Systemic Therapies for Advanced Pancreatic Neuroendocrine Tumors

Nitya Raj, MD*, Diane Reidy-Lagunes, MD, MS

INTRODUCTION

Well-differentiated neuroendocrine tumors (NETs) are an uncommon and heterogeneous group of neoplasms that arise throughout the body, most commonly in the lung and gastrointestinal tract. These tumors are subdivided into carcinoid tumors and pancreatic NETs (panNETs). Carcinoid tumors develop from the neuroendocrine

KEYWORDS

- Neuroendocrine tumors
- Pancreatic neuroendocrine tumors
- Carcinoid tumors
- Octreotide
- Lanreotide
- Sunitinib
- Everolimus

KEY POINTS

- Pancreatic neuroendocrine tumors (NETs) are genetically and clinically different than extrapancreatic NETs (ie, carcinoid tumors) and often respond to cytotoxic and targeted treatments.
- Asymptomatic patients with low-volume advanced pancreatic NETs often have indolent disease, and some can be followed expectantly. Careful evaluation of each individual patient with an initial interval of observation and assessment can help define who needs treatment sooner.
- Somatostatin analogues (octreotide and lanreotide) can decrease hormone production in functional tumors and can control neuroendocrine tumor growth; given their favorable toxicity profile, they are generally used as first-line treatment in unresectable patients.
- Sunitinib and everolimus are 2 targeted therapies approved for progressive pancreatic NETs and are generally reserved for use in tumors that have progressed on somatostatin analogue therapy.
- Pancreatic NETs can respond to cytotoxic chemotherapy; the most commonly used agents include alkylating, fluorouracil, and platinum drugs.

INTRODUCTION

Well-differentiated neuroendocrine tumors (NETs) are an uncommon and heterogeneous group of neoplasms that arise throughout the body, most commonly in the lung and gastrointestinal tract. These tumors are subdivided into carcinoid tumors and pancreatic NETs (panNETs). Carcinoid tumors develop from the neuroendocrine

Disclosure Statement: Dr D. Reidy-Lagunes is on the advisory board for Novartis, Pfizer, and Ipsen. In addition, Dr D. Reidy-Lagunes does both research and consulting for Novartis. Dr N. Raj has nothing to disclose.

Gastrointestinal Oncology Service, Division of Solid Tumor Oncology, Department of Medicine, Memorial Sloan Kettering Cancer Center, 300 East 66th Street, 1039, New York, NY 10065, USA

* Corresponding author.
E-mail address: rajn@mskcc.org

Hematol Oncol Clin N Am 30 (2016) 119–133
http://dx.doi.org/10.1016/j.hoc.2015.09.005
hemonc.theclinics.com

0889-8588/16/$ – see front matter © 2016 Elsevier Inc. All rights reserved.
tissues of the aerodigestive tract, and panNETs develop from the endocrine tissues of the pancreas (ie, islets of Langerhans). This group of well-differentiated NETs is both morphologically and clinically distinct from high-grade neuroendocrine carcinomas, tumors that are characterized by an extremely aggressive behavior and are treated along small cell lung cancer paradigms with platinum-based chemotherapy. Two epidemiologic data from the last 30 years have demonstrated that the incidence of NETs continues to increase, although there have been no significant changes in survival from this disease.

PanNETs are the second most common tumor of the pancreas and represent 1% to 2% of all pancreatic neoplasms. Although most panNETs are slow growing, after the development of metastatic disease (most commonly in the liver), median survival ranges from 2 to 5 years; most patients with liver metastases will die of the disease. About one-third of panNETs are functional tumors and produce clinical syndromes due to excessive hormone secretion; these functional panNETs are classified by the hormones they hypersecrete and include insulinoma (secrete insulin and cause hypoglycemia), gastrinoma (secrete gastrin and cause Zollinger-Ellison syndrome, which is characterized by severe peptic ulcer disease), glucagonoma (secrete glucagon and cause hyperglycemia), and vasoactive intestinal polypeptide (VIP) (VIPoma, secrete VIP and cause severe secretory diarrhea). Nonfunctional panNETs are tumors that do not secrete hormones or the products they secrete do not cause a clinical syndrome, such as pancreatic polypeptide, chromogranin A, ghrelin, neurotensin, subunits of chorionic gonadotropin, and neuron-specific enolase.

