Management of Well-Differentiated Neuroendocrine Tumors

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Abstract: Neuroendocrine tumors (NETs) are a heterogeneous group of epithelial neoplasms with predominantly neural and endocrine differentiation that have the ability to produce peptide hormones and other biologically active substances. The histologic characterization of NETs based on differentiation and grading is crucial to determining prognosis and treatment. Surgery still offers the best chance of cure for patients with NETs, and tumor resection is the preferred approach when possible. For locally advanced or metastatic disease, approaches to treatment can vary widely depending on the extent of disease and goals of therapy. A better understanding of the biology of NETs acquired over the last decade has facilitated the development of targeted therapies, such as everolimus and a variety of tyrosine kinase inhibitors. Furthermore, the field of theranostics has led to dramatic improvements in our diagnostic and treatment abilities. Chemotherapy has a role in the treatment of NETs, evidenced by the benefit shown with the combination of temozolomide and capecitabine to treat pancreatic NETs. Somatostatin analogues are a mainstay of treatment because they reduce secretory products and have antiproliferative effects on NET cells. In this work, we aim to review the landscape for the diagnosis and treatment of well-differentiated NETs.

Keywords
Carcinoid syndrome, everolimus, neuroendocrine tumors, octreotide, somatostatin, sunitinib

Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of epithelial neoplasms with predominantly neural and endocrine differentiation that have the ability to produce peptide hormones and other biologically active substances, such as serotonin.[1] Because they originate from neuroendocrine cells that are diffusely spread in the human body, NETs can arise in various locations and are broadly classified according to their site of origin, such as bronchial (pulmonary) and gastrointestinal NETs. Gastrointestinal NETs can also be categorized as foregut, midgut, and hindgut tumors according to the embryologic derivation of the organ where they originated. Although this embryologic classification is simple and seemingly

Table 1. Organ-Specific Immunohistochemistry Markers for Neuroendocrine Tumors

Organ	Positive IHC Markers[a]	Negative IHC Markers[a]
Lung	TTF-1, OTP	CDX2, ISL-1
Pancreas	PR, PDX-1, PAX 6, NESP55	ATRX, DAXX (loss of expression)
Midgut	CDX2, PrAP	ISL-1, TTF-1
Duodenal	PR, PDX-1, PAX 6/8	NESP55
Rectal	PrAP, SATB2	PDX-1

[a] IHC markers can aid in determining the tissue of origin; however, they should not be relied upon exclusively because inconsistencies may exist. The results should be interpreted in the context of the clinical presentation and imaging findings.

ATRX, alpha-thalassemia/mental retardation syndrome X-linked; CDX2, caudal type homeobox 2; DAXX, death domain–associated protein; IHC, immunohistochemistry; ISL-1, islet 1; NESP55, neuroendocrine secretory protein 55; OTP, orthopedia homeobox protein; PAX 6/8, paired box genes 6/8; PDX-1, pancreatic and duodenal homeobox 1; PR, progesterone receptor; PrAP, prostatic acid phosphatase; SATB1, special AT-rich sequence binding protein 1; TTF-1, thyroid transcription factor 1.

practical, it does not account for the genomic and clinical differences seen across tumor types within the same group. In addition, rare neoplasms, such as Merkel cell carcinoma of skin, are grouped under neuroendocrine neoplasms. Given the widespread nature of NETs, it is important to differentiate them from other endocrine tumors, such as paragangliomas and pheochromocytomas. Although NETs and paragangliomas/pheochromocytomas stain with synaptophysin and chromogranin, the presence of epithelial markers such as cytokeratin (AE1, AE3, cytokeratin 18, and CAM 5.2) favors a diagnosis of NETs.[2-4] In addition to the "generic" neuroendocrine markers, organ-specific markers can facilitate predicting the location of the primary NET. The presence of one of the markers is sufficiently specific as a standalone test for a primary tumor location, however, and the results should be interpreted in the context of the clinical presentation and findings on imaging.[2] Table 1 summarizes the organ-specific immunohistochemistry markers for NETs. Apart from the organ-specific classification, NETs are grouped in 3 grades based on the Ki67 proliferative index and mitotic rate, which have prognostic and treatment implications (Table 2).[5,6] It is critical to have an accurate histologic characterization of NETs, which are by definition well-differentiated tumors. Conversely, poorly differentiated tumors are classified as neuroendocrine carcinomas (NECs), which can have a dramatically different prognosis and entail a different approach to treatment. It is of crucial importance to understand that although the grade and degree of differentiation correlate closely with each other, they are not synonymous, and both variables should always be reported. All poorly differentiated NECs are grade 3, but not all grade 3 NETs are poorly differentiated.

A better understanding of the tumor biology of NETs, acquired over the last decade, has facilitated the development of targeted therapies, such as everolimus (Afinitor, Novartis), and a variety of tyrosine kinase inhibitors (eg sunitinib [Sutent, Pfizer], pazopanib [Votrient, Novartis], cabozantinib [Cabometyx, Exelixis], lenvatinib [Lenvima, Eisai], and surufatinib). Herein, we seek to summarize the pathophysiology and management of well-differentiated NETs. Moreover, we detail the ongoing clinical trials and their potential role in enlarging the treatment armamentarium for well-differentiated NETs.

