Gastroenteropancreatic Neuroendocrine Tumors

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Abstract: Neuroendocrine tumors (NETs) are heterogeneous malignancies arising from the diffuse neuroendocrine system. They frequently originate in the gastroenteropancreatic (GEP) tract and the bronchopulmonary tree, and their incidence has steadily increased in the last 3 decades. Fundamental biologic and genomic differences underlie the clinical heterogeneity of NETs, and distinct molecular features characterize NETs of different grades and different primary sites. Although surgery remains the cornerstone of treatment for localized tumors, systemic treatment options for patients with metastatic NETs have expanded considerably. Somatostatin analogs have demonstrated both antisecretory and antitumor efficacy. Peptide receptor radionuclide therapy with lutetium-177 dotatate (^{177}Lu-DOTATATE) has been approved for advanced GEP-NETs. The antitumor activity of everolimus has been demonstrated across a wide spectrum of NETs, and the antiangiogenic agent sunitinib has been approved for pancreatic NETs (pNETs). Chemotherapy with temozolomide and capecitabine has recently demonstrated an unprecedented prolongation of progression-free survival in a randomized trial of pNETs. Multiple retrospective series have reported the efficacy of liver-directed therapies both for palliating symptoms of hormone excess and for controlling tumor growth. Telotristat, an oral inhibitor of tryptophan hydroxylase, has been shown to reduce diarrhea in patients with carcinoid syndrome. Defining the therapeutic algorithm and identifying biomarkers predictive of response to treatments are among the main priorities for the next decade of research in the NET field. **CA: A Cancer J Clin. 2018;000:000-000.**
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Introduction

Neuroendocrine tumors (NETs) are heterogeneous neoplasms arising in secretory cells of the diffuse neuroendocrine system. They are characterized by a relatively indolent rate of growth and the ability to secrete a variety of peptide hormones and biogenic amines. Gastroenteropancreatic NETs (GEP-NETs) include carcinoid tumors of the gastrointestinal tract and pancreatic NETs (pNETs).[1] Whereas carcinoid tumors originate from enterochromaffin cells of the gut, pNETs are thought to arise in the islets of Langerhans, although an alternative origin from precursors in the ductal epithelium has been hypothesized.[2] GEP-NETs may present as hormonally functioning or nonfunctioning tumors and may have distinct clinical features based on their site of origin. One classification, based on embryonic derivation, distinguishes between foregut (gastroduodenal), midgut (jejunal, ileal, and cecal), and hindgut (distal colic and rectal) tumors.[3] Although hindgut NETs are rarely, if ever, associated with a hormonal syndrome, metastatic midgut carcinoids often secrete serotonin and other vasoactive substances, giving rise to the typical carcinoid syndrome, which often is characterized by flushing, diarrhea, and right-sided valvular heart disease.

The clinical aggressiveness of NETs can vary based on primary site. As a rule of thumb, NETs of the small intestine have relatively high malignant potential

but tend to progress indolently in the metastatic setting. Conversely, gastric and rectal NETs often have a low tendency to metastasize but can progress rapidly once they become metastatic. pNETs usually are silent hormonally but may produce a variety of peptide hormones, including insulin, gastrin, and glucagon, thus causing the respective clinical syndromes (insulinoma syndrome, gastrinoma syndrome, glucagonoma syndrome, etc).[4] Tumors should be described as functional only when signs and symptoms consistent with excess hormone secretion are found, regardless of hormone staining on immunohistochemical testing.[5] In this review, we summarize current understanding of the biology and genetics of NETs and summarize the most recent advancements in their clinical management.

Epidemiology

GEP-NETs represent the second most common digestive cancer in terms of prevalence.[6] In a series of 64,971 NETs reported to the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute, the reported annual age-adjusted incidence rate grew from 1.09 per 100,000 in 1973 to 6.98 per 100,000 in 2012.[7] Although the precise reasons for this expansion in diagnoses are unclear, trends in imaging and improved recognition of neuroendocrine histology are likely to play a role. The projected prevalence of NETs in the US population in 2014 was 171,321.[7]

The small intestine (30.8%), rectum (26.3%), colon (17.6%), pancreas (12.1%), and appendix (5.7%) are the most common primary NET sites in the digestive tract.[8] Whereas midgut NETs occur predominantly in white patients, rectal NETs develop more frequently in African American, Asian, and Native American patients. Female patients appear to be more prone to developing NETs of the stomach, appendix, or cecum, whereas NETs of the jejunum/ileum, duodenum, and rectum prevail in male patients.[6] Epidemiological inconsistencies have been reported recently between American and European countries versus Asian countries, where a higher incidence of rectal primaries is registered.[9–11] According to the SEER database, 53% of patients with NETs present with localized disease, 20% have locoregional disease, and 27% have distant metastases at the time of diagnosis.[7] However, estimates of metastatic rates vary because of referral patterns, and even national databases such as SEER may underreport tumors that are not considered malignant. Individuals with a family history of NET in a first-degree relative have a 3.6-fold increased risk of disease.[12] In a prospective evaluation of 129 individuals who had at least 2 blood relatives affected by small intestinal NETs, 29 had small bowel NETs identified by screening procedures.[13] No environmental risk factors have been definitively identified so far.

Pathology, Staging, and Prognosis

Tumor grade and differentiation are crucial determinants of the clinical behavior of GEP-NETs. Whereas grade refers to the proliferative activity of neoplastic cells, as measured by the mitotic rate and/or the Ki-67 index, differentiation refers to the extent to which tumor cells resemble their normal counterparts. Well-differentiated NETs consist of small, monomorphic cells arranged in islets or trabeculae with a "salt-and-pepper" chromatin pattern. Conversely, poorly differentiated tumors are often characterized as sheets of pleomorphic cells with extensive necrosis. Tumor grade is defined numerically, in which low-grade (grade 1 [G1]) tumors have a mitotic rate from 0 to 1 per 10 high-power fields (HPF) or a Ki-67 index from 0% to 2%, intermediate-grade (G2) tumors have a mitotic rate from 2 to 20 per 10 HPF or a Ki-67 index from 3% to 20%, and high-grade (G3) tumors have a mitotic rate greater than 20 per 10 HPF or a Ki-67 index greater than 20%.[14] Note that tumor grade always should be measured in the most mitotically active areas of the pathology specimen, because a considerable degree of intratumor heterogeneity has been reported.[15] According to the 2010 World Health Organization classification, well-differentiated NETs were subdivided as either G1 or G2 tumors, whereas poorly differentiated neuroendocrine carcinomas (NECs) were considered equivalent to G3 tumors.[16] Because well-differentiated, high-grade NETs clearly exist (primarily in the pancreas), the World Health Organization proposed a new classification in 2017 that distinguishes between well-differentiated (low-grade, intermediate-grade, or high-grade) pNETs and poorly differentiated (high-grade) pancreatic NECs (pNECs).[17] Large series[18,19] have proven the prognostic relevance of current grading systems for both small bowel NETs and pNETs. In midgut NETs, the 5-year survival rates for low-grade, intermediate-grade, and high-grade tumors were 79%, 74%, and 40%, respectively, whereas 5-year survival rates of 75%, 62%, and 7% were reported for G1, G2, and G3 pNETs, respectively.