Metastatic disease is a common presentation for most patients with panNETs, especially those with nonfunctioning tumors given the absence of clinical symptoms that would warrant earlier clinical evaluation.

Asymptomatic patients diagnosed with advanced, metastatic panNETs are often monitored initially; however, with time, often their disease will progress and require treatment. The typical indications for therapy are pain and symptoms due to tumor bulk, symptoms from hormone secretion for functional tumors, high tumor burden, or progression of disease under observation. Given the heterogeneous clinical presentations and complex spectrum of aggressiveness of panNETs, their treatment is challenging and requires multimodality management with surgeons, interventional radiologists, medical oncologists, endocrinologists, and gastroenterologists. This article focuses on the data and rationale supporting the use of systemic treatments for advanced, metastatic, well-differentiated panNETs.

**PATHOLOGY**

Since 2010, the classification of panNETs has been based on the revised criteria from the World Health Organization, which is defined by the cytologic grade and the proliferative index (as assessed by the Ki-67 and/or mitotic count). In these revised criteria, tumors are broken down by differentiation status (well and poorly differentiated) and grade (grade 1, low; grade 2, intermediate; and grade 3, high). Although the family of well-differentiated tumors are classically of the grade 1 or grade 2 type and generally have a more indolent, less aggressive course, grade 3 or high-grade neuroendocrine carcinomas are typically poorly differentiated and classified as large or small cell carcinomas; these grade 3 neuroendocrine carcinomas are highly aggressive, akin to small cell lung cancers, and are associated with a poor prognosis.

To support this belief, many studies have looked at the relationship between tumor grade and survival; not surprisingly, tumor grade seems to be correlated with survival; in one retrospective analysis of 425 patients with panNETs, the 5-year survival rates...
for grade 1, grade 2, and grade 3 tumors were 75%, 62%, and 7%, respectively. Unfortunately, this grading system is not universally incorporated into most of the clinical trials investigating panNETs and makes the interpretation of the published data somewhat challenging.

However, recent data also suggest that it may not be correct to consider all grade 3 gastroenteropancreatic (GEP)-NETs as a single entity. Specifically, it has been suggested that some well-differentiated grade 3 NETs may behave differently than poorly differentiated grade 3 NETs. Furthermore, data on treatment outcomes suggest that NETs with a Ki-67 proliferation index in the lower end of the G3 range respond less robustly to chemotherapy agents, such as platinum drugs. In one study, it was shown that grade 3 GEP-NETs with a Ki-67 proliferation index less than 55% were less responsive to first-line platinum-based chemotherapy, though this subgroup achieved longer survival in comparison with grade 3 GEP-NETs with a Ki-67 proliferation index of 55% or greater (14 months vs 10 months). Further corroborating these data, in an investigation of 45 patients specifically with grade 3 panNETs, studying survival and treatment response based on poorly or well-differentiated status, differences were appreciated both in survival and response by therapy type. Specifically, the well-differentiated subgroup demonstrated improved overall survival (OS) in comparison with the poorly differentiated subgroup (52.0 months vs 10.1 months). Looking at responses to therapy, although both poorly and well-differentiated grade 3 panNETs responded to alkylating chemotherapy agents, poorly differentiated tumors had a higher response to platinum agents. Based on the findings of these studies, current research efforts are directed toward a better understanding of grade 3 NETs, both pancreatic and extrapancreatic, as they seem to be a more heterogeneous group than originally thought.

**GENETICS**

**Inherited Pancreatic Neuroendocrine Tumors**

Although panNETs often develop sporadically, inherited panNETs occur and are generally associated with 4 genetic disorders. These disorders include multiple endocrine neoplasia type 1 (MEN1), von Hippel Lindau (VHL) disease, neurofibromatosis 1 (NF1; von Recklinghausen disease), and tuberous sclerosis complex (TSC). All of these genetic disorders demonstrate autosomal dominant inheritance; additionally, the genes implicated in these disorders (MEN1, VHL, NF1, and TSC1/2) are all tumor suppressor genes and play a critical role in cellular development. The most frequent occurrence of panNETs is in MEN1, followed by VHL, then NF1, and finally TSC.

