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Management of Gastroenteropancreatic Neuroendocrine Tumors

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INTRODUCTION

Neuroendocrine tumors (NETs) are a rare, heterogeneous group of neoplasms that arise from neuroendocrine cells located throughout the body. These tumors are characterized by variable but most often indolent biologic behavior. They are also classically characterized by their ability to secrete peptides, resulting in distinctive hormonal syndromes. Although NETs have been considered rare, recent studies suggest that they are more common than previously suspected. An analysis of the Surveillance, Epidemiology, and End Results (SEER) database demonstrated a significant increase in the incidence of NETs over time with an age-adjusted annual incidence in the United States of 5.25 cases per 100,000 population.[1] The increase in incidence is likely attributable to increasing awareness, improved diagnostic strategies, and possibly other undetermined environmental and genetic factors.

When NETs are diagnosed at an early stage, surgical resection is often curative. Unfortunately, curative surgery is rarely an option for patients with metastatic disease, and standard cytotoxic therapy for patients offers limited benefit. Treatment approaches with targeted therapy, including the use of agents targeting the vascular endothelial growth factor (VEGF) signaling pathway, the mammalian target of rapamycin (mTOR), and other pathways involved in neuroendocrine tumorigenesis, provide new therapeutic options for these patients. The aim of this review is to summarize advances in the diagnosis and management of well-differentiated, low-grade gastroenteropancreatic neuroendocrine tumors (GEP NETs). The management of poorly differentiated neuroendocrine carcinomas and mixed exocrine-endocrine tumors is beyond the scope of this review.

HISTOLOGIC CLASSIFICATION

NETs arising at different sites within the body are classified according to their histologic features. A number of histologic and anatomic classification systems have been proposed to describe these tumors (**Table 1**).[2–4] Although there are differences in the specific criteria for grading tumors, the clas-

Table 1. Nomenclature and Classification for Neuroendocrine Tumors

Differentiation	Grade	Mitotic Count*	Ki-67 Index†	Traditional	ENETS [2,3] WHO[4]
Well differentiated	Low grade (G1)	<2 per 10 HPF	≤2%	Carcinoid, islet cell, pancreatic (neuro)endocrine tumor	Neuroendocrine tumor, grade 1
	Intermediate grade (G2)	2–20 per 10 HPF	3%–20%	Carcinoid, atypical carcinoid,‡ islet cell, pancreatic (neuro)endocrine tumor	Neuroendocrine tumor, grade 2
Poorly differentiated	High grade (G3)	>20 per 10 HPF	>20%	Small cell carcinoma	Neuroendocrine carcinoma, grade 3, small cell
				Large cell neuroendocrine carcinoma	Neuroendocrine carcinoma grade 3, large cell

ENETS = European Neuroendocrine Tumor Society; WHO = World Health Organization.

*Counted in 10 high-power fields (HPF). High-power field = 2 mm^2, at least 40 fields (at 40x magnification) evaluated in areas of highest mitotic density. Cut-offs per *AJCC Cancer Staging Manual*, 7th ed.[5]

†MIB1 antibody; percentage of 2000 tumor cells in areas of highest nuclear labeling. Cut-offs per *AJCC Cancer Staging Manual*, 7th ed.[5]

‡Term "atypical carcinoid" only applies to intermediate-grade NET of the lung.

sification systems reflect the observation that NETs consist of a spectrum of disease ranging from indolent, well-differentiated, low-grade tumors to aggressive, poorly differentiated, high-grade tumors. In general, tumors with a high histologic grade, a mitotic count >20 per 10 high-powered fields (HPF), or a Ki-67 proliferation index of >20% represent aggressive neuroendocrine carcinomas that have a different natural history and response to treatment compared to low-grade, well-differentiated tumors.

Well-differentiated NETs can be broadly subclassified as either carcinoid or pancreatic NETs. Carcinoid tumors may arise from multiple different organ systems and traditionally have been classified according to site of embryonic origin, namely foregut (gastric, bronchial), midgut (small intestine, appendix, proximal large bowel), and hindgut (distal colon, rectum, genitourinary). While carcinoid and pancreatic NETs may have similar histologic characteristics, these 2 tumor subtypes have different biology and respond differently to therapy, with most therapeutic agents demonstrating higher response rates in pancreatic NET patients as compared with carcinoid NET patients.

GENETIC BASIS OF NEUROENDOCRINE TUMORS

There are no established environmental risk factors for carcinoid tumors, nor has a clear underlying genetic cause for carcinoid tumors been defined. Most carcinoid tumors occur as nonfamilial (sporadic) tumors. However, several genetic syndromes, including multiple endocrine neoplasia type 1 (MEN1), von Hippel-Lindau syndrome, neurofibromatosis type 1 (NF-1), and tuberous sclerosis, have been associated with gastrointestinal NETs. Although the majority of NETs are sporadic, the molecular genetics of these tumor susceptibility syndromes provide insight into the genetic mechanisms of this disease.

MEN1 is an autosomal dominant syndrome characterized by the development of parathyroid and pituitary adenomas and enteropancreatic NETs.