Immunohistochemical markers of neuroendocrine differentiation include synaptophysin, chromogranin A (CgA), neuron-specific enolase (NSE), and cluster of differentiation 56 (CD56) (neural cell adhesion molecule). Both synaptophysin and CgA are diffusely expressed in well-differentiated GEP-NETs, whereas poorly differentiated tumors often maintain synaptophysin positivity while losing CgA expression and acquiring NSE expression. In well-differentiated NETs, immunohistochemical labeling for thyroid transcription factor 1 (TTF1), caudal type homeobox 2 (CDX2), and insulin gene enhancer protein 1 (ISL1) (as proteins typical of the pulmonary, gastrointestinal, and pancreatic lineage, respectively) can be used to identify the primary site of metastatic tumors.[20]

The first TNM staging classification of NETs was proposed by Rindi et al[21] in 2006. Both the European Neuroendocrine Tumor Society (ENETS) and the American Joint Committee on Cancer adopted this staging system for midgut and hindgut NETs, whereas slightly different classifications were embraced for pNETs.[22,23] As a general rule, early-stage GEP-NETs are associated with a very favorable long-term prognosis, whereas survival outcomes of patients with metastatic disease greatly depend on both tumor grade and primary site.

Tumor Biology

Up to 14 distinct types of neuroendocrine cells have been identified in the gastrointestinal tract and pancreas, where they regulate bowel motility and hormone secretion.[24] Historically regarded as originating from the neural crest, neuroendocrine cells are currently thought to derive from endodermal precursors. NETs are characterized by high-density expression of somatostatin receptors (SSTRs). SSTRs are G-protein–coupled receptors with 7 transmembrane domains and are encoded by 5 highly conserved genes ($SSTR_1$-$SSTR_5$). In NETs, SSTRs modulate proliferation and protein synthesis and regulate hormone secretion by counteracting the prosecretory stimuli deriving from β-adrenoreceptors and adenylyl cyclase.[25] Well-differentiated NETs express SSTRs at an increased frequency and higher levels compared with poorly differentiated tumors. A predominance of $SSTR_2$ expression is commonly observed in GEP-NETs.[26] Aberrant activation of signaling by the mammalian target of rapamycin (mTOR) is a hallmark of NETs, regardless of primary site. mTOR modulates cell survival and proliferation, angiogenesis, and metabolism, and mutations in the mTOR pathway are observed in approximately 15% of pNETs.[27,28] Overexpression of mTOR and/or its downstream targets is frequently detected in nonpancreatic NETs and is associated with a poorer prognosis.[29] Tumor neoangiogenesis has been identified as a key event in NET progression. Overexpression of proangiogenic factors, including vascular endothelial growth factor (VEGF), fibroblast growth factor, platelet-derived growth factor (PDGF), and their receptors, has been reported.[30,31] Therefore, it is not surprising that NETs are among the most vascularized cancers.

Molecular Genetics

Fundamental genomic, epigenomic, and transcriptomic differences have been observed among GEP-NETs of different primary sites and degrees of differentiation. In pNETs, losses of genetic material have been described more often than chromosomal gains.[32] In a seminal whole-exome study of 68 sporadic pNETs, somatic mutations of multiple endocrine neoplasia type 1 (*MEN1*) and death domain-associated protein/α-thalassemia mental retardation syndrome (*DAXX/ATRX*) were identified in 44% and 43% of tumors, respectively, whereas 14% of samples had mutations in genes implicated in the mTOR pathway, including phosphatase and tensin homolog (*PTEN*), tuberous sclerosis complex 2 (*TSC2*), and phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit α (*PIK3CA*).[27] Similar findings recently were reported in a whole-genome sequencing study of 102 primary pNETs that also identified 4 signaling pathways commonly dysregulated in such tumors: 1) DNA damage repair; 2) chromatin remodeling; 3) telomere maintenance; and 4) mTOR activation. A higher than expected proportion of germline mutations has been demonstrated in clinically sporadic pNETs with mutations of the genes mutY homolog (*MUTYH*), checkpoint kinase 2 (*CHEK2*), and *BRCA2* recurring in 11% of patients.[28]

The exact sequence of gene mutations capable of driving the development and progression of pNETs is currently unknown. Available evidence suggests that mutations of *MEN1* play a key role in tumor initiation, whereas late alterations of *DAXX/ATRX* seem to be implicated in tumor progression.[33] Loss of DAXX/ATRX expression has been associated with activation of the alternative lengthening of telomeres (ALT) pathway and chromosomal instability,[34] and poor outcomes have been reported for patients with ALT-positive tumors.[34–36] Three distinct molecular subtypes of pNETs recently have been identified: 1) the islet/insulinoma tumor subtype is characterized by low grade and limited metastatic potential; 2) the metastasis-like primary subtype is characterized by high proliferative activity and aggressive behavior; and 3) the MEN1-like/intermediate subtype shows moderate metastatic potential.[37]

Compared with other pNETs, insulinomas have unique genomic features. A recent study of 113 Asian patients with insulinoma identified gain-of-function mutations in the Yin Yang 1 (*YY1*) gene in 30% of samples.[38] However, the frequency of *YY1* mutations in the white population appears to be considerably lower.[39] Poorly differentiated pNECs have a strikingly different appearance compared with well-differentiated tumors in terms of genomic landscape. Loss of retinoblastoma (Rb) and mutations of Kirsten rat sarcoma viral oncogene homolog (*KRAS*) have been recently reported in 55% and 49% of patients with pNECs, in whom such molecular alterations seem to predict response to platinum-based chemotherapy.[40] Overall, the frequency of mutations is substantially higher in NECs than in NETs.[41]

The molecular landscape of gastrointestinal NETs is much less well understood than that of pNETs. Loss of chromosome 18 has been reported in 60% to 90% of small bowel NETs, but the biologic significance of this alteration

is largely unknown.[42] Overall, a low mutational rate (0.1 somatic single nucleotide variants/10^5 nucleotides) has been observed in intestinal NETs, with recurring mutations or deletions of the cyclin-dependent kinase inhibitor 1B gene *CDKN1B* in 8% of patients.[43,44] The mutational status of *CDKN1B* does not correlate with disease presentation, clinical course, or prognosis and exhibits relatively high intratumor and intertumor heterogeneity.[45] Global DNA hypomethylation is a characteristic feature of small bowel carcinoids, and tumors with a high methylation index have clinically aggressive behavior.[46] Progressive changes in DNA methylation have been detected between primary tumors and their metastases, suggesting that epigenetic dysregulation may play a pivotal role in the progression of small bowel NETs.[47]