**Nonfamilial (Sporadic) Pancreatic Neuroendocrine Tumors**

More recently, effort has been made to better understand the genetic basis of nonfamilial panNETs through whole-exome sequencing; in this study, the exomic sequences of approximately 18,000 protein-coding genes in 10 nonfamilial panNETs were determined (small cell and large cell neuroendocrine carcinomas were excluded in order to ensure the set of tumors studied was clinically homogeneous). The most commonly mutated genes in these 10 tumor samples were then screened in an additional 58 panNETs. In addition to observing an increased number of mutations in genes implicated in chromatin remodeling, mutations in the mammalian target of rapamycin (mTOR) pathway were also identified. Specifically, 44% of the tumors had somatic inactivating mutations in MEN1, the gene that encodes menin, which is a component of the histone methyltransferase complex. Forty-three percent of the tumors had mutations in genes encoding death-domain-associated protein (DAXX) and alpha thalassemia/mental retardation syndrome X-linked (ATRX), these
proteins are subunits of a chromatin remodeling complex; no tumor had mutations in both DAXX and ATRX, which was expected given that these proteins function within the same pathway. Approximately 18% of the tumors had mutations along the mammalian target of rapamycin (mTOR) pathway; 7.3% of these mutations were in phosphatase and tensin homolog (PTEN), 8.8% in TSC2, and 1.4% in phosphatidylinositol-4, 5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA).

In the aforementioned study, the patient population was composed of individuals pursuing surgical resection with curative intent, and those with metastatic disease. Looking specifically at survival in different subgroups, prolonged OS was appreciated in patients with mutations in MEN1, DAXX/ATRX, or the combination of both MEN1 and DAXX/ATRX. This survival benefit was most pronounced in those patients with the combination of mutations; in patients with mutations in both MEN1 and DAXX/ATRX, 100% survived for a minimum of 10 years; however, 60% of patients who lacked these mutations died within 5 years of diagnosis.

The aforementioned study has been critical to our understanding of the genomic basis of sporadic panNETs. The findings demonstrate that patients with mutations in chromatin remodeling genes may represent a more favorable panNET subgroup. In addition, this study also highlights the subgroup of patients with panNETs who may demonstrate a more favorable response to the mTOR inhibitor everolimus; further studies to test this hypothesis are ongoing.

SYSTEMIC TREATMENT OF ADVANCED PANCREATIC NEUROENDOCRINE TUMORS

The treatment of patients with advanced, metastatic panNETs, whether inherited or sporadic, is approached in a multidisciplinary manner and may include surgical resection, liver-directed therapies, and/or systemic treatments. In unresectable patients, the goals of these therapies are to palliate tumor-related symptoms and prolong the life span.

There are multiple systemic therapy options available for the treatment of metastatic panNETs. These systemic options include somatostatin analogue therapy, targeted agents, and cytotoxic chemotherapy.

**Somatostatin Analogues**

Somatostatin and its synthetic analogues (ie, octreotide and lanreotide) bind to G-protein coupled receptors on the cell surface to exert their effects. There are 5 known subtypes of somatostatin receptors (SST1–SST5), and binding of somatostatin to these receptors can inhibit the release of hormones and secretory proteins and also stall tumor growth, offering cytostatic control.

More than 75% of panNETs express somatostatin receptors (most commonly SST2) on their surface and are octreotide avid on somatostatin analogue scintigraphy (ie, indium-111 pentetreotide [Octreoscan]).\(^{17,18}\) In octreotide-positive disease, somatostatin analogues are often used as first line, as they are well tolerated, treat functional symptoms (in those tumors that are hormone secreting), and have been demonstrated to have an antiproliferative, cytostatic effect on the growth of tumors.