In addition, patients can exhibit multiple lipomas, adrenal or thyroid adenomas, cutaneous angiofibromas, and bronchial or thymic carcinoid tumors. The syndrome results from an inactivating mutation of the *MEN1* gene located on chromosome 11q13.[6] The protein encoded by *MEN1*, menin, has been shown to localize to the nucleus and regulate gene transcription. Loss of heterozygosity of 11q13 has been demonstrated in both *MEN1*-associated pancreatic NETs and in over 50% of sporadic pancreatic NETs.[7] Germline MEN1 mutations are identifiable in 70% to 90% of typical MEN1 families. Sporadic tumors, including gastroenteropancreatic NETs and bronchial carcinoid tumors, less commonly harbor *MEN1* gene mutations, suggesting that *MEN1* mutations are involved in the pathogenesis of only a subset of sporadic NETs.[8]

Von Hippel-Lindau syndrome is an autosomal dominant neoplasia syndrome that results from germline mutations in the *VHL* gene, which is located on chromosome 3p25 and functions as a tumor suppressor gene that regulates hypoxia-induced cell proliferation and angiogenesis. The most common tumors associated with *VHL* mutations include hemangioblastomas and renal clear cell carcinoma; patients with Von Hippel-Lindau syndrome may also develop NETs, including pheochromocytoma, pancreatic NETs, and carcinoid tumors.

NF-1 and tuberous sclerosis are both rare autosomal dominant tumor susceptibility syndromes that have been associated with ampullary carcinoids, duodenal and pancreatic somatostatinomas, and nonfunctioning GEP NETs. These syndromes are caused by inactivating mutations in the tumor suppressor genes *NF1* (17q11.2) and *TSC1* (9q34) and *TSC2* (16p13.3), respectively.[8] *NF1* encodes the protein neurofibromin, which regulates *TSC1* and *TSC2*.[9] *TSC1* and *TSC2* form a tumor suppressor heterodimer that inhibits mTOR. Loss of function of the *NF1* gene causes mTOR activation and tumor development.

Loss of heterozygosity and comparative genomic hybridization studies have demonstrated that both chromosomal losses and gains are common events in sporadic NETs. Characteristic allelic imbalances have been observed in sporadic carcinoid and pancreatic NET.[6] The patterns of genomic alterations in gastrointestinal NETs differ from the patterns that occur with other NETs. Amplification of chromosomal loci is less common in gastrointestinal NETs as compared to pancreatic NETs. Losses on chromosome 18q are particularly common in small bowel carcinoid tumors but are infrequent in pancreatic NETs and bronchial NETs.[10–12]

Exomic sequencing has also provided insight into the genetic basis of NETs. In a study involving exomic sequencing of non-familial pancreatic NETs, Jiao et al found that the most frequently mutated genes encoded proteins involved in chromatin remodeling.[13] Forty-four percent of tumors had somatic inactivating mutations in *MEN1*, and 43% had mutations in genes encoding either *DAXX* (death-domain-associated protein) and *ATRX* (α thalassemia/mental retardation syndrome X-linked). Mutations in genes in the mTOR pathway occurred in 14% of tumors.

CLINICAL EVALUATION

CASE PRESENTATION

A 60-year-old man without significant family or past medical history presents to the emergency department with symptoms of nausea, vomiting, and acute-onset abdominal pain. Physical examination is notable for lower abdominal ten-

Table 2. Clinical Presentation of Neuroendocrine Tumors

Tumor	Symptoms or Signs
Pancreatic neuroendocrine tumors	
Insulinoma	Hypoglycemia resulting in intermittent confusion, sweating, weakness, nausea; loss of consciousness may occur in severe cases
Glucagonoma	Rash (necrotizing migratory erythema), cachexia, diabetes, deep venous thrombosis
VIPoma, Verner-Morrison syndrome, WDHA syndrome	Profound secretory diarrhea, electrolyte disturbances
Gastrinoma, Zollinger-Ellison syndrome	Acid hypersecretion resulting in refractory peptic ulcer disease, abdominal pain, and diarrhea
Somatostatinoma	Diabetes, diarrhea, cholelithiasis
PPoma "nonfunctioning"	May be first diagnosed due to mass effect
Carcinoid	
Foregut	
Bronchial carcinoids	Cough, hemoptysis, post-obstructive pneumonia, Cushing's syndrome; carcinoid syndrome rare
Gastric carcinoids	Usually asymptomatic and found incidentally
Midgut	
Small intestine carcinoids	Intermittent bowel obstruction or mesenteric ischemia; carcinoid syndrome common when metastatic
Appendiceal carcinoids	Usually found incidentally; may cause carcinoid syndrome when metastatic
Hindgut	
Rectal carcinoids	Either found incidentally or discovered due to bleeding, pain, and constipation; rarely cause hormonal symptoms, even when metastatic

PPoma = pancreatic polypeptidoma; VIPoma = vasoactive intestinal peptide tumor; WDHA = watery diarrhea, hypokalemia, and achlorhydria.

derness. The patient denies diarrhea. A computed tomography (CT) scan of the abdomen reveals a mass in the mesentery that is inseparable from the distal ileum and is associated with surrounding inflammatory changes.

The patient is admitted for exploratory laparotomy. Surgical findings are notable for a mass located at the root of the mesentery. Frozen section reveals a well-differentiated, low-grade NET. On further examination of the small bowel, there are multiple nodules, some clearly visible and others palpable, involving portions of the ileum. There is no evidence of any other masses throughout the abdomen and peritoneum or in the liver.

- **What are the clinical manifestations of localized NETs?**

CARCINOID NETS

The clinical manifestations of NETs vary depending upon both their site of origin and any specific systemic symptoms related to hormonal hypersecretion, if present (**Table 2**). A commonly used classification scheme groups carcinoid tumors according to their presumed derivation from the embryonic gut: foregut (bronchial and gastric), midgut (small intestine and appendiceal), and hindgut (rectal); of these, midgut tumors are the most common.[14] Patients with small bowel carci-

noids generally present in the sixth or seventh decade of life, most commonly with abdominal pain or small bowel obstruction as their chief complaint. Approximately 5% to 7% of patients with jejunoileal carcinoids will present with the carcinoid syndrome (*see* "Carcinoid Syndrome" section below), at which time hepatic metastases also are usually present.[15]