Clinical Presentation

Most GEP-NETs are sporadic, but they also can arise as part of inherited familial syndromes, including multiple endocrine neoplasia type 1 (MEN-1), Von-Hippel Lindau (VHL) syndrome, tuberous sclerosis, and neurofibromatosis type 1. MEN-1 is an autosomal-dominant syndrome caused by mutations of the gene *MEN1*, which encodes for menin, a nuclear protein that regulates transcription through chromatin remodeling.[48] Clinically, the syndrome is characterized by neuroendocrine neoplasms of the anterior pituitary, parathyroid glands, and pancreas. Pancreatic NETs arising in the context of MEN-1, most commonly gastrinomas and nonfunctioning tumors, are typically multifocal.[49] Most MEN1-associated pNETs are exceptionally slow-growing and modestly impact life expectancy.[50] VHL syndrome is an autosomal-dominant syndrome caused by mutations in the *VHL* gene located on chromosome 3p25. This gene encodes for a protein involved in degradation of the α subunits of hypoxia-inducible factor (HIF) in an oxygen-dependent manner. Lack of degradation of HIF-1α results in uncontrolled production of hypoxia-associated cytokines, including VEGF and PDGF. The syndrome may manifest with a variety of benign and malignant neoplasms, including clear renal cell carcinomas, pheochromocytomas (often bilateral), hemangioblastomas, retinal angiomas, paragangliomas, and pNETs (the latter develop in approximately 10% of cases).[51] Tuberous sclerosis is an autosomal-dominant syndrome caused by inactivating mutations of either the *TSC1* gene or the *TSC2* gene, which encode for hamartin and tuberin, respectively, thus forming a complex that inhibits mTOR signaling. Tuberous sclerosis is characterized by widespread, low-grade tumors and hamartomas in multiple organs, including the brain, heart, skin, eyes, kidney, lung, and liver. pNETs are described in only 1% to 5% of cases.[52] Neurofibromatosis type 1, formerly named von Recklinghausen disease, is an autosomal-dominant phakomatosis caused by the deregulation of the Ras and mTOR pathway deriving from mutation of the guanosine triphosphatase protein neurofibromin. The syndrome is characterized by ubiquitous neurofibromas; multiple cafe-au-lait skin spots; and susceptibility to gliomas, myeloid leukemia, pheochromocytomas, and occasionally pNETs.[53]

Pancreatic NETs

Up to 90% of pNETs are hormonally silent.[54] Nonfunctioning tumors seem to have worse prognosis compared with functioning neoplasms, probably as result of late diagnosis. Increasing numbers of nonfunctioning pNETs are diagnosed incidentally, and the optimal management of small (<2 cm), asymptomatic, incidentally detected tumors is controversial.[55] Insulinomas are the most common subtype of functioning pNET, with an annual incidence of 0.5 per 100,000.[56] Insulinomas are usually smaller than 2 cm, solitary, hypervascular, and tend to exhibit very low malignant potential. The clinical presentation of insulinomas is characterized by the classic "Whipple triad," consisting of symptomatic hypoglycemia, low blood glucose levels, and relief of symptoms after glucose administration.[57] Gastrinomas are typically malignant tumors and cause the Zollinger-Ellison syndrome, which is characterized by peptic ulceration, heartburn, and diarrhea. Diarrhea may occur due to the passage of excess gastric acid into the small intestine. The symptoms of Zollinger-Ellison syndrome may be palliated effectively with high-dose proton pump inhibitors.[58] Vasoactive intestinal polypeptide (VIP) stimulates intestinal secretion and inhibits electrolyte and water absorption. Consequently, VIPomas are associated with profuse, watery diarrhea and electrolyte abnormalities, including hypokalemia (Verner-Morrison syndrome).[59] The clinical manifestations of glucagonomas include hyperglycemia, weight loss, venous thromboses, glossitis, and an unusual rash called necrolytic migratory erythema, likely caused by amino-acid or zinc deficiencies.[60] Somatostatinomas are characterized by the effects of hypersecretion of somatostatin and usually present with steatorrhea, achlorhydria, diabetes mellitus, and cholelithiasis. Rarely, pNETs may secrete adrenocorticotropic hormone, parathyroid hormone-related peptide, growth hormone-releasing hormone, cholecystokinin, and serotonin, giving rise to the respective clinical syndromes.[61]

Small Bowel NETs

Most small bowel NETs originate in the distal ileum.[62] Approximately 25% of patients have multifocal tumors at the time of diagnosis, often clustered in close proximity to each other.[18] Although the malignant potential of intestinal NETs correlates with tumor size, even subcentimeter

neoplasms can metastasize.[63] Liver, mesentery, and peritoneum are frequent sites of metastases. Lymph node metastases at the root of the mesentery may be associated with dense desmoplastic fibrosis, causing tethering of the bowel and mesenteric ischemia.[64] Crampy or intermittent abdominal pain and/or intestinal obstruction are common presenting manifestations. However, increasing numbers of patients are diagnosed incidentally after undergoing radiographic or endoscopic procedures for other indications.[18] Duodenal carcinoids may present with duodenal or biliary obstruction but usually are detected incidentally.[65] Hormonally functioning duodenal NETs are uncommon.

Most advanced midgut NETs produce serotonin as well as other vasoactive substances that cause carcinoid syndrome. Carcinoid syndrome usually occurs in patients with liver metastases that secrete serotonin directly into the systemic (rather than portal) circulation.[1] In an analysis of 91 patients with typical carcinoid syndrome, diarrhea, flushing, and bronchospasm occurred in 73%, 65%, and 8% of cases, respectively.[66] Although diarrhea is triggered mainly by serotonin through stimulation of the serotonin 2A receptors, flushing is attributable primarily to prostaglandins and tachykinins, including substance P and kallikrein.[67,68] Flushing typically involves the face, neck, and upper torso and may be precipitated by alcohol, stress, spices, and tyramine-containing foods. Carcinoid heart disease typically occurs in patients with highly elevated levels of serum serotonin which causes fibrosis of the right-sided cardiac valves, leading to tricuspid regurgitation and pulmonary valve stenosis.[69] The incidence of carcinoid heart disease has been declining in recent years, probably as consequence of the use of serotonin-inhibiting therapies.[70]