Tumorigenesis, Molecular Pathogenesis, and Pathologic Characteristics of Well-Differentiated NETs

NETs are highly heterogeneous tumors despite being classified together under the single umbrella of "NETs." Tumorigenesis and molecular pathogenesis are highly variable and depend on the tumor location. For instance, mutations of chromatin remodeling genes (*MEN1*, *DAXX*, and *ATRX*) are common in pancreatic NETs and correlate with the prognosis.[7,8] As an example, in a study of predominantly localized pancreatic NETs, the presence of mutations in *MEN1*, *DAXX*, or *ATRX* was associated with a worse prognosis.[9] The association with prognosis may in part depend on the stage of the disease. In addition, histone methyltransferases and mammalian target of rapamycin (mTOR) pathways (*PTEN, TSC2*) are also commonly implicated in pancreatic NETs.[7,10] However, in small-bowel NETs, although mTOR pathway alterations occur in approximately one-third of tumors, epigenetic phenomena have more often been implicated in tumorigenesis.[11] Whole-genome and next-generation sequencing studies involving small-bowel NETs have implicated gain of function in chromosomes 4, 5, and 14; loss of chromosome 18; and inactivation of *CDKN1/APC*.[11] Although pancreatic NETs are hereditary in a minority of patients and associated with certain germline mutations and syndromic associations, small-bowel NETs are mostly

Table 2. WHO Classification of Well-Differentiated Neuroendocrine Tumors

NET Type	Ki67 Index[a]	Mitotic Rate
Pancreatic (2017 WHO Classification)		
Grade 1	<3%	<2/10 HPF
Grade 2	3%-20%	2-20/10 HPF
Grade 3	>20%	>20/10 HPF
Gastroenteropancreatic (2019 WHO Classification)		
Grade 1	<3%	<2/10 HPF
Grade 2	3%-20%	2-20/10 HPF
Grade 3	>20%	>20/10 HPF
Lung (2015 WHO Classification)		
NET Type	**Necrosis**	**Mitotic Rate**
Typical carcinoid	Absent	0-1/10 HPF
Atypical carcinoid	Focal/punctate	2-10/HPF

[a] The Ki67 proliferative index is not used in the current WHO classification of lung neuroendocrine tumors.

HPF, high-power field; NET, neuroendocrine tumor; WHO, World Health Organization.

sporadic.[12] The tumorigenesis of NETs has recently been discussed extensively in a detailed review by Mafficini and colleagues.[11]

Management of Well-Differentiated NETs

NETs can be classified as functional (<25% of all NETs) or nonfunctional.[13] Given the ability of the tumors to cause hormonal symptoms such as flushing and diarrhea (ie, carcinoid syndrome), management of the symptoms of functional syndromes is an important component of the treatment of well-differentiated NETs. The therapeutic plan, therefore, should focus on controlling both tumor growth and the symptoms of functional tumors. A broad overview of the therapeutic agents used in small-intestinal, pancreatic, and bronchial well-differentiated NETs is provided in Table 3.

Management of Locoregional Disease

Overall, regardless of the site of origin, curative resection is generally recommended whenever possible, although some exceptions exist in which observation can be considered. Currently, adjuvant therapy has no role in the management of well-differentiated NETs.

Bronchial/Pulmonary. Surgical resection with curative intent is the preferred approach for stages I through III NETs when possible.[14] Locoregional bronchial and thymic NETs can potentially be cured by surgical resection alone, with a 5-year survival rate as high as 97% (typical carcinoids) seen in a national series.[15] The type of surgery can range from segmentectomy to pneumonectomy with lymph node dissection, depending on the location and extent of disease.[16] The survival of patients with atypical carcinoids and a higher T stage is inferior to that of patients with typical carcinoids and smaller primary tumors.[17]

Gastroduodenal. Gastric NETs are broadly classified into 3 types, with a fourth type considered provisional.[18] Type 1 gastric NETs are associated with gastric achlorhydria and are the most benign type, constituting 70% to 80% of all gastric NETs. Type 2 gastric NETs occur as a part of multiple endocrine neoplasia (MEN) 1 syndrome–associated pancreatic or duodenal gastrinomas (Zollinger-Ellison syndrome). Type 3 gastric NETs are sporadic tumors that occur in the absence of gastric achlorhydria or Zollinger-Ellison syndrome and may constitute up to 20% of all gastric NETs. Most patients (65%) have local or hepatic metastases at the time of presentation.[19]

Surgical resection of gastric NETs is individualized according to the type and functional status of the tumor.[18] Active surveillance is a reasonable option in subcentimeter type 1 gastric NETs. Endoscopic surgical resection of NETs is considered for tumors beyond 1 cm, given the increased risk for metastases. In contrast, types 3 and 4 gastric NETs are managed by partial or complete gastrectomy coupled with lymphadenectomy owing to the high risk for early metastases.[19] Endoscopic surgical resection is a reasonable option in subcentimeter duodenal NETs, whereas larger tumors are better managed with duodenectomy.