These symptoms, as well as syndromes associated with hormone secretion, should prompt both imaging and laboratory studies. Evaluation of serum and urine markers can facilitate the diagnosis of carcinoid tumors. Midgut carcinoid tumors are associated with increased production of serotonin, which can be measured either in the plasma or as the serotonin metabolite 5-hydroxyindoleacetic acid (HIAA). Urinary 5-HIAA levels have greater specificity than plasma serotonin levels and typically are measured to confirm the diagnosis and to monitor patients with metastatic disease. Levels of chromogranin A (CGA), a soluble secretory glycoprotein normally contained in neuroendocrine cell vesicles, are elevated in up to 80% of GEP NETs (including carcinoid tumors) and are especially useful in the diagnosis of nonfunctioning tumors.[16] Imaging studies such as CT or magnetic resonance imaging (MRI) can localize larger primary tumors as well as detect metastases to lymph nodes and the liver. Somatostatin receptor scintigraphy provides another useful imaging modality for the detection of metastatic disease in patients with NETs. More than 90% of GEP NETs, including nonfunctioning islet cell tumors and carcinoid tumors, have high concentrations of somatostatin receptors and can be imaged with somatostatin analogs labeled with gamma-emitting radionuclides. The most widely used radionuclide tracer for scintigraphy is ^{111}indium (In)-DTPA-octreotide. The uptake of radiolabeled octreotide is also predictive of a clinical response to therapy with somatostatin analogs.[17]

Small bowel carcinoid tumors can be difficult to localize since imaging techniques, such as CT scan and small bowel barium contrast studies, and standard first-line studies for assessing abdominal pain or abdominal symptoms frequently fail to identify the primary tumor. When detected and surgically removed, they are most frequently located in the distal ileum and are often multicentric, occasionally appearing as dozens of lesions lining the small bowel. Mesenteric fibrosis and associated ischemia, caused by a characteristic desmoplastic reaction, are often present in association with small bowel carcinoids.

PANCREATIC NETS

Pancreatic endocrine tumors can arise anywhere throughout the pancreas, although they more commonly arise in the pancreatic tail than pancreatic adenocarcinomas. Pancreatic NETs are classified based on their clinical manifestations as either functional or nonfunctional tumors. Functional tumors are associated with symptoms caused by hormone secretion. The best-characterized syndromes associated with functional pancreatic NETs are those associated with insulinoma, glucagonoma, vasoactive intestinal peptide tumor (VIPoma), and gastrinoma (Table 2). Functional pancreatic endocrine tumors can be diagnosed based on the presence of symptoms caused by excessive hormone secretion and associated biochemical abnormalities. Up to 30% to 40% of pancreatic NETs are nonfunctioning and are generally detected due to symptoms related to their large size, invasion of adjacent organs, or presence of metastases. Nonfunctioning tumors are not associated with hormonal syndromes but may be associated with elevated levels of hormones, such as pancreatic polypeptide or CgA.

Multiphasic CT and MRI scans are highly sensitive for detecting primary pancreatic NETs, with sensitivity using modern imaging techniques exceeding 80%.[18,19] For patients with hormonal symptoms and a suspected pancreatic NET, endoscopic ultrasound with fine-needle aspiration can assist in diagnosis.[20]

MANAGEMENT

LOCALIZED CARCINOID TUMORS

For patients with localized carcinoid tumors, surgical resection alone is often curative. Five-year survival depends primarily on the extent of disease. Survival in patients with localized disease is influenced primarily by disease site and tumor size.[20,21] Localized carcinoid tumors of the appendix and rectum have the best prognosis (5-year survival rate, 80%–90%), whereas tumors of the colon and small intestine are associated with the worst prognosis (5-year survival rate, 57%–74%). [1,16] The site of disease and, at times, the size of the tumor influence the surgical management of localized carcinoid tumors. For symptomatic small bowel carcinoid tumors such as those seen in the case patient, resection of the small bowel primary tumor along with associated mesenteric metastases leads to significant reduction in tumor-related symptoms of pain and obstruction. Therefore, surgical resection is recommended even in patients with known metastatic disease.

LOCALIZED PANCREATIC NETS

The management of patients with localized pancreatic NETs is also primarily surgical; when tumors are completely resected, the prognosis is generally good. Patients with MEN1 or other genetic syndromes, however, have a high probability of recurrence, and the multiplicity of tumors makes curative resection difficult.[22] In cases where an isolated lesion is seen with preoperative imaging studies, however, an attempt at resection is often considered to prevent development of more advanced disease and to relieve symptoms of excessive hormone production.

Specific symptomatic treatment is also indicated in patients with functional pancreatic NETs. Dietary modification combined with diazoxide administration is usually successful in the initial management of hypoglycemia caused by insulinoma.[23] Proton pump inhibitors are highly effective in controlling the symptoms associated with gastric hypersecretion due to gastrinoma.[24–27] Somatostatin analogues are generally successful in the initial management of patients with glucagonoma syndrome and in controlling the secretory diarrhea associated with the VIPoma syndrome.[28] Patients with glucagonomas who are refractory to somatostatin analogs may also benefit from the intravenous infusion of amino acids.[29]

CASE CONTINUED

The patient undergoes resection of the small bowel segments containing visible and palpable tumor nodules. Additionally, the lymphatic drainage and mesenteric mass are resected. Surgical pathology reveals a well-differentiated carcinoid tumor of the small intestine, present as multiple intramural nodules and the mesenteric mass. There is evidence of lymphovascular invasion and perineural invasion. One of 8 lymph nodes contains evidence of carcinoid tumor.

