Available at: https://www.nccn.org/professionals/physician_gls/PDF/neuroendocrine.pdf. Accessed May 9, 2018.

34. Derpen SA, Blume J, Bobbey AI, et al. 68Ga-DOTATATE compared with 111In-DTPA-octreotide and conventional imaging for pulmonary and gastroenteropancreatic neuroendocrine tumours: a systematic review and meta-analysis. J Nucl Med. 2016;57:872–878.

35. Derpen SA, Liu E, Blume JD, et al. Safety and efficacy of 68Ga-DOTATATE PET/CT for diagnosis, staging, and treatment management of neuroendocrine tumors. J Nucl Med. 2016;57:708–714.

36. Halfdanarson TR, Howe JR, Haraldsdottir S, et al. Circulating tumor markers in patients with neuroendocrine tumors—a clinical perspective. Int J Endocr Oncol. 2015;2:89–99.

37. Rustagi S, Warner RR, Divino CM. Serum pancreastatin: the next predictive neuroendocrine tumor marker. J Surg Oncol. 2013;108:126–128.

38. Sherman SK, Maxwell JE, O’Dorisio MS, et al. Pancreastatin predicts survival in neuroendocrine tumors. Ann Surg Oncol. 2014;21:2971–2980.

39. Khan TM, Garg M, Warner RR, et al. Elevated serum pancreastatin is an indicator of hepatic metastasis in patients with small bowel neuroendocrine tumors. Pancreas. 2016;45:1032–1035.

40. Singh S, Granberg D, Wolin E, et al. Patient-reported burden of a neuroendocrine tumor (NET) diagnosis: results from the first global survey of patients with NETS. J Glob Oncol. 2016;3:43–53.

41. Wolin EM, Leyden J, Goldstein G, et al. Patient-reported experience of diagnosis, management, and burden of neuroendocrine tumors: results
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from a large patient survey in the United States. Pancreas. 2017;46: 639–647.

42. Schiller LR, Pardi DS, Sellin JH. Chronic diarrhea: diagnosis and management. Clin Gastroenterol Hepatol. 2017;15:182–193.e3.

43. Vinik AI, Silva MP, Woltering EA, et al. Biochemical testing for neuroendocrine tumors. Pancreas. 2009;38:876–889.

44. Singh S, Chan DL, Moody L, et al. Recurrence in resected gastroenteropancreatic neuroendocrine tumors. JAMA Oncol. 2018;4: 583–585.

45. Cives M, Pellé E, Silvestris F. The management of refractory carcinoid syndrome: challenges and opportunities ahead. J Med Econ. 2018;21: 241–243.

46. Pearman TP, Beaumont JL, Cellà D, et al. Health-related quality of life in patients with neuroendocrine tumors: an investigation of treatment type, disease status, and symptom burden. Support Care Cancer. 2016;24: 3695–3703.

47. Bharucha AE, Seide BM, Zinsmeister AR, et al. Relation of bowel habits to fecal incontinence in women. Am J Gastroenterol. 2008;103:1470–1475.

48. Isenbergh-Zedra E, Macgregor M, Matsoukas K, et al. Antidiapressant use in patients with carcinoid tumors: results of a systematic review. J Psychosom Res. 2017;97:154–155. abstract 42.

49. Fröjd C, Larsson G, Lampic C, et al. Health related quality of life and psychosocial function among patients with carcinoid tumors. A longitudinal, prospective, and comparative study. Health Qual Life Outcomes. 2007;5:18.

50. Haugland T, Vatn MH, Veenstra M, et al. Health related quality of life in patients with neuroendocrine tumors compared with the general Norwegian population. Qual Life Res. 2009;18:719–726.

51. Gelhorn HL, Kulke MH, O’Dorisio T, et al. Patient-reported symptom experiences in patients with carcinoid syndrome after participation in a study of telotristat etiprate: a qualitative interview approach. Clin Ther. 2016;38:759–768.

52. Haugland T, Veenstra M, Vatn MH, et al. Improvement in stress, general self-efficacy, and health related quality of life following patient education for patients with neuroendocrine tumors: a pilot study. Nurs Res Pract. 2013;2013:695820.

53. Beaumont JL, Cellà D, Phan AT, et al. Comparison of health-related quality of life in patients with neuroendocrine tumors with quality of life in the general US population. Pancreas. 2012;41:461–466.

54. Broder MS, Chang E, Romanus D, et al. Healthcare and economic impact of diarrhea in patients with carcinoid syndrome. World J Gastroenterol. 2016;22:2118–2125.

55. Cai B, Neary MP, Broder MS. Economic burden of illness of malignant gastrointestinal neuroendocrine tumors (NET). North American Neuroendocrine Tumor Society. 2016. Abstract. Pancreas. 2016;46: 443–444.