Pancreatic. About 40% of patients who have pancreatic NETs present with locoregional disease.[20,21] Surgical

Table 3. Systemic Treatment Options for Advanced, Well-Differentiated Neuroendocrine Tumors

Pancreatic NETs	Gastrointestinal NETs	Lung NETs (Typical Carcinoid)
Somatostatin analogues (lanreotide, octreotide)	Somatostatin analogues (lanreotide, octreotide)	Somatostatin analogues[b,c] (lanreotide, octreotide)
Everolimus	Everolimus	Everolimus
Sunitinib	^{177}Lu-DOTATATE[a]	^{177}Lu-DOTATATE[a,b]
Surufatinib (in China only)	Pazopanib[b]	
Lenvatinib[b]	Lenvatinib[b]	
Cabozantinib[b]	Surufatinib (in China only)	
Chemotherapy: temozolomide, capecitabine, streptozocin, 5-FU, platinum agents	FOLFOX	Temozolomide and capecitabine[b]
^{177}Lu-DOTATATE[a]		

[a] Based on prospective and retrospective series; randomized phase 3 data are lacking in bronchial and pancreatic NETs.

[b] Off-label use.

[c] If somatostatin receptor imaging result is positive.

5-FU, 5-fluorouracil; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; NETs, neuroendocrine tumors.

resection of pancreatic NETs remains the mainstay of therapy, especially for grade 2 (Ki67 ≥3%) tumors, symptomatic or functioning tumors, and tumors measuring at least 2 cm.[22] Enucleation may be an option for small, localized pancreatic NETs.[23] For patients with larger tumors in whom lymph node metastasis is strongly suspected, a more involved surgery (ie, Whipple procedure, distal pancreatectomy) is the preferred approach.[24] A determination of the optimal surgical approach for nonfunctional, low-grade pancreatic NETs smaller than 2 cm requires a risk-benefit assessment and an informed discussion with the patient, as the risk for metastases is low.[25] Surgical resection of the primary disease and disease debulking (eg, liver debulking), along with systemic therapy, may play a role in the management of symptomatic and functional pancreatic NETs.

Small and Large Bowel. Although surgical resection is the cornerstone of treatment for midgut NETs, the type of surgical resection depends on the location of the disease. For instance, jejunal and proximal ileal tumors are managed by partial bowel resection, whereas hemicolectomy is a preferred approach for distal ileal and ileocecal valve tumors. It is important to note that the entire small bowel should be palpated at the time of surgical exploration, given that the disease is multifocal in up to 50% of cases. The prognosis of patients with multifocal small-bowel NETs is similar to that of patients with unifocal NETs.[26,27] Resection of the primary tumor is a reasonable option in stage IV disease, especially in symptomatic patients (pain due to venous ischemia, or obstruction due to a desmoplastic reaction from such problems as mesenteric metastases, perforation, and hemorrhage), but the effect of primary tumor resection on survival remains unclear.[28-30]

In patients with appendiceal NETs, appendectomy is preferred when tumors are smaller than 1 cm, whereas right hemicolectomy may be considered when tumors are larger than 2 cm. The survival benefit with right hemicolectomy is debated, and the procedure can lead to substantial adverse effects on quality of life. Alternatively, patients can be followed carefully with imaging, with subsequent hemicolectomy undertaken if concerns arise about progression or recurrence.[31,32] For patients with tumors between 1 and 2 cm, hemicolectomy can be considered if invasion to the mesoappendix is present or if the tumor is located at the base of the appendix.[32] Endoscopic tumor resection can be tried for colorectal NETs smaller than 2 cm, whereas in the case of larger rectal NETs, better results are obtained when abdominoperineal resection is coupled with lymph node sampling. For larger colonic NETs, partial colectomy is preferred.

Management of Neuroendocrine Liver Metastases

The liver is the most common site of distant NET metastases, and hepatic metastases are the major predictor of survival in this disease. Notably, 80% to 90% of small-bowel NETs and 60% to 70% of pancreatic NETs eventually metastasize to the liver.[33] Additionally, imaging studies may not detect all hepatic metastases, given the possibility of NET micrometastases.[34,35] In the presence of oligometastatic disease, surgical resection of the primary tumor along with neuroendocrine liver metastases (NELMs), when feasible, has been shown to be associated with prolonged progression-free survival (PFS).[36,37] Segmental resection, radiofrequency ablation, and

transarterial procedures such as transarterial chemoembolization (TACE) and transarterial radioembolization (TARE) are reasonable alternatives, with variable success in terms of providing durable disease control. In patients with liver-only metastatic disease, liver transplant may be a reasonable option, with a 5-year overall survival (OS) rate of 63%.[38,39] However, it is important to note that transplant should be considered only for a carefully selected patient population.[40]

Management of Hormonal Symptoms of Functional NETs

Carcinoid Syndrome. Advanced midgut NETs are known to produce vasoactive substances such as serotonin, prostaglandins, kallikrein, substance P, etc. These vasoactive agents are thought to be metabolized in the liver. However, in the presence of hepatic, nodal, or bone NET metastases, these agents are released directly into the systemic circulation, bypassing hepatic degradation and ultimately causing carcinoid syndrome. Although predominantly midgut NETs are implicated in carcinoid syndrome, thymic, bronchial, and pancreatic NETs (rarely) are also known to cause carcinoid syndrome. The exact prevalence of carcinoid syndrome is unknown, but studies have suggested that 20% to 30% of patients with NETs may have a functional syndrome.[13] Diarrhea and flushing are the most common manifestations of carcinoid syndrome; bronchospasm is seen less frequently.[41] Although diarrhea is attributable to serotonin, which stimulates serotonin 2A receptors, flushing is thought to be triggered by bradykinin, histamine, substance P, and other substances. It is important to note that chronic diarrhea in patients with NETs can be multifactorial, possibly stemming from exocrine pancreatic insufficiency, short-bowel syndrome, bacterial overgrowth, and bile acid malabsorption (secondary to bowel surgery).[42] It is important to note that exocrine pancreatic insufficiency develops in the majority of patients on somatostatin analogues (SSAs). Therefore, clinicians are encouraged to obtain an appropriate evaluation and manage accordingly with pancreatic enzyme replacement, antibiotics, and/or cholestyramine.