- **What is the role of radiographic imaging and biochemical monitoring in detecting metastases in patients with NETs?**

The predominant site of metastatic spread in patients with gastrointestinal NETs is the liver. Ab-

dominal CT scan or MRI is generally the imaging study of choice for detecting metastatic spread. Somatostatin receptor scintigraphy provides another useful imaging modality for detecting metastatic disease in patients with NETs. With the exception of insulinomas (of which only 50% express type 2 somatostatin receptors), more than 90% of NETs, including nonfunctioning pancreatic tumors and carcinoid tumors, contain high concentrations of somatostatin receptors and can be imaged with a radiolabeled form of the somatostatin analog octreotide (^{111}indium-pentetreotide).[30,31] The uptake of radiolabeled octreotide is also predictive of a clinical response to therapy with somatostatin analogues.[17]

Biochemical markers provide a means to confirm an initial diagnosis of neuroendocrine malignancy and to follow subsequent treatment response. Serial measurement of the serotonin metabolite 5-HIAA in 24-hour urine collections is used in the diagnosis and subsequent monitoring of patients with metastatic carcinoid tumors. Although elevated urinary 5-HIAA levels are highly specific for carcinoid tumors, they are not particularly sensitive. In one study, only 73% of patients with metastatic carcinoid tumors had elevated levels.[32] Furthermore, 5-HIAA levels are generally elevated in patients with metastatic midgut carcinoid tumors but are less useful in patients with either foregut (bronchial, gastric) or hindgut (rectal) carcinoid tumors, which less commonly secrete serotonin. Plasma CgA concentrations are a more sensitive marker than urinary 5-HIAA levels in patients with carcinoid tumors, and can also be used as a marker in patients with both functional and nonfunctional pancreatic endocrine tumors. In patients receiving stable doses of somatostatin analogs, consistent increases in plasma CgA levels over time may reflect loss of secretory control and/or tumor growth.[33] Plasma CgA levels have also been shown to have prognostic value.[34,35] In a series of patients with metastatic NETs, CgA level over twice the upper limit of normal was associated with shorter survival.[35]

CASE CONTINUED

Postoperatively, the patient's CgA level is normal at 11.1 ng/mL (normal, ≤36.4 ng/mL). The 24-hour urine 5-HIAA level is also normal at 4.5 mg/24 hours (normal, ≤6 mg/24 hours). There is no evidence of octreotide-avid disease on octreotide scintigraphy scan. A CT scan of the abdomen reveals surgical changes but no evidence of bowel wall thickening, abnormal lymphadenopathy, or liver metastases.

The patient is followed closely postoperatively with routine physical examination and reassessment of tumor markers every 6 months. He is well until approximately 2 years postoperatively, when he develops symptoms of right upper quadrant discomfort, frequent loose stools, and episodes of cutaneous flushing.

- **What are the clinical manifestations of metastatic NETs?**

The clinical course of patients with metastatic carcinoid and pancreatic NETs is highly variable. Some patients with indolent tumors may remain symptom free for years, even without treatment. Others have symptomatic metastatic disease, from either tumor bulk or hormonal hypersecretion, and require therapy. Patients with functioning metastatic pancreatic NETs will typically have symptoms related to the type of hormone secreted (Table 2). The symptoms experienced by the case patient are indicative of carcinoid syndrome.

CARCINOID SYNDROME

In patients with metastatic carcinoid tumors, the secretion of serotonin and other vasoactive sub-

stances causes the carcinoid syndrome. Classic carcinoid symptoms include flushing of the upper body, watery diarrhea, facial edema, sweating, wheezing, dyspnea, abdominal pain, and, in severe cases, hemodynamic instability. Patients with long-standing symptoms often have nasal telangiectasia and permanent skin discoloration. Episodes of the carcinoid syndrome are usually intermittent and may last from a few minutes to several days. Common precipitating factors include stress or ingestion of alcohol. The carcinoid syndrome is caused by tumor-secreted products that gain direct access to the systemic circulation and bypass metabolism in the liver. It is associated primarily with midgut carcinoid tumors and occurs almost exclusively in the setting of metastatic rather than localized disease.[36]

Right-sided carcinoid heart disease occurs in up to two-thirds of patients with the carcinoid syndrome.[37,38] Carcinoid heart lesions are characterized by plaque-like, fibrous endocardial thickening that classically involves the right side of the heart and often causes retraction and fixation of the leaflets of the tricuspid and pulmonary valves. Tricuspid regurgitation is a nearly universal finding; tricuspid stenosis, pulmonary regurgitation, and pulmonary stenosis may also occur.[39] Left-sided heart disease occurs in less than 10% of patients, usually in the setting of patent foramen ovale. The preponderance of lesions in the right heart suggests that carcinoid heart disease may be related to factors such as serotonin or atrial natriuretic peptide, which are secreted by liver metastases into the hepatic vein.[37]

Patients with carcinoid heart disease who are asymptomatic or exhibit minimal symptoms are usually followed clinically. For symptomatic patients, cardiac surgery offers definitive therapy for symptoms and may be associated with survival benefit. The optimal timing of surgery in relation to the severity of valve dysfunction and symptoms has not been identified. Generally, patients who develop cardiovascular symptoms related to carcinoid heart disease, such as symptoms of right ventricular failure with progressive fatigue, impaired exercise capacity, or decline in right ventricular function, may be evaluated for valve replacement surgery.[40,41]

CASE CONTINUED

The patient undergoes an abdominal CT scan that demonstrates multiple liver lesions consistent with metastatic disease. His CgA level has increased to 155.7 ng/mL, and 24-hour urine 5-HIAA level has increased to 23.1 mg/24 hour. An octreotide scan reveals the liver lesions to be octreotide-avid.