**Somatostatin analogues and control of symptoms from hormone secretion**

Therapy with octreotide and lanreotide has revolutionized the way we care for patients with hormone-producing, functional panNETs. As previously discussed, functional panNETs include insulinomas, gastrinomas, glucagonomas, and VIPomas. Somatostatin analogues seem to be highly useful in the treatment of functional symptoms from VIPomas and glucagonomas, with an improvement seen in secretory diarrhea in VIPomas and an improvement in necrolytic migratory erythema, a characteristic blistering skin rash, in glucagonomas.\(^{19-21}\)
Although insulinomas and gastrinomas are the most common types of functional panNETs, somatostatin analogues seem to have a more limited role in controlling their hormone-related symptoms. In particular, when initiating somatostatin analogue therapy on insulinomas, close monitoring of glucose levels is required, as there can be transient worsening of hypoglycemia; hypoglycemia can occur as nearly half of insulinomas do not express SST2 and somatostatin analogue therapy can blunt a compensatory glucagon response. In gastrinomas, rather than somatostatin analogues, proton pump inhibitors are the preferred treatment to blunt the effects of excessive gastric acid production.

**Somatostatin analogues and control of tumor growth**

In addition to treating hormone-related symptoms in functional tumors, octreotide and lanreotide have a role in controlling tumor growth. The earliest studies investigating a cytostatic role for somatostatin analogues included patients with many types of NETs, questioning the applicability to panNETs alone. The only randomized data to support an antiproliferative role for octreotide in the treatment of NETs came from the phase III Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients with Metastatic Neuroendocrine Midgut Tumors (PROMID) study, but this study only included midgut tumors and not pancreatic NETs. In this study, 85 patients were randomized to either placebo or octreotide long-acting-release (LAR) 30 mg intramuscularly monthly until progression of disease or death. The primary end point was time to tumor progression (TTP), and the investigators observed a significant difference in TTP in the octreotide LAR and placebo groups (14.3 months vs 6 months, $P < .000072$). In clinical practice and by the National Comprehensive Cancer Network’s guidelines, physicians were extrapolating the use of octreotide in midgut tumors to use in pancreatic NET; but no prospective randomized data exist.

The Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors (CLARINET) study, however, confirmed the antiproliferative effect of somatostatin analogues in GEP-NETs. In this double-blind, placebo-controlled, multinational study in patients with low- or intermediate-grade, moderately or well-differentiated NETs (45% panNETs), 204 patients were randomized to receive an extended-release aqueous-gel formulation of lanreotide (Autogel) at a dose of 120 mg or placebo once every 28 days for 96 weeks; the primary end point was progression-free survival (PFS), defined as time to disease progression or death. The investigators observed that lanreotide was associated with significantly prolonged PFS in comparison with placebo (median not reached vs median of 18 months, $P < .001$). There were no significant differences between the two groups in quality of life (QOL) or OS. The most common adverse event was diarrhea, which was more prevalent in patients receiving lanreotide (26% in the lanreotide group and 9% in the placebo group). This study confirmed that in comparison with placebo, lanreotide is safely tolerated and significantly prolongs PFS in patients with metastatic NETs; based on these findings, lanreotide is approved by the Food and Drug Administration (FDA) to treat unresectable well-differentiated GEP-NETs. Of note, lanreotide is the only somatostatin analogue FDA approved for cytostatic tumor control in the treatment of NETs; however, octreotide is thought to have similar efficacy in controlling tumor growth.

**TARGETED THERAPIES**

In recent years, targeted agents have been evaluated as therapy options for panNETs. All NETs are known to be highly vascular; for this reason, targeted angiogenic inhibitors have been heavily investigated as a treatment option in the spectrum of NETs.
Specific biological agents that have been studied include those directed against vascular endothelial growth factor (VEGF) as well as those targeting mTOR. Sunitinib and everolimus are the only targeted therapies approved for progressive panNETs. Both single and combination therapies have been tested in clinical trials.

**Sunitinib**

Sunitinib is a small-molecule tyrosine kinase inhibitor that blocks many receptor tyrosine kinases, including VEGF receptor 1 to 3, platelet-derived growth factor receptor (PDGFR), mast/stem cell growth factor receptor (c-KIT), RET, and Fms-Related Tyrosine Kinase 3 (FLT-3). A phase II multicenter study investigated the efficacy of sunitinib in both carcinoid and panNETs (107 treated patients; 41 carcinoid and 66 panNET). Patients were treated with sunitinib 50 mg for 4 weeks followed by a 2-week break. The overall objective response rate in panNETs was 16.7% (11 of 66 patients), and 68% (45 of 66 patients) had stable disease; in panNETs, the median TTP was 7.7 months and 1-year OS was 81.1%. In comparison, only 2.4% of patients with carcinoid tumors achieved a confirmed partial response. The findings suggested that sunitinib has antitumor activity in panNETs; however, a lack of efficacy was seen in carcinoid tumors.