SSAs, such as octreotide and lanreotide (Somatuline Depot, Ipsen Biopharmaceuticals), are very effective in managing the symptoms of carcinoid syndrome, with an overall response rate (ORR) of 64% to 75%.[43,44] For patients with worsening carcinoid syndrome, clinicians may consider increasing the frequency (the CLARINET FORTE trial showed improvements in PFS and the disease control rate with administration of lanreotide autogel at 120 mg every 14 days in patients with midgut NETs or pancreatic NETs that had progressed on lanreotide at 120 mg every 28 days) and/or the dose of long-acting SSAs, or adding breakthrough short-acting SSAs.[45] In patients with refractory diarrhea, telotristat (Xermelo, TerSera Therapeutics), a tryptophan hydroxylase inhibitor, may be indicated.[46-48] In a phase 3 trial that included patients with diarrhea refractory to SSA treatment, telotristat at the US Food and Drug Administration (FDA)–approved dose of 250 mg decreased stool frequency by 1.7 (from a baseline of $\geq$4).[46] Lastly, peptide receptor radionuclide therapy (PPRT) was recently shown to be effective in controlling the symptoms of patients with carcinoid syndrome, even in the absence of radiographic tumor progression.[49]

Carcinoid heart disease, which is seen in up to 50% of patients with carcinoid syndrome, affects predominantly the right-sided heart valves. Typical clinical findings are those of right-sided heart failure: lower extremity edema, cardiac murmurs (often both systolic and diastolic), jugular venous distention, palpable hepatomegaly, and exertional dyspnea.[50] All patients with carcinoid syndrome, as well as patients with evidence of serotonin overproduction (manifested by elevated 5-hydroxyindoleacetic acid in a fasting plasma sample or 24-hour urine collection), should be screened with echocardiography, with particular attention paid to the right-sided heart valves.[51] Although many patients may be managed medically, some will need cardiac valve replacement.

Carcinoid crisis is a very rare perioperative or stress-associated endocrine emergency that is manifested by circulatory collapse triggered by an acute release of NET-associated vasoactive amines into systemic circulation. Common triggers for carcinoid crisis are catecholamines, anesthetic agents, physical stress, infections, and manipulation of tumors. The management of carcinoid crisis may require a combination of SSAs, often in high doses, as well as intravenous fluids and vasopressors if needed.[52]

Other NET-Associated Hormonal Syndromes. Other possible hormonal syndromes caused by NETs include insulinoma, gastrinoma (also known as Zollinger-Ellison syndrome), VIPoma (also known as Verner-Morrison syndrome), somatostatinoma, and glucagonoma.

Insulinoma. Insulinomas are rare functional pancreatic NETs, with a worldwide annual incidence of 1 to 4.0 per 100,000. The majority of insulinomas (>90%) are benign, and they can be sporadic or occur as a part MEN 1 syndrome. Prevention of hypoglycemia is the primary goal in the management of insulinoma, which can be achieved by debulking the primary tumor and metastatic disease via surgery and/or liver-directed therapies (ie, bland embolization). Consultation with a dietitian can be beneficial in

terms of counseling patients regarding appropriate dietary interventions. In addition, patient education about the signs and symptoms of hypoglycemia and vigilant monitoring of blood glucose are critical for decreasing serious hypoglycemic events.

Diazoxide is known to decrease insulin secretion by activating potassium channels in pancreatic islet cells.[53] The drug has achieved the desired benefit of decreasing hypoglycemic events in approximately 50% to 59% of patients with insulinomas.[54,55] Clinicians should monitor for side effects such as thrombocytopenia, hirsutism, and fluid overload. The drug is available as oral suspension at a concentration of 50 mg/mL. The typical dose is 3 to 8 mg/kg in 3 divided doses, depending on the frequency of hypoglycemic episodes and the side effect profile.