Gastric NETs

Gastric NETs arise from subepithelial, histamine-secreting, enterochromaffin-like cells and may be subdivided into 3 types. Type I gastric NETs occur in patients with chronic atrophic gastritis and account for approximately 80% of gastric carcinoids.[71] The chronic absence of gastric acid stimulates antral G cells to secrete excess serum gastrin, which, in turn, causes gastric neuroendocrine cell hyperplasia and the development of multifocal, polypoid NETs. Type I NETs generally behave in a benign fashion, and aggressive treatment is rarely, if ever, indicated. Most guidelines recommend endoscopic surveillance every 12 to 24 months with snare polypectomy of tumors.[72] Netazepide, an oral antagonist of the gastrin/cholecystokinin receptors, has been shown to eradicate type I gastric NETs,[73] but its use is still investigational. The detection of elevated serum gastrin levels, evidence of chronic atrophic gastritis on biopsy, and high gastric pH are key elements for the diagnosis of type I gastric NETs. Type II gastric carcinoids are caused by hypergastrinemia in the setting of an underlying gastrinoma, primarily in patients with MEN1. Consequently, patients who have type II gastric NETs usually present with symptoms of Zollinger-Ellison syndrome, such as diarrhea, heartburn, and peptic ulceration. Tumors tend to be small, multifocal, and relatively unaggressive. The detection of elevated serum gastrin levels and low gastric pH are frequent in type II gastric carcinoids. Management is conservative, and tumors possibly will regress with successful treatment of the underlying gastrinoma.[74] Type III (or sporadic) gastric NETs occur in fewer than 15% of cases and are not associated with gastrin overproduction. Their malignant potential is considerably higher compared with that of type I and II tumors, and radical resection is often required for local or locally advanced cases. Small, superficial type III gastric carcinoids may be managed with surgical wedge or endoscopic resection.[75]

Appendiceal and Colorectal NETs

NETs of the appendix are identified in 1 of 300 appendectomy specimens, nearly always incidentally during surgery for appendicitis. The malignant potential of appendiceal NETs appears to be related strictly to tumor size. In a large series of patients, no metastases were observed in 127 patients who had tumors smaller than 2 cm.[76] Consequently, simple appendectomy was considered adequate for tumors less than 2 cm, whereas completion with right hemicolectomy was recommended for tumors greater than 2 cm. However, locoregional or distant metastases have been described in recent years in patients with tumors measuring 1 or 2 cm in diameter.[77] Negative prognostic factors for tumors in this size range include location in the base of the appendix, lymphovascular invasion, or extensive invasion into the mesoappendix.

Patients with colorectal NETs may present with rectal bleeding, pain, or a change in bowel habits. However, most rectal NETs are discovered incidentally during lower endoscopy and often are small and submucosal.[78] Low-grade rectal NETs measuring less than 1 cm rarely metastasize and usually are resected endoscopically or transanally. Conversely, rectal NETs measuring greater than 2 cm present with stage IV disease in greater than 50% of patients. The metastatic potential of intermediate-size tumors correlates with depth of invasion of the muscularis propria.[79] Colonic NETs distal to the cecum tend to be more aggressive than rectal NETs and are often poorly differentiated.[80]

Diagnosis

The diagnosis of GEP-NETs is based on clinical presentation, pathology, and conventional or functional imaging. Patients who present with symptoms of carcinoid syndrome should undergo measurement of

24-hour urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA), which is the breakdown product of serotonin.[81] In recent years, it has been reported that a plasma 5-HIAA assay is equivalent in accuracy to 24-hour urine 5-HIAA measurement.[82] Patients with pNET who present with suspected hormonal syndromes should undergo testing for the corresponding hormone level. If it is elevated, then the hormone concentration may be followed over time and used as a biomarker of progression or response to treatment.[1]

Conventional imaging plays a key role for the assessment of location and extent of GEP-NETs. Cross-sectional imaging using computed tomography (CT) or magnetic resonance imaging (MRI) scans should focus on the abdomen for pNETs and on the abdomen and pelvis for midgut carcinoids. Guidelines recommend 3-phase CT scans for the optimal evaluation of liver metastases.[83] However, in a series of 64 patients with metastatic gastrointestinal NETs, MRI was associated with higher sensitivity than CT for the detection of small liver metastases.[84] Gadoxetate contrast may be used to optimize the detection of subcentimeter liver metastases.[85] Functional imaging studies for patients with NET are based primarily on tumor SSTR expression and historically were performed using indium-111 (^{111}In) pentetreotide SSTR scintigraphy (SRS) (OctreoScan; Mallinckrodt Medical, St Louis, Missouri). In recent years, gallium-68 (^{68}Ga)-DOTATATE PET/CT scanning has become the preferred modality for SSTR imaging as result of its higher sensitivity, reduced radiation exposure, and improved convenience to patients (1 day vs multiday scanning). ^{68}Ga-DOTATATE PET/CT imaging is useful for baseline whole-body staging, detecting of small lymph node or bone metastases, and identification of the primary site in cases of occult primary tumor. In 1 study of 131 patients with known or suspected NETs, a ^{68}Ga-DOTATATE PET/CT detected 95% of total lesions, compared with 45% detected with cross-sectional imaging and 31% detected with OctreoScan. In particular, the rate of detection for bone metastases was 95%, 15%, and 12% with ^{68}Ga-DOTATATE PET/CT, OctreoScan, and conventional imaging, respectively (P <.001).[86] Overall, ^{68}Ga-DOTATATE PET/CT has sensitivity greater than 94% and specificity greater than 92% for NETs.[87] High levels of ^{68}Ga uptake also may be observed in meningioma, non-Hodgkin lymphoma, breast cancer, papillary thyroid cancer, and thyroid adenoma.[88] Levels of radiotracer uptake with either SRS or ^{68}Ga-PET/CT correlate with the degree of SSTR expression and the response to peptide receptor radionuclide therapy (PRRT), whereas the predictive value for response to cold somatostatin analogs (SSAs) is still debated.[89,90] Given their high proliferative activity and low expression of SSTRs, poorly differentiated NETs are commonly imaged by ^{18}F-fluorodeoxyglucose PET/CT. In well-differentiated NETs ^{18}F-fluorodeoxyglucose PET uptake can correlate negatively with prognosis; however, the use of this imaging modality is not routinely recommended.[91,92]