56. Chuang CC, Bhurke S, Chen SY, et al. Clinical characteristics, treatment patterns, and economic burden in patients treated for neuroendocrine tumors in the United States: a retrospective cohort study. J Med Econ. 2015;18:126–136.

57. Hess GP, Chen CC, Liu Z, et al. Clinical burden of illness in patients with neuroendocrine tumors. Pancreas. 2012;41:1058–1062.

58. Weckert MO, Kaltas G, Hörsch D, et al. Changes in weight associated with telotristat ethyl in the treatment of carcinoid syndrome. Clin Ther. 2018;40:952–962.e2.

59. Lips CJ, Lentjes EG, Höppener JW. The spectrum of carcinoid tumours and carcinoid syndromes. Ann Clin Biochem. 2003;40:612–627.

60. Sikander A, Rana SV, Prasad KK. Role of serotonin in gastrointestinal motility and irritable bowel syndrome. Clin Chim Acta. 2009;403:47–55.

61. Costedío MM, Hyman N, Maeve GM. Serotonin and its role in colonic function and in gastrointestinal disorders. Dis Colon Rectum. 2007;50: 376–388.

62. Bertrand PP, Bertrand RL. Serotonin release and uptake in the gastrointestinal tract. Auton Neurosci. 2010;153:47–57.

63. Mawe GM, Hoffman JM. Serotonin signalling in the gut—functions, dysfunctions and therapeutic targets. Nat Rev Gastroenterol Hepatol. 2013;10:473–486.

64. Molina-Cerrillo J, Alonso-Gordo A, Martinez-Saez O, et al. Inhibition of peripheral synthesis of serotonin as a new target in neuroendocrine tumors. Oncologist. 2016;21:701–707.

65. Aluri V, Dillon JS. Biochemical testing in neuroendocrine tumors. Endocr Rel Metab Clin North Am. 2017;46:669–677.

66. Gregersen T, Haase AM, Slagletcher V, et al. Regional gastrointestinal transit times in patients with carcinoid diarrhea: assessment with the novel 3D-transit system. J Neurogastroenterol Motil. 2015;21: 423–433.

67. Vinik AI, Woltering EA, Warner RR, et al. NANETS consensus guidelines for the diagnosis of neuroendocrine tumor. Pancreas. 2010;39:713–734.

68. Khan MA, Walter TB, Buchanan-Hughes AC, et al. Differential diagnosis (DDx) of carcinoid syndrome diarrhoea (CSD): a systematic literature review (SLR). Abstract J08. Barcelona, Spain: Presented at the 16th Annual European Neuroendocrine Tumor Society Conference. March 6–8, 2019.

69. Shah GM, Shah RG, Veillette H, et al. Biochemical assessment of niacin deficiency among carcinoid cancer patients. Am J Gastroenterol. 2005;100:2307–2314.

70. Bourna G, van Faassen M, Kats-Ugurlu G, et al. Niacin (Vitamin B3) supplementation in patients with serotonin-producing neuroendocrine tumor. Neuroendocrinology. 2016;103:489–494.

71. Wolin EM. The expanding role of somatostatin analogs in the management of neuroendocrine tumors. Gastrointest Cancer Res. 2012;5:161–168.

72. SOMATULINE® DEPOT (lanreotide) Injection [Package insert]. Basking Ridge, NJ: Ipsen Pharma Biotech; 2014. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022074s011lbl.pdf. Accessed July 19, 2018.

73. SANDOSTATIN LAR® (octreotide acetate for injectable suspension) [Package insert]. East Hanover, New Jersey: Novartis Pharmaceuticals Corp; 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021008s021lbl.pdf. Accessed May 14, 2018.

74. Lamare A, McCallum L, Nuttall C, et al. Somatostatin analogue-induced pancreatic exocrine insufficiency in patients with neuroendocrine tumors: results of a prospective observational study. Expert Rev Gastroenterol Hepatol. 2018;12:723–731.

75. Camilleri M. Bile Acid diarrhea: prevalence, pathogenesis, and therapy. Gut Liver. 2015;9:332–339.

76. Kumpf VJ. Pharmacologic management of diarrhea in patients with short bowel syndrome. JPEN J Parenter Enteral Nutr. 2014;38(suppl 1): 38s–44s.

77. Seetharam P, Rodrigues G. Short Bowel Syndrome: A Review of Management Options. Saudi J Gastroenterol. 2011;17:229–235.

78. Kunz PL. Carcinoid and neuroendocrine tumors: building on success. J Clin Oncol. 2015;33:1855–1863.

79. Chauhan A, Miller RC, Lu Q, et al. The antidiarrheal efficacy of a proprietary amino acid mixture (Enterade®) in neuroendocrine tumor (NETs) patients. J Clin Oncol. 2018;36;abstract e22217.