SSAs historically have been used in the management of hypoglycemic events in insulinoma, with ORRs ranging from 58% to 67%.[56] It is important to point out that SSAs can also limit the secretion of counter-regulatory hormones such as glucagon, so that exacerbating hypoglycemia with the initiation of SSAs is a possibility.[57] Therefore, it is advisable to start with short-acting SSAs while the patient is under close supervision, preferably in a hospital. Patients who have been shown to derive clinical benefit from short-acting agents can eventually be transitioned to long-acting formulations. Among the available SSAs, pasireotide (Signifor, Recordati) has theoretical advantages over other agents, such as octreotide and lanreotide (Somatuline Depot, Ipsen Pharma), which have translated into practical success in various reports.[58-60] Both in vitro and in vivo studies have demonstrated that insulin secretion in insulinomas is mediated primarily through somatostatin receptors 2 and 5.[61,62] Interestingly, compared with the first-generation SSA octreotide, pasireotide has a higher (30- to 40-fold) binding affinity for somatostatin 5 receptors, theoretically making it a better drug than first-generation SSAs. However, the practical utility of pasireotide in the management of metastatic insulinomas is yet to be determined.[63,64] Everolimus has been shown to be helpful in controlling the hypoglycemia of insulinoma and may provide tumor control as well.[65] In addition to SSAs, PRRT appears to have substantial activity against hypoglycemia in patients with malignant insulinoma, and its use is increasing.[66]

Gastrinoma. Gastrinomas are gastrin-secreting NETs that commonly occur in the "gastric triangle" formed by the junction of the cystic duct and common bile duct, the junction of the second and third parts of the duodenum, and the junction of the body and neck of the pancreas. Approximately 50% of gastrinomas are malignant, with lymph nodes the most common sites of metastasis, and approximately 25% of gastrinomas occur as a part of MEN 1 syndrome. The twice-daily administration of high doses of proton pump inhibitors (40-120 mg) is typically needed to control symptoms of acid reflux in patients with a gastrinoma. Second-generation antihistamines can be added in refractory cases. Surgical resection of the culprit tumor is a definitive therapy and often very successful.[67] Systemic (ie, SSAs) and/or local (ie, liver-directed) therapies are reserved for patients with disease deemed not to be amenable to surgical interventions.[68] Lastly, as in the treatment of insulinoma, PRRT appears to be a valuable tool in the treatment of symptomatic gastrinoma.[66]

VIPoma and Somatostatinoma. Patients with Verner-Morrison syndrome typically require hospital admission for aggressive hydration and electrolyte support. SSAs, surgical resection of the culprit tumor, or antiproliferative therapy should be initiated in the appropriate clinical context for the definitive management of VIPoma, gastrinoma, and somatostatinoma syndromes.[69]

Management of Advanced NETs

Decisions regarding the timing and type of systemic treatment for advanced NETs depend on multiple factors related to the symptoms (from hormonal secretion or bulky disease), pace of disease progression (depending on the grade), and disease location.

Active Surveillance. Watchful waiting, or active surveillance, may be used in selected patients with low-grade (ie, grade 1 or 2) tumors and a low tumor burden. The European Neuroendocrine Tumor Society (ENETS) Consensus Guidelines Update published in 2016 endorsed consideration of active surveillance for grade 1 and low-Ki67 grade 2 pancreatic NETs smaller than 2 cm.[70,71] Active surveillance may be done with endoscopic ultrasonography, computed tomography, or magnetic resonance imaging. According to the ENETS Guidelines, active surveillance can be considered for asymptomatic patients who have nonfunctional, stable, low-grade midgut tumors with a Ki67 index no higher than 10%.[72]

Somatostatin Analogues. The role of SSAs in tumors with a Ki67 index below 10% has been evaluated in 2 seminal phase 3 trials.[73,74] The PROMID study compared the benefit of octreotide long-acting release (LAR) at 30 mg with that of placebo in grade 1 inoperable or metastatic midgut NETs.[73] Octreotide LAR resulted in a PFS benefit (14.3 vs 6 months), along with an ORR of 2%. The study did not, however, show an overall survival (OS) benefit, likely because the patients on placebo eventually received octreotide at the time of disease progression. In another multicenter, international phase 3 trial (CLARINET), lanreotide administered monthly at 120 mg was

compared with placebo in nonfunctional, somatostatin receptor–positive gastroenteropancreatic (GEP) NETs with a Ki67 index below 10%.[74] Notably, most of the patients in the study cohort (69%) had grade 1 disease. Although no OS benefit was noted with lanreotide, the drug resulted in a statistically and clinically significant PFS benefit (33 vs 18 months). Patients randomly assigned to the placebo cohort could switch to lanreotide upon progression. Interestingly, the PFS attained with active surveillance and a switch to lanreotide upon progression resulted in a PFS benefit similar to that achieved with the early start of lanreotide. This finding supports the idea of watchful waiting or active surveillance in selected patients with asymptomatic low-grade tumors.

Pasireotide, an SSA with broad activity against somatostatin receptors (1, 2, 3, and 5), also has shown enhanced antiproliferative activity in NET cells in preclinical studies, especially in bronchial NET cell lines.[63,75] The affinity of pasireotide for type 2 somatostatin receptors is 2.5-fold lower than that of octreotide, whereas its affinity for types 1, 3, and 5 receptors is 30-fold, 5-fold, and 40-fold higher, respectively, than that of octreotide. Notably, lung carcinoids are known to have lower levels of type 2 somatostatin receptors and higher levels of types 1 and 5, so that pasireotide is an attractive option for patients with lung carcinoids.

Peptide Receptor Radionuclide Therapy. PRRT exploits the expression of somatostatin receptors (namely type 2) on the surface of NET cells and delivers a radionuclide at the cellular level.[76] Radioactively labeled SSAs are composed of a radionuclide isotope such as yttrium 90 (^{90}Y) or lutetium 177 (^{177}Lu), a chelator (eg, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid [TATE]), and a peptide (eg, octreotide).