Treatment of Localized Tumors

Surgery is the mainstay for the treatment of local or locoregional GEP-NETs. Patients with pNETs that are symptomatic, intermediate-to-high grade, or measure greater than 2 cm should undergo formal oncologic surgery, such as Whipple resection or distal pancreatectomy/splenectomy. Enucleation represents an alternative option for small, localized pancreatic NETs but may lack oncologic adequacy in terms of lymphadenectomy and clearance of resection margins.[93] The management of small (<2 cm), low-grade, nonfunctioning, incidentally detected pNETs is currently controversial. Although some centers advocate resection for all surgically fit patients based on possible risk of malignant tumor behavior, others advocate surveillance given the very small likelihood of progression over time. ENETS guidelines offer a "watch-and-wait" approach as an option for patients with pNETs measuring less than 2 cm.[94] Among patients with MEN1 syndrome, guidelines generally recommend resection of tumors that are clearly enlarging, greater than 2 cm in diameter, or hormonally functional, resulting in uncontrolled symptoms. Surgical decisions in this syndrome are complicated by the multifocality of pancreatic neuroendocrine neoplasia.[95] The surgical approach for midgut NETs primarily depends on tumor location. Partial small bowel resections are usually performed for jejunal or proximal ileal tumors, whereas right hemicolectomy is indicated for tumors arising in or near the ileocecal valve. Because of the high frequency of multifocal tumors (approximately 25% of cases), the entire bowel should be palpated during the surgical procedure. Resection of the involved small bowel mesentery is recommended for lymph node sampling. There is some controversy regarding the need of locoregional surgery in patients with stage IV small bowel NETs. In a recent analysis of 363 patients who had small bowel NETs and distant metastases with no abdominal symptoms, prophylactic upfront intestinal surgery conferred no survival advantage compared with delayed surgery or no surgery.[96] Primary tumor resection may be proposed for patients who are experiencing symptoms (pain, bleeding, intermittent bowel obstruction) or are likely to survive enough to experience such symptoms.[97]

As a rule of thumb, simple appendectomy can be considered sufficient for appendiceal NETs measuring less than 1 cm, whereas completion with right hemicolectomy is

recommended for tumors greater than 2 cm. Hemicolectomy also should be considered in patients who have tumors of intermediate size (1-2 cm) in the presence of significant mesoappendix invasion or location of the tumor in the appendiceal base.[76,77]

Rectal NETs less than 2 cm in diameter can be managed with endoscopic resection or transanal excision. Low anterior resection or abdominoperineal resection with lymph node sampling should be performed for larger rectal tumors. A formal partial colectomy is usually indicated for colonic NETs.[98–100]

Follow-up

GEP-NETs are typically slow-growing tumors; therefore, tumor markers and imaging studies should be obtained at relatively infrequent intervals (4-12 months). Treatment decisions should not be based solely on tumor marker changes. It is questionable whether functional imaging is useful in the follow-up of patients with NETs. In a recent retrospective analysis, annual SRS or ^{68}Ga-DOTATATE PET/CT reportedly affected the management (defined as indication to biopsy, initiation of new medical or surgical therapy, need for further imaging) of three-quarters of patients who

TABLE 1. Completed Key Randomized Trials for the Evaluation of Antiproliferative Agents in Patients With Neuroendocrine Tumors

STUDY	CONTROL VS INVESTIGATIONAL ARM	NO. OF PATIENTS	POPULATION ENROLLED	MEDIAN PFS (CONTROL VS INVESTIGATIONAL ARM)	ORR (CONTROL VS INVESTIGATIONAL ARM)	REFERENCE
pNET						
RADIANT-3	Placebo vs everolimus 10 mg	420	Progressive pNETs	4.6 mo vs 11 mo	2% vs 5%	Yao 2011[105]
Sunitinib	Placebo vs sunitinib 37.5 mg	171	Progressive pNETs	5.5 mo vs 11.4 mo	0% vs 9%	Raymond 2011[106]
ECOG E2211	Temozolomide vs CAPTEM every 4 wk	144	Progressive pNETs	14.4 mo vs 22.7 mo	27.8% vs 33.3%	Kunz 2018[107]
Non-pNET						
PROMID	Placebo vs octreotide LAR 30 mg every 4 wk	84	Treatment-naive midgut NETs	6 mo vs 14.3 mo[a]	2% vs 2%	Rinke 2009[108]
CLARINET	Placebo vs lanreotide autogel 120 mg every 4 wk	204	Advanced, SSTR+ GEP-NETs	18 mo vs NR	NR	Caplin 2014[109]
SWOG S0518	Interferon-α-2b 3 times per wk plus octreotide 20 mg every 3 wk vs bevacizumab 15 mg/kg plus octreotide 20 mg every 3 wk	427	Progressive NETs with poor prognostic features	15.4 mo vs 16.6 mo	4% vs 12%	Yao 2017[110]
RADIANT-2	Placebo plus octreotide LAR vs everolimus 10 mg plus octreotide LAR	429	Progressive functional GI/lung NETs	11.3 mo vs 16.4 mo	2% vs 2%	Pavel 2011[111]
RADIANT-4	Placebo vs everolimus 10 mg	302		3.9 mo vs 11 mo	1% vs 2%	Yao 2016[112]
NETTER-1	Octreotide 60 mg every 4 wk vs 4 cycles of ^{177}Lu-DOTATATE	230	Progressive, SSTR+ midgut NETs	8.4 mo vs NR	3% vs 18%	Strosberg 2017[113]

Abbreviations: +, positive; ^{177}Lu-DOTATATE, lutetium-177 dotatate; CAPTEM, capecitabine-temozolomide; ECOG, Eastern Cooperative Oncology Group; GEP-NET, gastroenteropancreatic neuroendocrine tumor; GI, gastrointestinal; LAR, long-acting repeatable; NETs, neuroendocrine tumors; NR, not reached; ORR, overall response rate; PFS, progression-free survival; pNET, pancreatic neuroendocrine tumor; SSTR, somatostatin receptor; SWOG, Southwest Oncology Group.

[a]Values indicate the time to progression.

had stage IV GEP-NETs.[101] However, potential benefits and costs of such an approach should be carefully weighted in the context of a usually indolent disease. Postoperative imaging surveillance of radically resected GEP-NETs can be performed at intervals ranging from every 6 months to every 2 years, depending on the biologic aggressiveness of the neoplasm, as determined by the Ki-67 index, mitotic activity, degree of differentiation, presence of lymphovascular or perineural invasion, clearance of margins, and quality of the surgery performed.[92] Cross-sectional imaging (CT or MRI) is considered standard, whereas the routine use of functional imaging is not endorsed.[92,102] Because recurrences can occur many years after the diagnosis,[103,104] long-term follow-up (5-10 years) is advisable for both pNETs and small bowel carcinoids. Surveillance beyond 10 years can be considered in individualized patients, considering the low and decreasing risk of recurrence at that point.[92]

Treatment of Advanced Tumors

In recent years, the therapeutic armamentarium for metastatic GEP-NETs has expanded considerably. New systemic treatments for tumor and syndrome control have been shown to delay progression as well as diminish symptoms related to hormone secretion. Liver-directed therapy also remains a key treatment modality for patients with hepatic-dominant tumors. Table 1 summarizes the main findings of randomized trials in patients with NETs.[105–113]