- **How are the symptoms of carcinoid syndrome managed?**

The carcinoid syndrome, as well as other hormonal syndromes associated with NETs, can often be controlled with somatostatin analogs. Somatostatin is a 14–amino acid peptide that acts to inhibit secretion of a broad range of hormones by binding to somatostatin receptors, which are expressed on the majority of NETs.[42] In an initial study, the subcutaneous administration of the somatostatin analog octreotide, administered at a dosage of 150 µg 3 times a day, improved the symptoms of carcinoid syndrome in 88% of patients.[43] Lanreotide, another somatostatin analog, appears to be similar to octreotide in its clinical efficacy for carcinoid syndrome and can be self-administered as a long-acting subcutaneous injection. A randomized study of lanreotide versus octreotide in 33 patients with carcinoid syndrome demonstrated similar rates of symptom control and reduction of biochemical markers.[44]

The use of a long-acting depot octreotide, which can be administered on a monthly basis, has largely obviated the need for patients to inject themselves on a daily basis. However, patients may also use short-acting octreotide injections for breakthrough symptoms.

PREVENTION AND MANAGEMENT OF CARCINOID CRISIS

Carcinoid crisis is a life-threatening form of carcinoid syndrome triggered by specific events, presumably stimulating release of an overwhelming amount of biologically active compounds such as catecholamines. Specific symptoms include flushing, diarrhea, tachycardia, arrhythmias, hypertension or hypotension, bronchospasm, and altered mental status. Symptoms are generally refractory to fluid resuscitation and administration of vasopressors.

Carcinoid crisis may be precipitated by chemotherapy, anesthesia, or surgery; intraoperative complications have been reported in 11% of patients who have carcinoid syndrome.[45] Subcutaneous administration of octreotide 300 µg perioperatively reduces the incidence of carcinoid crisis, and intraoperative octreotide should be readily available during any surgical procedure. A continuous intravenous drip of octreotide may also be used during carcinoid crisis.[33]

CASE CONTINUED

The patient presents to his oncologist to discuss options for managing his recurrent disease and symptoms of carcinoid syndrome. The patient is started on therapy with short-acting subcutaneous octreotide. After a 2-week trial of the subcutaneous short-acting octreotide, he is transitioned to the long-acting release depot formulation given every 4 weeks. Shortly after starting therapy, the patient's symptoms of flushing and diarrhea resolve. Restaging CT scans performed 3 months after his diagnosis of metastatic carcinoid tumor demonstrate overall stable disease. His disease is radiographically stable and his symptoms related to carcinoid syndrome are well controlled for approximately 1 year. However, at that point, he develops symptoms of increasing right upper quadrant pain and worsening diarrhea. Laboratory testing reveals increases in his CgA level to 316.8 ng/mL and 24-hour urine 5-HIAA level to 40.3 mg/24 hour. Additionally, restaging CT scans demonstrate an increase in both the size and number of his liver metastases.

- **What treatment options are available for patients with progressive metastatic disease?**

Although patients with metastatic NETs may pursue various treatment options, there is little consensus on a single, standard treatment approach. The following section discusses the various treatment approaches that may be used.

SURGERY

In selected cases, metastatic liver disease can be surgically resected. However, a high number of liver metastases may preclude hepatic resection. Several retrospective surgical series have suggested that patients who undergo either complete resection or aggressive "debulking" of hepatic metastases have improved quality of life and improved survival times compared with patients who do not undergo surgery.[46–50] The lack of formal randomization and potential for selection bias make definitive interpretation of these results difficult.

Orthotopic liver transplantation (OLT) has been attempted in few patients who have liver-isolated metastatic disease.[51–53] The impact of transplanta-

tion on the natural history of patients is difficult to assess since selected patients may have indolent disease regardless of the therapeutic approach. Furthermore, the lack of available transplants also precludes OLT as a treatment option in many locations.

HEPATIC ARTERY EMBOLIZATION

Hepatic arterial embolization is a commonly used procedure in patients with hepatic metastases who are not candidates for surgical resection. This is based on the principle that tumors in the liver derive most of their blood supply from the hepatic artery, whereas normal hepatocytes derive their blood supply from the portal vein. Embolization can be performed by infusing a gel foam powder into the hepatic artery (bland embolization) or in conjunction with chemotherapy (ie, doxorubicin, cisplatin or streptozocin) or radioactive isotopes (ie, yttrium-90). Embolization response rates are measured either by a decrease in hormonal secretion or by radiographic regression and are generally greater than 50%.[54–57] However, the duration of response can be brief, ranging from 4 to 51 months in one uncontrolled patient series.[54] In one of the largest series of patients undergoing embolization or chemoembolization for carcinoid tumors (n = 81), the median duration of response was 17 months, and the probability of progression-free survival (PFS) at 1, 2, and 3 years was 75%, 35%, and 11%, respectively.[54] Early studies of chemoembolization for hepatic tumors reported a significant incidence of postembolization complications that included renal failure, hepatic necrosis, and sepsis.[56] Recent improvements in technique have reduced the incidence of such complications, making embolization an important and generally safe treatment option for patients with NETs. Postembolization syndrome is the most common complication and consists of transient symptoms, such as pain, nausea, fever, fatigue, and biochemical abnormalities in liver enzymes.[58] Severe complications such as gastrointestinal bleeding, hepatic abscess, and liver failure are rare. Additionally, the risk of carcinoid crisis can be minimized by use of somatostatin analogs prior to embolization.

SOMATOSTATIN ANALOGS

Recent studies have demonstrated that in addition to an improvement in symptoms, treatment with octreotide is associated with a direct antitumor effect in patients with small bowel carcinoid tumors. In the PROMID trial, 85 patients with locally inoperable or metastatic small bowel carcinoid tumors were randomly assigned to receive treatment with either octreotide or placebo.[59] The median time to tumor progression was significantly longer with octreotide compared to placebo (14.3 versus 6 months). Ongoing randomized studies are evaluating whether somatostatin analogs have a similar effect in patients with nonfunctioning carcinoid tumors or pancreatic NETs.