The landmark NETTER-1 trial was a phase 3 randomized trial of lutetium Lu 177 DOTATATE (Lutathera, Advanced Accelerator Applications) in patients with advanced, somatostatin receptor–positive midgut NETs that had progressed on a standard dose of octreotide LAR.[77] The radionuclide ^{177}Lu-DOTATATE was administered every 8 weeks for a total of 4 cycles in combination with octreotide at 30 mg every 28 days; the control group received high-dose octreotide LAR at 60 mg every 28 days. The ^{177}Lu-DOTATATE cohort had a better ORR (18% vs 3%) that translated into a 79% reduction in risk for death (P<.0001). A strong trend toward improved OS was noted (P=.004), and the study showed a significant improvement in PFS with the use of ^{177}Lu-DOTATATE (28.5 vs 8.5 months; P<.0001). On the basis of these data, ^{177}Lu-DOTATATE was approved by the FDA in January 2018 for the treatment of locally advanced or metastatic grade 1 or 2 GEP NETs. Although ^{177}Lu-DOTATATE was approved for tumor control, it has also been shown to be of substantial value in relieving the symptoms of carcinoid syndrome in patients with advanced symptomatic disease.[49,78]

Although the FDA-approved use of ^{177}Lu-DOTATATE is for GEP NETs, the data have been extrapolated to other somatostatin receptor–positive gastrointestinal NETs and bronchial NETs.[79] A pooled analysis of 2 prospective and 6 retrospective analyses that evaluated the role of PRRT in pancreatic NETs demonstrated PFS values ranging from 20 to 39 months and OS values ranging from 37 to 79 months.[80] The wide range of PFS and OS values observed may be attributed to the heterogeneity of the studies involved in the pooled analysis. The ongoing NETTER-2 trial is designed to compare the benefits of ^{177}Lu-DOTATATE as a first-line therapy in combination with octreotide LAR at 30 mg with the benefits of octreotide LAR at 60 mg in patients who have advanced grade 2 or 3 GEP NETs (NCT03972488). Another trial (COMPETE) is enrolling patients to compare ^{177}Lu-edotreotide, also called ^{177}Lu-DOTATOC, with everolimus as a first-line therapy in GEP NETs (NCT03049189).

Newer approaches are being studied to help advance the field of PRRT. One of them is the use of α-particle radionuclides (ie, actinium Ac 225 DOTATOC and bismuth Bi 213 DOTATOC). Compared with β-particles, α-particles are characterized by a higher degree of linear energy transfer and the delivery of energy over a shorter range, thus limiting the exposure of surrounding tissue to radiation.[81] Given these properties, α-particle emitters are considered to be better DNA-damaging agents, with better tumoricidal activity. The role of targeted α-particle therapy is being investigated actively. Another area of great interest in NET theranostics is the use of somatostatin receptor antagonists in PRRT therapy. Compared with somatostatin agonists, somatostatin antagonists have been shown to bind more extensively to tumors with better retention time, thereby limiting the exposure of healthy tissues to radioactive pharmaceuticals.[82,83]

Targeted Therapy. NETs are highly vascular tumors, and vascular endothelial growth factor (VEGF) has been shown to be a key driver of angiogenesis.[84] In addition, pancreatic NETs are characterized by a relatively high expression of VEGF receptor (VEGFR) 2, VEGFR 3, platelet-derived growth factor receptor (PDGFR)-α, and PDGFR-β.[84] Given the activity of sunitinib (Sutent, Pfizer) on VEGFRs and PDGFRs, the drug was evaluated in pancreatic NETs. A randomized, placebo-controlled phase 3 trial that compared sunitinib at 37.5 mg daily with placebo in progressive, low- to intermediate-grade pancreatic NETs demonstrated a PFS benefit (11.1 vs 5.5

Table 4. Selected Key Clinical Trials of Antiproliferative Agents in Well-Differentiated Neuroendocrine Tumors