Palliation of Hormonal Symptoms

Somatostatin analogs

The human hormone somatostatin was first isolated in 1973 and described as a hypothalamic inhibitor of growth hormone. Subsequently, it became clear that somatostatin is a universal endocrine "off-switch" as result of its exocrine, endocrine, paracrine, and autocrine inhibitory effects. Somatostatin's actions in the digestive tract include inhibition of bowel motility, reduction of mesenteric blood flow, inhibition of gallbladder contraction and intestinal absorption, and suppression of the secretion of hormones, including serotonin, gastrin, and cholecystokinin. The clinical utility of native human somatostatin has been limited by its short half-life of approximately 2 minutes. To improve the pharmacokinetics of somatostatin, SSAs were developed with prolonged duration of action.[25]

The SSAs octreotide and lanreotide share a similar pharmacodynamic profile, binding with high affinity to $SSTR_2$ and with moderate affinity to $SSTR_5$. A landmark trial evaluated octreotide 150 μg 3 times daily in 25 patients with carcinoid syndrome and reported rapid palliation of flushing and diarrhea in 88% of patients and major reductions of 5-HIAA levels in 72%.[114] Multiple subsequent studies reported similar symptom control rates with either octreotide or lanreotide,[25] and a crossover study comparing the 2 SSAs in 33 patients with carcinoid syndrome demonstrated no significant differences between octreotide and lanreotide in terms of symptom control as well as improvement in quality of life.[115] A randomized phase 3 trial of patients with carcinoid syndrome compared immediate-release subcutaneous octreotide every 8 hours with octreotide long-acting repeatable (LAR) at doses of 10, 20, or 30 mg monthly and demonstrated that the intramuscular LAR formulation was at least as effective as subcutaneous octreotide.[116]

Carcinoid crisis is an episode of circulatory collapse caused by an acute release of serotonin and other vasoactive substances into the circulation. Typically, carcinoid crisis is an intraoperative emergency, because common triggers include general anesthesia, epinephrine, and physical manipulation of tumors. Patients with known carcinoid syndrome who undergo surgery should receive a supplementary dose of octreotide 250 to 500 μg subcutaneously or intravenously 1 or 2 hours before the procedure.[117] Hypotension occurring in the setting of carcinoid crisis may be managed with bolus intravenous doses of octreotide up to 1 mg until control of symptoms is achieved or with continuous intravenous infusion of octreotide at 50 to 200 μg per hour after the bolus dose.[118] The role of prophylactic octreotide in the management of carcinoid crisis recently has been questioned, because rates of intraoperative complications were reported as similar in patients who did or did not receive preoperative octreotide bolus or continuous octreotide infusion.[119,120] Nonetheless, ENETS guidelines recommend perioperative octreotide prophylaxis in patients with carcinoid syndrome.[121]

Both octreotide and lanreotide are active at controlling hormonal symptoms associated with functioning pNETs. In particular, SSA treatment significantly improves symptoms in up to 90% of patients with VIPoma, and similar rates of success are described for the control of necrolytic migratory erythema in patients with glucagonoma. SSAs also are effective in palliating symptoms in patients with gastrinoma, although high-dose proton pump inhibitors may be even more essential in controlling the gastric acid overproduction. Patients with advanced insulinoma respond poorly to SSAs, likely because of low expression of $SSTR_2$ by these tumors. Exacerbation of hypoglycemia also has been described in patients with insulinoma who receive treatment with SSAs and has been attributed to inhibition of the counter-regulatory hormone glucagon.[25]

Patients who experience exacerbation of hormone symptoms toward the final week of each treatment cycle may benefit from increased frequency of SSA administration. Supplemental dosing of short-acting octreotide may serve to

control breakthrough symptoms. In patients who experience suboptimal control of their hormone excess symptoms during treatment with standard doses of SSA, escalation to above-label doses may result in improved symptom palliation.[122]

The side effects of SSAs are generally mild and include nausea, gas, diarrhea, steatorrhea, and bloating. Long-term administration of SSAs can result in an increased rate of biliary stone and sludge formation because of the inhibitory effects on gallbladder contractility.[25] Prophylactic cholecystectomy should be proposed to patients who are likely to require long-term SSA therapy if they undergo abdominal surgery for other reasons.

Telotristat ethyl

Telotristat ethyl is an inhibitor of tryptophan hydroxylase, the rate-limiting enzyme in the conversion of tryptophan into serotonin. Telotristat has been investigated in the double-blind, placebo-controlled, phase 3 TELESTAR trial.[123] This 3-arm study randomized 135 patients experiencing 4 or more bowel movements per day despite SSA therapy to telotristat 250 or 500 mg 3 times per day versus placebo over a 12-week period. Treatment with telotristat (combined with SSA) was associated with a statistically significant reduction in the average number of daily bowel movements compared with placebo (P <.01). Moreover, mean reductions in urinary levels of 5-HIAA were significantly greater in patients on the telotristat arms compared with those who received placebo (P = .001). The tolerability profile of telotristat is favorable, with mild nausea and hepatic enzyme elevations as the main side effects of the treatment. When evaluating a patient with a metastatic NET and diarrhea, it is also important to consider other potential etiologies, such as pancreatic exocrine insufficiency (which is often caused by SSAs), bile salt malabsorption (caused by ileocecectomy), or short gut syndrome, as these may respond to other antidiarrheal measures.

Inhibition of Tumor Growth

Somatostatin analogs

Multiple retrospective and phase 2 studies have investigated the antitumor effects of SSAs in patients with GEP-NETs. Although rates of objective radiographic response were low (generally <5%), disease stabilization was observed in approximately 40% to 60% of patients.[25] On this basis, the double-blind, placebo-controlled, phase 3 PROMID trial[108] randomized 85 patients with well-differentiated, advanced midgut NETs to receive either octreotide LAR 30 mg every 4 weeks or placebo. The trial reported a statistically significant improvement in the median time to progression from 6 months on the placebo arm to 14.3 months on the experimental arm (hazard ratio, 0.34; P = .000072). Crossover of the majority of patients on placebo to octreotide hindered any reliable conclusions on overall survival (OS).[124] The double-blind, placebo-controlled, phase 3 CLARINET study[109] randomized 204 patients who had OctreoScan-positive, hormonally nonfunctioning GEP-NETs with a Ki-67 index less than 10% to receive lanreotide 120 mg once every 4 weeks or placebo. A run-in phase of 3 to 6 months of observation was required to document progression status before randomization, and 96% of enrolled patients were found to have radiographically stable disease. After a median study drug exposure of 24 months, lanreotide was associated with a significant prolongation of progression-free survival (PFS) compared with placebo (median PFS not reached vs 18 months; hazard ratio, 0.47 [P = .001]). Currently, there is no evidence to support the preferential use of octreotide or lanreotide for the control of tumor growth in patients with GEP-NETs. It is also questionable whether treatment with SSAs is inherently superior to a "watch-and-wait" approach in patients with very slow-growing disease. The question of continuing SSAs beyond tumor progression after first-line therapy has not been addressed in a prospective trial.