Novel somatostatin analogs that are more broadly targeted and have higher affinities for somatostatin receptors have recently been developed. Pasireotide (SOM230) is a multi-ligand somatostatin analog that has exhibited high-binding affinity to the somatostatin receptors sst1, sst2, sst3, and sst5. Compared with octreotide, pasireotide has 30-, 5- and 40-times greater binding affinity for sst1, sst3, and sst5 receptors, respectively, and comparable affinity for sst2.[60] In a phase II trial, 44 patients with metastatic carcinoid tumors whose symptoms of diarrhea and flushing were inadequately controlled by octreotide LAR received pasireotide 300 µg subcutaneously twice per day and escalated to a maximum dose of 1200 µg twice per day every 3 days until symptom control was achieved. Control

of symptoms was achieved in 12 of 44 patients (27%).[61] Randomized studies more formally assessing the role of pasireotide in controlling refractory hormonal symptoms or in controlling tumor growth are anticipated.

INTERFERON ALFA

The ability of interferon alfa (IFN-α) to stimulate T-cell function and to control the secretion of tumor products led to its initial use in patients with the carcinoid syndrome.[62] In clinical trials, doses of IFN-α have ranged from 3 to 9 MU subcutaneously (SC) administered from 3 to 7 times per week. The addition of IFN-α to therapy with somatostatin analogs has been reported to be effective in controlling symptoms in patients with the carcinoid syndrome who may be resistant to somatostatin analogs alone.[63,64] Therapy with low-dose IFN-α has been reported to result in biochemical responses in approximately 40% of patients with metastatic NETs and is occasionally associated with tumor regression.[65]

The widespread use of interferon has been limited both by uncertainty about its antitumor efficacy and its potential for side effects, which can include fatigue and depression. In a prospective trial of 68 patients with metastatic midgut carcinoid tumor who were randomized to octreotide with or without IFN-α, patients receiving combined therapy had a significantly reduced risk of tumor progression when compared to patients receiving octreotide alone, suggesting that the addition of interferon had antitumor effect.[66] Other studies, however, have not shown an effect of the addition of interferon to somatostatin analog therapy on tumor progression.[67,68] These studies, however, were likely underpowered to detect significant differences between the arms. Interferon is currently being compared to bevacizumab in a large randomized study performed by the Southwest Oncology Group (SWOG) and the North American Intergroup (S0518).

CYTOTOXIC CHEMOTHERAPY

Cytotoxic chemotherapy has been minimally active in patients with advanced carcinoid tumors. Studies examining the efficacy of streptozocin-containing regimens[69] or dacarbazine[70] in patients with carcinoid tumors have demonstrated low response rates and significant toxicity. Temozolomide is an oral and more easily tolerated analog of dacarbazine. In a retrospective series that included 44 carcinoid tumor patients treated with temozolomide-based regimens, only one patient (2%) had a tumor response.[71] The majority of patients in this series, however, had gastrointestinal primary tumors. Recent series have reported that temozolomide may be active in some patients with bronchial carcinoid tumors. In one retrospective study that included 13 patients with bronchial carcinoid treated with temozolomide, 4 (31%) had a partial response.[72]

In contrast to carcinoid tumors, pancreatic NETs may respond well to treatment with streptozocin and other alkylating agents (**Table 3**).[71–79] In an initial randomized trial, the combination of streptozocin and doxorubicin was associated with a combined biochemical and radiologic response rate of 69% along with survival benefit.[73] Streptozocin was subsequently approved by the FDA as a treatment for patients with pancreatic NETs. The very high reported response rates in this study have been questioned and are likely the result of the use of nonstandard response criteria. A retrospective analysis of 84 patients with either locally advanced or metastatic pancreatic endocrine tumors receiving a 3-drug regimen of streptozocin, 5-fluorouracil, and doxorubicin showed that this regimen was associated with an overall response rate of 39% and a median survival

Table 3. Selected Trials of Cytotoxic Chemotherapy in Advanced Pancreatic Neuroendocrine Tumors

Regimen	Patients (*n*)	Tumor Response Rate (%)	Median Progression-Free Survival	Median Overall Survival	Reference
Prospective studies					
Chlorozotocin	33	30	17 mo*	18.0 mo	
Fluorouracil + streptozocin	33	45	14 mo*	16.8 mo	Moertel et al, 1992[73]
Doxorubicin + streptozocin	36	69	18 mo*	26.4 mo	
Dacarbazine	50	34	NR	19.3 mo	Ramanathan et al, 2001[74]
Temozolomide + thalidomide	11	45	NR	NR	Kulke et al, 2006[75]
Temozolomide + bevacizumab	15	33	14.3 mo	41.7	Chan et al, 2006[76]
Temozolomide + everolimus	24	35	NR	NR	Kulke et al, 2010[77]
Retrospective studies					
Streptozocin + doxorubicin + fluorouracil	84	39	18 mo	37 mo	Kouvaraki et al, 2004[78]
Temozolomide (diverse regimens)	53	34	13.6 mo	35.3 mo	Kulke et al, 2009[71]
Temozolomide (single agent)	12	8	NR	NR	Ekeblad et al, 2007[72]
Temozolomide + capecitabine	30	70	18	NR	Strosberg et al, 2011[79]

NR = not reported.