Study (Enrollment)	Inclusion Criteria	Therapies Evaluated	Median PFS Benefit, mo	ORR, %
Pancreatic NETs				
Raymond et al (n=171)[85]	Progressive pancreatic NETs	Sunitinib 37.5 mg vs placebo	Sunitinib: 11.4 Placebo: 5.5	Sunitinib: 9 Placebo: 0
RADIANT-3 (n=420)[98]	Progressive pancreatic NETs	Everolimus 10 mg vs placebo	Everolimus: 11 Placebo: 4.6	Everolimus: 5 Placebo: 2
ECOG E2211[105]	Progressive pancreatic NETs	Temozolomide vs CAPTEM	CAPTEM: 22.7 Temozolomide: 14.4	CAPTEM: 33 Temozolomide: 28
SANET-p (n=172)[89]	Progressive pancreatic NETs	Surufatinib 300 mg vs placebo	Surufatinib: 11 Placebo: 3.7	Surufatinib: 19 Placebo: 2
GETNE-1509 (n=55)[96]	Progressive pancreatic NETs	Lenvatinib 24 mg/d	Lenvatinib: 15.5	Lenvatinib: 42
Nonpancreatic NETs				
PROMID (n=84)[73]	Untreated midgut NETs	Octreotide LAR 30 mg (every 4 wk) vs placebo	Octreotide: 14.3 Placebo: 6	Octreotide: 2 Placebo: 2
CLARINET (n=204)[74]	Advanced, SSTR+ GEP NETs	lanreotide 120 mg (every 4 wk) vs placebo	Lanreotide: 38.5 Placebo: 18	Lanreotide: not reached
RADIANT-2 (n=429)[100]	Low- to intermediate-grade progressive carcinoids	Everolimus 10 mg vs placebo	Everolimus: 16.4 Placebo: 11.3	Everolimus: 2 Placebo: 2
RADIANT-4 (n=302)[99]	Progressive GI or bronchial NETs	Everolimus 10 mg vs placebo	Everolimus: 11 Placebo: 3.9	Everolimus: 2 Placebo: 1
NETTER-1 (n=230)[77]	Progressive SSTR+ midgut NETs	^{177}Lu-dotatate vs octreotide 60 mg	^{177}Lu-dotatate: 28.5 Placebo: 8.5	^{177}Lu-Dotatate: 18 Placebo: 3
SANET-ep (n=198)[90]	Progressive extrapancreatic NETs	Surufatinib 300 mg vs placebo	Surufatinib: 9.2 Placebo: 3.8	Surufatinib: 10 Placebo: 0
Alliance A021202 (n=171)[94]	Progressive extrapancreatic NETs (small-bowel primary: 67%)	Pazopanib 800 mg/d vs placebo	Pazopanib: 11.6 Placebo: 8.5	
AXINET trial-GETNE-1107 (n=256)[95]	Progressive extrapancreatic NETs	Octreotide LAR 30 mg every 4 wk + axitinib 5 mg twice a day vs octreotide LAR 30 mg every 4 wk + placebo	Axitinib: 17.2 Placebo: 12.3 (*P*=.17)	Axitinib: 17.5 Placebo: 3.8 (*P*=.0004)
GETNE-1509 (n=56)[96]	Progressive extrapancreatic NETs	Lenvatinib 24 mg/d	Lenvatinib: 15.4	Lenvatinib: 16

CAPTEM, capecitabine and temozolamide; GEP, gastroenteropancreatic; GI, gastrointestinal, LAR, long-acting release; mo, months; NETs, neuroendocrine tumors; ORR, overall response rate; PFS, progression-free survival; SSTR+, somatostatin receptor–positive; wk, wk.

months; *P*<.001).[85] The ORR was less than 10%, and a trend toward improved OS (not statistically significant) was noted. The drug was approved by the FDA for the use in progressive pancreatic NETs.

One of the possible acquired mechanisms of resistance to sunitinib is thought to be the accumulation of tumor-associated macrophages that can stimulate pro-angiogenic factors.[86] Surufatinib is a novel tyrosine kinase inhibitor targeting VEGFR 1, 2, and 3, fibroblast growth factor receptor (FGFR) 1, and macrophage colony stimulating factor receptor 1. Surufatinib has demonstrated encouraging results in phase 1, 2, and 3 trials (SANET-p and SANET-ep) in China, resulting in its approval in China.[87-89] In the phase 3 SANET-p trial, 172 patients with progressive, well-differentiated pancreatic NETs were randomly assigned to surufatinib at 300 mg once a day or to placebo.[89] The trial was discontinued prematurely, given the encouraging results of surufatinib vs placebo in terms of PFS benefit (10.9 vs 3.7 months; *P*=.001). Notably, 88% of the patients in

the surufatinib cohort had grade 2 disease, and most of them had extensive metastasis to the liver, lymph nodes, lungs, and bone. The most common side effects were hypertension (38%), proteinuria (10%), and hypertriglyceridemia (7%). Similar encouraging results indicating PFS benefit were demonstrated in a phase 3 trial that compared surufatinib at 300 mg daily with placebo in patients with advanced extrapancreatic NETs (9.2 vs 3.8 months; *P*<.0001).[90] Most of the patients (84%) had grade 2 disease with a Ki67 index above 3%. The primary tumors were widely distributed, located in the extrapancreatic gastrointestinal tract (47%), thymus and mediastinum (14%), bronchi (9%), and liver (7%). The population in the SANET-ep trial differed from the population of patients with extrapancreatic NETs typically seen at Western NET referral centers; a small minority of them had small-bowel primary tumors or functional tumors, and all of the patients in the study were relatively lightly pretreated compared with a Western population. The activity of surufatinib in a more heavily pretreated population of patients with NET needs to be studied further, but a small phase 2 trial in the United States suggests that the drug may be active in a more heavily pretreated population.[91]

Cabozantinib (Cabometyx, Exelixis), another oral tyrosine kinase inhibitor, targets the VEGFR, RET, AXL, and c-MET pathways.[92] Activation of c-MET has been implicated in pancreatic neuroendocrine tumorigenesis.[11] In addition, expression of c-MET was associated with shorter survival, making cabozantinib an attractive option. A phase 2 trial evaluated the role of cabozantinib in patients with progressive, advanced pancreatic (n=20) or extrapancreatic NETs (n=41).[93] Cabozantinib achieved a PFS of 21.8 months in pancreatic and 31.4 months in extrapancreatic NETs. The phase 2 data look promising, and the results of ongoing phase 3 trials are eagerly awaited, especially the Alliance A021602 (CABINET) trial (NCT03375320). Most recently, pazopanib (Votrient, Novartis; Alliance A021202), lenvatinib (Lenvima, Eisai; TALENT, GETNE1509), and axitinib (Inlyta, Pfizer; AXINET trial, GETNE-1107) have been evaluated in progressive extrapancreatic NETs. These trials have yielded encouraging results with pazopanib and lenvatinib (Table 4).[94-96] Lenvatinib also showed encouraging ORRs in pancreatic NETs.[96]