Radiolabeled somatostatin analogs

PRRT is a form of systemic radiotherapy that allows targeted delivery of radionuclides to tumor cells expressing high levels of SSTRs. Structurally, radiolabeled SSAs consist of a radionuclide isotope, a carrier molecule (usually octreotide or octreotate), and a chelator (usually DOTA or diethylenetriamine pentaacetic acid) that binds them, stabilizing the complex.[90]

Early clinical trials of PRRT in patients with GEP-NETs used octreotide labeled with high doses of ^{111}In and reported frequent palliation of carcinoid syndrome symptoms despite low objective response rates. Subsequent studies documented significant antitumor activity of SSAs labeled with either yttrium-90 (^{90}Y) or lutetium-177 (^{177}Lu). In particular, the overall response rates (ORRs) reported across studies of ^{90}Y-DOTATOC in GEP-NETs varied between 4% and 38%, with the median PFS ranging from 16 to 29 months.[125] In a large, prospective, institutional database of patients treated with ^{177}Lu-DOTATATE, objective response rates ranged from 31% in patients who had midgut NETs to 55% in those who had pNETs, with intermediate response rates in those who had colorectal and gastroduodenal NETs.[126] Side effects associated with ^{90}Y include renal insufficiency (but the occurrence of this side effect may be reduced by prophylactic amino acid infusion) and bone marrow toxicities. A substantially lower risk of nephrotoxicity has been observed with ^{177}Lu-based PRRT. Acute leukemia and myelodysplastic syndromes have been

reported in approximately 2% of patients who received PRRT.[90]

High-level evidence for the antitumor activity of PRRT with lutetium has been provided by the NETTER-1 study.[113] This randomized, phase 3 trial investigated ^{177}Lu-DOTATATE every 8 weeks for 4 cycles plus octreotide 30 mg every 4 weeks versus high-dose octreotide LAR (60 mg every 4 weeks) in 229 patients with advanced, OctreoScan-positive, midgut NETs who progressed on standard-dose octreotide LAR. After a median follow-up of 14 months, ^{177}Lu-DOTATATE resulted in a 79% reduction in the risk of progression or death compared with high-dose octreotide (hazard ratio, 0.21; 95% confidence interval, 0.13-0.33 [P <.0001]). The median PFS was 8 months on the control arm of the study and was not reached with ^{177}Lu-DOTATATE at the time of primary analysis. Strong early signals for OS improvement were observed in the PRRT arm, with a hazard ratio of 0.4 (P = .004). Lutetium therapy yielded an ORR of 18% versus 3% with octreotide. Treatment with ^{177}Lu-DOTATATE was well tolerated, and the most common grade 1 and 2 side effects were vomiting and nausea. Grade 3 or 4 neutropenia and thrombocytopenia occurred in 1% and 2% of patients treated with ^{177}Lu-DOTATATE, respectively. On the basis of results from the NETTER-1 trial as well as evidence from prior single-arm studies, PRRT with ^{177}Lu-DOTATATE recently was approved for the treatment of patients who have advanced GEP-NETs with evidence of SSTR expression on imaging studies.

A standard course of treatment with ^{177}Lu-DOTATATE consists of 4 cycles administered every 8 weeks. However, there is evidence that patients who benefit from PRRT but subsequently progress can be retreated up to a lifetime maximum of approximately 8 cycles.[127] There is a substantial correlation between levels of radiotracer uptake on OctreoScan or ^{68}Ga-DOTATOC PET/CT scan and response to PRRT, so that functional imaging can be used to preselect patients who are most likely to benefit from treatment.[89]

Everolimus

Everolimus, an oral inhibitor of mTOR, has been investigated extensively in patients with NETs. In the phase 3 RADIANT-2 study,[111] 429 patients with hormonally active carcinoid tumors were randomly assigned to everolimus plus octreotide versus placebo plus octreotide. At central review, the median PFS increased from 11.3 months on the placebo arm to 16.4 months on the everolimus arm (hazard ratio, 0.77; P = .026). These results did not meet the prespecified statistical significance threshold, generating some controversy regarding the role of everolimus in NETs associated with carcinoid syndrome (primarily of midgut origin). No trend toward improved OS with everolimus was observed in this study.[128]

The phase 3 RADIANT-3 trial[105] randomized 410 patients with low-grade to intermediate-grade pNETs to receive everolimus 10 mg daily versus placebo. The median PFS increased from 4.6 months on the placebo arm to 11 months in the everolimus arm (hazard ratio, 0.35; P <.001). A nonsignificant trend toward an improvement in OS with everolimus was noted.[129] On the basis of the results of the RADIANT-3 trial, everolimus was approved for patients with advanced pNETs. More recently, the double-blind, phase 3 RADIANT-4 study[112] compared everolimus versus placebo in 302 patients with advanced, progressive, well-differentiated, nonfunctioning NETs of lung and gastrointestinal origin. The median PFS improved from 3.9 months on the placebo arm to 11 months on the everolimus arm (hazard ratio, 0.48; P = .00001). On this basis, everolimus also was approved in nonfunctioning lung and gastrointestinal NETs. Side effects of everolimus include hyperglycemia, cytopenias, oral ulcers, rash, diarrhea, and atypical infections. Because of its risk/benefit profile, everolimus should be reserved for patients with clinically significant disease progression. Objective response rates associated with this drug are less than 10%.

Antiangiogenic agents

The oral tyrosine kinase inhibitor sunitinib targets PDGF receptor and subtypes 1, 2, and 3 of the VEGF receptor. A double-blind, placebo-controlled, phase 3 study[106] investigated sunitinib 37.5 mg daily in 171 patients who had with low-grade to intermediate-grade, progressive pNETs. The trial demonstrated a statistically significant improvement in median PFS from 5.5 months on the placebo arm to 11.1 months on the sunitinib arm (hazard ratio, 0.42; P <.001). Sunitinib caused a nonsignificant OS improvement of approximately 10 months compared with placebo.[130] Sunitinib is approved for patients with advanced progressive pNETs. Objective response rates associated with the drug are usually less than 10%. Toxicities include nausea, diarrhea, fatigue, cytopenia, hypertension, and palmar-plantar erythrodysesthesia. Currently, there are no phase 3 studies demonstrating benefit with a VEGF-inhibiting drug in nonpancreatic NETs.