*Reported as duration of tumor regression.

duration of 37 months.[78] Despite the demonstrated efficacy of streptozocin-based regimens, their potential toxicity has precluded their more widespread use in patients with advanced pancreatic NETs. Recent prospective and retrospective studies have suggested that oral temozolomide-based regimens may be comparable in efficacy and more tolerable than streptozocin-based regimens (Table 3). In retrospective series, temozolomide-based therapy has been associated with overall response rates of 8% to 70%.[71,72,79] Temozolomide has been evaluated prospectively in combination with thalidomide, bevacizumab, or everolimus, with overall response rates of 24% to 45%.[75–77] Most recently, activity has been observed with a regimen incorporating low-dose, metronomic temozolomide.[80] While temozolomide-based therapy is clearly active in pancreatic NET, neither the optimal dosing regimen for temozolomide nor the relative activity of temozolomide as a single agent or in combination with other therapeutic agents has been clearly established.

The cytotoxic effect of temozolomide has been attributed to its ability to induce DNA methylation at the O^6 position of guanine. The sensitivity of tumor cells to alkylating agents, including temozolomide, has been associated with decreased levels of the DNA repair enzyme, O^6-methylguanine DNA methyltransferase (MGMT). MGMT deficiency appears to be more common in pancreatic NETs than in carcinoid tumors, potentially explaining the greater sensitivity of pancreatic NETs to treatment with the alkylating agents streptozocin or temozolomide.[71] MGMT expression potentially could be used as a predictive marker in future studies of these tumors.

Table 4. Phase II Studies of Biologically Targeted Therapies in Neuroendocrine Tumors

Agent	Molecular Target(s)	No. Patients	Tumor	Tumor Response Rate (%)	Median TTP or PFS	Reference
VEGF pathway inhibitors						
Bevacizumab	VEGF	22	Carcinoid	18	NR	Yao et al, 2008[89]
Sunitinib	VEGFR-1, -2, -3; PDGFR-α, -β; KIT; RET; CSF-1R; FLT3	41	Carcinoid	2	10.2 mo	Kulke et al, 2008[88]
		61	Pancreatic NET	16	7.7 mo	
Sorafenib	VEGFR, PDGFR, Braf	50	Carcinoid	7	7.8 mo	Hobday et al, 2007[90]
		43	Pancreatic NET	11	11.9 mo	
Pazopanib	VEGFR-1, -2, and -3, PDGF-α, PDGF-β, and c-kit	22	Carcinoid	0	12.7 mo	Phan et al, 2010[91]
		29	Pancreatic NET	17	11.7 mo	
mTOR inhibitors						
Everolimus	mTOR	30	Carcinoid	17	63 wk	Yao et al, 2008[92]
		30	Pancreatic NET	27	50 wk	
Everolimus	mTOR	115	Pancreatic NET	9	9.7 mo	Yao et al, 2010[93]
Everolimus + octreotide		45	Pancreatic NET	4	16.7 mo	
Temsirolimus	mTOR	21	Carcinoid	5	6.0 mo	Duran et al, 2006[94]
		15	Pancreatic NET	7	10.6 mo	

NR = not reported; mTOR = mammalian target of rapamycin; NET = neuroendocrine tumor; PFS = progression-free survival; TTP = time to progression; VEGF = vascular endothelial growth factor.

MOLECULARLY TARGETED THERAPY

VEGF Pathway Inhibitors

A key role for angiogenesis and VEGF pathway signaling in NET is suggested by clinical observations that NETs are vascular tumors. Expression of VEGF has been demonstrated in carcinoid and pancreatic NETs.[81,82] Increased expression of VEGF receptor-2 (VEGFR-2) has been demonstrated on tissue from gastrointestinal carcinoid tumors and a carcinoid cell line.[83,84] Additionally, pancreatic NETs also show widespread expression of VEGFR-2 and -3 in addition to platelet-derived growth factor receptors (PDGFRs) α and β and stem-cell factor receptor (c-kit).[85–87]

Sunitinib has shown activity against a range of signaling pathways and growth factors/receptors including VEGFR-1, -2 and -3, PDGFR-α and -β, KIT, RET, FMS-like tyrosine kinase-3 (FLT3), and colony-stimulating factor receptor (CSF-1R). In a multi-institutional phase II study enrolling 109 patients with advanced NET, partial responses were observed in 2% of the carcinoid cohort and 16% of the pancreatic neuroendocrine cohort (**Table 4**).[88–94] Based on evidence of activity in this study, an international randomized phase III study to confirm the activity of sunitinib in pancreatic NET was undertaken (**Table 5**).[95-97] The study was halted prior to a planned interim analysis, after enrollment of 171 patients, 86 of whom received sunitinib and 85 of whom received placebo.[96] Sunitinib was associated with a median PFS of 11.4 months, as compared with 5.5 months for placebo ($P < 0.001$). The objec-

Table 5. Randomized Trials of Biologically Targeted Therapies in Neuroendocrine Tumors

Agent	Patients	Tumor Response Rate (%)	Median TTP or PFS	Reference
Carcinoid tumor				
Everolimus + octreotide LAR	216	2	16.4 mo	Pavel et al, 2011[95]
versus				
Placebo + octreotide LAR	214	2	11.3 mo	
Octreotide + bevacizumab	SWOG S0518/North American Intergroup			
versus	Accrual completed			
Octreotide + placebo				
Pancreatic neuroendocrine tumor				
Sunitinib	86	9	11.4 mo	Raymond et al, 2011[96]
versus				
Placebo	85	0	5.5 mo	
Everolimus	207	5	11 mo	Yao et al, 2011[97]
versus				
Placebo	203	2	4.6 mo	
Everolimus				
versus		CALGB 80701		
Everolimus		Ongoing		
plus bevacizumab				

PFS = progression-free survival; TTP = time to progression.

tive response rate was 9% in the sunitinib group compared to 0% in the placebo group.