80. Lee SY, Cheow PC, Teo JY, et al. Surgical treatment of neuroendocrine liver metastases. Int J Hepatol. 2012;2012:146590.

81. Kennedy A, Bester L, Salem R, et al. Role of hepatic intra-arterial therapies in metastatic neuroendocrine tumors (NET): guidelines from the NET-Liver-Metastases Consensus Conference. HPB (Oxford). 2015;17:29–37.

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82. de Baere T, Deschamps F, Tsolikas L, et al. GEP-NETS update: Interventional radiology: role in the treatment of liver metastases from GEP-NETS. *Eur J Endocrinol.*, 2015;172:R151–R166.

83. Engelman ES, Leon-Ferre R, Naraev BG, et al. Comparison of transarterial liver-directed therapies for low-grade metastatic neuroendocrine tumors in a single institution. *Pancreas*. 2014;43:219–225.

84. Pericleous M, Caplin ME, Tsochatzis E, et al. Hepatic artery embolization in advanced neuroendocrine tumors: efficacy and long-term outcomes. *Asia Pac J Clin Oncol*. 2016;12:61–69.

85. Elf AK, Andersson M, Henrikson O, et al. Radioembolization versus bland embolization for hepatic metastases from small intestinal neuroendocrine tumors: short-term results of a randomized clinical trial. *World J Surg*. 2018;42:506–513.

86. Su YK, Mackey RV, Raza A, et al. Long-term hepatotoxicity of yttrium-90 radioembolization as treatment of metastatic neuroendocrine tumor to the liver. *J Vasc Interv Radiol*. 2017;28:1520–1526.

87. Strosberg J, El-Haddad G, Wolin E, et al. NETTER-1 Trial Investigators. Phase 3 trial of 177Lu-DOTATATE for midgut neuroendocrine tumors. *N Engl J Med*. 2017;376:125–135.

88. Strosberg J, Wolin EM, Chasen B, et al. Improved time to quality of life deterioration in patients with progressive midgut neuroendocrine tumors treated with 177Lu-DOTATATE: The NETTER-1 phase III trial. Abstract 438PD. *Ann Oncol*. 2017;28:S14:1.

89. Strosberg J, Wolin E, Chasen B, et al. Health-related quality of life in patients with progressive midgut neuroendocrine tumors treated with 177Lu-DOTATATE in the phase III NETTER-1 Trial. *J Clin Oncol*. 2018;36:2578–2584.

90. Strosberg J. NETTER-1 Phase III trial suggests quality of life improvements in patients with midgut neuroendocrine tumors. *J Nucl Med*. 2017;58(suppl 1):244:abstract.

91. Kwekkeboom DJ, Kam BL, van Essen M, et al. Somatostatin-receptor-based imaging and therapy of gastroenteropancreatic neuroendocrine tumors. *Endocr Relat Cancer*. 2010;17:R53–R73.

92. Zandee W, Blazevic A, Brabander T, et al. Peptide receptor radionuclide therapy with Lu-DOTATATE for symptomatic control of refractory carcinoid syndrome. In: Abstracts. *Neuroendocrinology*. 2019;108(suppl 1):1–273:abstract 307.

93. Husser C, Scholz S, Fries M, et al. Telotristat ethyl (TE) in patients with carcinoid syndrome (CS) symptoms: results from TELEPATH study. In: Abstracts. *Neuroendocrinology*. 2019;108(suppl 1):1–301:abstract 306.

94. Reubi JC, Schonbrunn A. Illuminating somatostatin action at somatostatin analogs. *Future Oncol*. 2018;14:315–326. abstract 341–342.

95. Dillon JS, Chandrasekharan C. Telotristat ethyl: a novel agent for the therapy of carcinoid syndrome diarrhea. *Future Oncol*. 2018;14:1155–1164.

96. Garsed K, Chernova J, Hastings M, et al. A randomised trial of ondansetron for the treatment of irritable bowel syndrome with diarrhoea. *Gut*. 2014;63:1617–1625.

97. Kiesewetter B, Raderer M. Ondansetron for diarrhea associated with neuroendocrine tumors. *N Engl J Med*. 2013;368:1947–1948.

98. Kiesewetter B, Duan H, Lamm W, et al. Oral ondansetron offers effective antidiarrheal activity for carcinoid syndrome refractory to somatostatin analogs. *Oncologist*. 2019;24:255–258.

99. Moertel CG, Kvolts LK, Rubin J. A study of cyproheptadine in the treatment of metastatic carcinoid tumor and the malignant carcinoid syndrome. *Cancer*. 1991;67:33–36.