Bevacizumab is a monoclonal antibody against VEGF. Although preliminary evidence suggested the antitumor activity of the drug,[131] no benefit in PFS was recorded in a recent phase 3 trial sponsored by the Southwest Oncology Group that compared bevacizumab plus octreotide versus interferon (IFN) plus octreotide in 427 patients who had high-risk carcinoid tumors.[110]

Interferons

Several randomized studies[132–135] have investigated the antiproliferative activity of IFN in combination with either octreotide or lanreotide, and failed to demonstrate a clear

advantage of the combination therapy compared with SSA monotherapy. However, such studies were not adequately powered to evaluate the impact of IFN on survival and enrolled heterogeneous patient populations. Because of a narrow toxicity/benefit ratio, the use of IFN in patients with GEP-NETs is currently limited.

Chemotherapy

Cytotoxic agents are the cornerstone of therapy for patients with poorly differentiated GEP-NECs. Several small studies of platinum and etoposide in poorly differentiated gastrointestinal NECs have demonstrated objective response rates ranging from 42% to 67%.[135,136] Carboplatin has shown equivalent efficacy and lower toxicity compared with cisplatin in a large retrospective study.[137] Responses to platinum-based regimens are rapid in patients with NECs, but remissions are usually short-lived. There are few known, effective second-line therapies for GEP-NECs. Both FOLFIRI (folinic acid, 5-fluorouracil [5-FU], and irinotecan) and FOLFIRINOX (FOLFIRI plus oxaliplatin) have recently demonstrated some activity in patients who progress on platinum-containing regimens.[138,139]

Among well-differentiated tumors, pNETs appear to be particularly sensitive to streptozocin or temozolomide, typically combined with fluoropyrimidines such as 5-FU or capecitabine. In a retrospective study investigating the combination of streptozocin, 5-FU, and doxorubicin in 84 patients with pNETs, a response rate of 39% was reported.[140] Temozolomide has shown antitumor activity in pNETs either as monotherapy or in combination with capecitabine or bevacizumab. Overall, temozolomide-based studies have demonstrated objective response rates ranging from 33% to 70%, with the highest response rates reported in studies that combined temozolomide with capecitabine.[141–145] Recently, an Eastern Cooperative Oncology Group-sponsored, prospective, randomized, phase 2 trial[107] investigated temozolomide alone versus temozolomide plus capecitabine in 144 patients with progressive G1/G2 pNETs. The combination of temozolomide and capecitabine was associated with a significantly improved PFS (median PFS, 14.4 months in the temozolomide arm vs 22.7 months in the temozolomide/capecitabine arm; hazard ratio, 0.58 [P = .023]) and OS (median OS, 38 months in the temozolomide arm vs not reached in the temozolomide/capecitabine arm; hazard ratio, 0.41 [P = .012]). It is currently unclear whether expression of the DNA repair enzyme methyl-guanine-methyltransferase may predict response to temozolomide-based regimens.[142,145–147]

Locoregional treatments

Liver-directed therapies are designed to palliate or prevent symptoms related to tumor growth or hormonal secretion. Locoregional treatments include cytoreductive liver surgery in patients with resectable disease, liver embolization in patients with unresectable tumors, and liver transplantation in highly selected patients with unresectable disease confined to the liver. So far, most studies of liver-directed therapies have been retrospective, and no randomized trials have confirmed the benefit of locoregional treatments.

Cytoreductive surgery is often recommended if at least 90% of liver tumors can be resected.[148,149] Various ablative procedures, including alcohol ablation, cryoablation, and radiofrequency ablation, also are performed commonly, either intraoperatively or percutaneously.[150,151] Long-term survival durations seem to favor debulking surgery versus other locoregional treatments, although the extent to which the outcomes are related to patient selection rather than the surgical intervention is uncertain. Hepatic transarterial embolization is typically performed in patients with progressive unresectable liver metastases, and various occlusive or particulate materials have been used in clinical practice. The rationale for embolization is that liver metastases primarily are vascularized from the hepatic arterial circulation, whereas normal liver parenchyma is supplied primarily from the portal vein. Two or 3 staged lobal embolizations are often necessary to treat the entire liver. Postembolization syndrome consists of abdominal pain, nausea, fatigue, and fever.[152,153] Transarterial chemoembolization is performed by infusing an emulsion of cytotoxic drugs, such as cisplatin or doxorubicin, with lipiodol. Institutional series report objective response rates averaging approximately 50% and symptomatic response rates of approximately 75%.[151] There is no clear indication regarding when to prefer chemoembolization rather than bland embolization. An ongoing, 3-arm, randomized clinical trial is comparing bland embolization, chemoembolization, and drug-eluting beads. Radioembolization is a form of liver-directed treatment that delivers ^{90}Y beads embedded in either a glass microsphere or a resin microsphere intra-arterially. Response rates appear comparable to those achieved with bland embolization or chemoembolization. Long-term hepatic dysfunction is increasingly recognized as a late complication of radioembolization.[154–156] Liver transplantation is performed rarely in highly select patients with liver-only disease. A nonrandomized study investigated liver transplantation versus no transplantation in 88 patients who met strict criteria of transplant eligibility. A significant survival benefit was reported in the transplantation group, with a 10-year OS rate of 51% in the transplantation arm versus 22% in the nontransplantation group (P = .001).[157]

Selection and Sequencing of Treatments

Data to guide the selection of treatment after progression of disease on SSAs are scarce, because nearly all randomized studies have compared investigational drugs versus

placebo or other interventions of uncertain benefit (ie, high-dose octreotide). For metastatic midgut NETs, ^{177}Lu-DOTATATE treatment is associated with the highest level of evidence for patients with progressing, SSTR-expressive tumors. Liver embolization also appears to be highly active in patients with liver-dominant disease, although the level of evidence supporting embolization is substantially lower. The benefit of everolimus among patients with typical midgut NETs and carcinoid syndrome is uncertain because of equivocal results from the RADIANT-2 study. Telotristat is appropriate for patients who have refractory diarrhea associated with carcinoid syndrome.

Patients with metastatic pNETs have a larger number of treatment options. First-line SSAs are generally used for patients with SSTR-positive disease. Beyond that, both everolimus and sunitinib are approved for the treatment of progressive disease based on results from phase 3 studies demonstrating an improvement in PFS over placebo (median PFS, approximately 11 months with both drugs). However, capecitabine/temozolomide treatment also can be considered a standard of care based on results from a randomized phase 2 study demonstrating high response rates, exceptionally prolonged PFS (approximately 23 months), and favorable OS results. ^{177}Lu-DOTATATE treatment also has been associated with high response rates and long median durations of PFS in large institutional series. Ultimately, randomized studies comparing active drugs are needed to provide additional data on the appropriate sequencing of treatments.

Conclusions

Our understanding of the biology of GEP-NETs has improved substantially in the last decade. Consequently, the treatment landscape has expanded considerably. Multiple phase 3 trials have led to the approval of new treatments for either symptom or tumor control. The challenges of the next decade will include defining the most appropriate treatment algorithm, the individualization of treatment based on clinical and/or biologic features, and the evaluation of innovative therapies, including immunotherapy. ■

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