Two other small molecule tyrosine kinase inhibitors (TKIs), sorafenib, and pazopanib, have also been evaluated in NET (Table 4). Sorafenib has activity against VEGFR-2, PDGFR-β, and b-Raf and was evaluated in a phase II study that included 43 patients with pancreatic NETs and 50 patients with carcinoid. In a preliminary analysis, responses were observed in 7% of the carcinoid patients and 11% of the patients with pancreatic NET.[90] Pazopanib, a TKI of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α/β, and c-kit, was evaluated in a prospective study of 51 patients with advanced NET, including 29 with pancreatic NETs. The response rate among patients with pancreatic NETs was 17%; no patients with carcinoid experienced a radiographic response (by RECIST).[91]

Although response rates to TKIs in carcinoid tumors have been low, all studies report a high rate of disease stabilization and potentially encouraging PFS durations. The activity of these TKIs in advanced carcinoid remains uncertain in the absence of randomized studies.

Bevacizumab, a monoclonal antibody against VEGF, has been evaluated in a randomized phase II study of patients with advanced or metastatic carcinoid tumors on a stable dose of octreotide. Patients were randomly assigned to 18 weeks of bevacizumab or pegylated IFN-α 2b.[89] At disease progression or at the completion of 18 weeks of therapy (whichever came first), all patients received bevacizumab plus IFN-α. During the first 18 weeks of therapy, 18% of the bevacizumab-treated patients experienced radiographic partial responses, and 77% had stable disease. Furthermore,

after 18 weeks, 95% of patients treated with octreotide plus bevacizumab remained progression-free compared with only 68% of those receiving octreotide plus IFN-α. Based on these results, SWOG has completed a large, randomized study of bevacizumab versus interferon in patients with advanced carcinoid tumors (Table 5).

mTOR Pathway Inhibitors

The mTOR is a serine-threonine kinase that participates in the regulation of cell growth, proliferation, and apoptosis through modulation of the cell cycle.[98] Signaling through the PI3K/AKT/mTOR pathway leads to increased translation of proteins regulating cell cycle progression and metabolism.[99] mTOR mediates downstream signaling from a number of pathways, including VEGF and insulin-like growth factor (IGF), that are implicated in NET growth. Additionally, gene expression analyses have demonstrated altered expression of genes in the mTOR pathway.[100] Furthermore, recent gene sequencing studies of pancreatic NETs have revealed mutations in genes in the mTOR pathway in 14% of tumors.[13] Temsirolimus and everolimus are rapamycin derivatives that have been evaluated in NET (Table 4). Weekly intravenous temsirolimus was associated with a response rate of 6% in a study of 36 patients with advanced, progressive NET. Outcomes were similar between patients with carcinoid and pancreatic NETs.[94]

Everolimus was initially evaluated in NET in a single-institution study, in which 30 patients with carcinoid tumors and 30 with pancreatic NETs received everolimus plus depot octreotide. The overall tumor response rate in evaluable patients was 17% in carcinoid and 27% in pancreatic NET.[92] In a follow-up multinational phase II study (RADIANT-1) enrolling 160 patients with advanced pancreatic NETs and evidence of radiographic progression following chemotherapy, treatment with everolimus was associated with an overall response rate of 9%.[93] A subsequent randomized phase III (RADIANT-3) study involving 410 patients with progressive advanced pancreatic NETs demonstrated significant improvements in PFS associated with everolimus as compared to placebo (11 months versus 4.6 months ($P < 0.0001$, Table 5).[97] Estimates of the proportion of patients alive and progression-free at 18 months were 34% with everolimus as compared to 9% with placebo, indicating a prolonged and durable benefit with everolimus. Forty-six percent of patients had not received prior chemotherapy, and 50% of patients had not received previous treatment with long-acting somatostatin analog therapy. Benefit of everolimus was evident irrespective of status regarding prior chemotherapy or somatostatin analog therapy.

The activity of everolimus in carcinoid tumors was evaluated in a randomized phase III study (RADIANT-2) of 429 patients with advanced carcinoid tumors who were randomly assigned to depot octreotide (30 mg IM every 28 days) with everolimus (10 mg daily) or placebo. Based on investigator-assessed progression, combined therapy was associated with a median PFS duration of 12.0 months as compared to 8.6 months with placebo ($P = 0.018$).[95] However, based on central radiology review, which was the pre-defined primary endpoint, the difference between everolimus and placebo did not reach statistical significance. Further studies evaluating everolimus in advanced carcinoid are anticipated.

CASE CONCLUSION

The patient undergoes hepatic arterial chemoembolization to treat his progressive liver metastases, which are associated with increasing abdominal pain. Peri- and intraoperatively, he re-

ceives octreotide to prevent carcinoid crisis. After recovery from the procedure, the patient experiences improvement in his symptoms of pain and diarrhea. He continues to receive monthly octreotide therapy to help control his symptoms related to carcinoid syndrome. If his disease continues to progress, treatment on a clinical trial utilizing an inhibitor of the VEGF pathway has been discussed.

CONCLUSION

In conclusion, systemic treatment options for patients with advanced NET have recently become more defined. Somatostatin analogs can improve symptoms of hormonal excess, and recent data also suggests that they are associated with antiproliferative effects. Novel somatostatin analogs have been developed and are being investigated. Furthermore, placebo-controlled randomized studies have demonstrated improved PFS durations in patients with pancreatic NETs treated with the targeted agents sunitinib or everolimus. Future studies will likely further define the role of VEGF and mTOR inhibitors in advanced carcinoid tumors. While the targeted agents are associated with favorable toxicity profiles in comparison to many cytotoxic regimens, significant tumor regression is uncommon. Thus, streptozocin or temozolomide-based regimens, which are associated with relatively high tumor response rates in patients with pancreatic NET, can be considered after failure of targeted agents or in symptomatic pancreatic NET patients for whom significant tumor response is desired.

BOARD REVIEW QUESTIONS

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