In addition to activation of the VEGFR and c-MET pathways, the mTOR signaling and insulin-like growth factor 1 pathways have been implicated in NET oncogenesis.[97] The mTOR inhibitor everolimus gained FDA approval for use in pancreatic (RADIANT-3) and extrapancreatic low- to intermediate-grade, nonfunctioning NETs (RADIANT-4) on the basis of the PFS benefit demonstrated in randomized, placebo-controlled phase 3 trials (Table 4).[98-100] Both trials demonstrated a PFS of 11 months, which was significantly longer than the 4 months seen with placebo (*P*<.001).

Role of Chemotherapy. Given the relatively indolent nature of low- to intermediate-grade, well-differentiated NETs, chemotherapy has been largely ineffective, especially for small-bowel NETs.[101,102] Moreover, most of the data for pancreatic NETs stem from retrospective analyses and small phase 2 trials. Nonetheless, chemotherapy has demonstrated encouraging results in intermediate- to high-grade, rapidly progressing or bulky pancreatic NETs, with response rates ranging from 30% to 70%.[103] Well-differentiated pancreatic NETs appear to be particularly responsive to streptozocin (Zanosar, Teva) or temozolomide, especially in combination with fluoropyrimidines. In a retrospective analysis involving 89 patients with pancreatic NETs, streptozocin in combination with doxorubicin and fluorouracil resulted in an ORR of 39%.[104] Similarly encouraging results were demonstrated with temozolomide, either alone or in combination with capecitabine.[103] The benefit of combination therapy with temozolomide and capecitabine (CAPTEM) was demonstrated in a prospective phase 2 trial in 144 patients with progressive grade 1 or 2 advanced pancreatic NETs.[105] Notably, in comparison with temozolomide monotherapy, the combination therapy resulted in benefit for both PFS (22.7 vs 14.4 months; *P*=.02) and OS (not reached vs 38 months; *P*=.01). Other cytotoxic regimens with activity in pancreatic NETs are streptozocin-based regimens, FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin), and CAPOX (capecitabine and oxaliplatin), which typically are used in later lines following CAPTEM.[106,107]

Sequencing Therapy in Advanced Disease. Table 4 summarizes the key randomized clinical trials in well-differentiated, advanced NETs. Surgical therapy remains the mainstay of treatment for disease amenable to resection. Liver-directed therapy (ie, ablation, yttrium 90) has a role in cytoreduction and/or hormonal control. In advanced disease, surgical resection of the primary tumor is reserved for patients with symptomatic disease, such as bowel obstruction, or with bulky disease that is causing compressive symptoms.

One of the key clinical challenges is identifying the right sequence of therapy for patients with advanced disease. One of the major limitations is that we lack concrete, data-driven evidence regarding the appropriate sequence of therapy with chemotherapy agents, targeted therapy, and PRRT. Depending on the patient's performance status and the overall clinical picture, active surveillance is a reasonable option for small (<2 cm), indolent (Ki67 index <3%), and localized pancreatic NETs. SSAs play

a prominent role in the management of grade 1 and grade 2 NETs, given their advantages regarding PFS and quality of life. In patients who have pancreatic NETs that are bulky and symptomatic, chemotherapy (ie, capecitabine and temozolomide) or PRRT may be a preferred option, given the higher response rates.[108] In contrast, noncytotoxic agents such as tyrosine kinase inhibitors (ie, sunitinib, pazopanib, cabozantinib) or everolimus may be favored in combination with or after SSAs when stabilization of disease (vs objective response) is needed. It is important to note that all the targeted therapy trials are placebo-controlled, so that concrete evidence of the superiority of one over the other is lacking. Thus, the choice of a specific targeted therapy should be individualized. In the United States, everolimus is the only targeted therapy approved for extrapancreatic NETs, and we can choose between sunitinib and everolimus for pancreatic NETs.

Conclusion

Over the last decade, dramatic progress has been made in expanding our knowledge of the key molecular pathways of NET tumorigenesis and developing therapies to target them. When managing patients with various NETs, the clinician must consider the uniqueness of each patient and the heterogeneity of the disease. The challenges for the next decade in the field of NET research include acquiring a better understanding of the tumorigenesis of various NETs, defining the mechanisms of resistance to various targeted therapies, identifying predictive biomarkers, defining the most appropriate treatment algorithm, and evaluating novel therapies.

Disclosures

Drs Tella, Starr, Kommalapati, and Sonbol declare no competing interests related to the work discussed. Dr Halfdanarson has served in an advisory board/consultancy role for Terumo, Lexicon, ScioScientific, and Curium (personal) and for Advanced Accelerator Applications, Novartis, and Ipsen Biopharmaceuticals (institutional). Dr Halfdanarson has received institutional research support from Advanced Accelerator Applications, Novartis, Thermo Fisher Scientific, Agios, Basilea, Turnstone Biologics, and ArQule. This work did not require/involve any funding or financial support.

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