Based on the findings from this phase II study, a multinational, randomized double-blind placebo-controlled phase III trial was conducted of sunitinib in patients with advanced, well-differentiated panNETs. In this study, 171 patients were randomly assigned to either sunitinib 37.5 mg/d or placebo; the study was discontinued early after observation of more serious adverse events and deaths in the placebo group as well as improved PFS in the sunitinib group. Specifically, the median PFS was 11.4 months in the sunitinib group, compared with 5.5 months in the placebo group. The objective response rate was also improved with sunitinib in comparison with placebo (9.3% vs 0%). Sunitinib was most commonly associated with gastrointestinal side effects (diarrhea, nausea, vomiting) as well as asthenia and fatigue. These positive findings led to the FDA approval of sunitinib in progressive panNETs. In a more recent updated analysis of the survival data, at 2 years of additional follow-up, median OS was 33 months with sunitinib and 26.7 months with placebo ($P = .11$).

**Everolimus**

Everolimus is an oral inhibitor of mTOR, a serine-threonine kinase that impacts cell proliferation, cell survival, and also controls angiogenic pathways via hypoxia-inducible factor-1a, VEGF, and by endothelial and smooth muscle cell proliferation. In the phase II setting, everolimus demonstrated promising antitumor activity in both carcinoid tumors and panNETs. Based on these findings, RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT 3) Study Group, a randomized double-blind placebo-controlled study of 410 patients with low- or intermediate-grade, progressive, and advanced panNETs, was conducted. In this study, patients were randomized to receive everolimus or placebo, and the investigators observed a significantly improved median PFS of 11.0 months with everolimus compared with 4.6 months with placebo. In the everolimus arm, the response rate was 5%, in comparison with 2% in the placebo arm. The most common adverse events were grade 1 or 2 and included stomatitis, rash, diarrhea, fatigue, and infections. More serious grade 3 or 4 events seen with everolimus included anemia (6%) and hyperglycemia (5%). Based on the RADIANT 3 study, everolimus received FDA approval in the treatment of panNETs. The findings of RADIANT 3 were concordant with those from whole-exome sequencing of panNETs, in which mutations along the mTOR pathway were observed with increased frequency, suggestive that this tumor type may respond to mTOR inhibition.
CYTOTOXIC CHEMOTHERAPY

Through multiple studies, a role for chemotherapy (both single drug and combination drugs) has been demonstrated in the management of panNETs. Chemotherapy is most commonly used in the presence of a more aggressive clinical course and symptomatic, heavy tumor burden. In the treatment of panNETs, chemotherapy has been demonstrated to have both palliative and antitumor effects, though evidence regarding OS is conflicting. Chemotherapy agents that have been investigated and commonly used for the treatment of NETs include alkylating agents (streptozocin, temozolomide, dacarbazine) and platinum agents.

**Alkylating Agents: Streptozocin**

Three alkylating agents, streptozocin, temozolomide, and dacarbazine, have demonstrated activity in the management of panNETs. The earliest evidence for use of alkylating agents came from a case report in 1968 of a patient with a panNET who was suffering from recurrent hypoglycemia and received symptomatic relief as well as a decrease in hepatic tumor burden while on therapy with streptozocin. Then, in 1971, through a phase II study, a 5-day intensive course of streptozocin was evaluated and demonstrated to be active against panNETs.

A multicenter trial led by the Eastern Cooperative Oncology Group (ECOG) was conducted in which 105 patients with advanced panNETs were randomized to one of 3 treatment regimens: streptozocin plus 5-fluorouracil (5-FU), streptozocin plus doxorubicin, or chlorozotocin alone. In terms of tumor regression, streptozocin plus doxorubicin was superior to streptozocin plus 5-FU (69% vs 45%, \( P < 0.05 \)). It is important to recognize that, in this study, markers of response included radiographic tumor regression or alternatively improvements in tumor seen on physical examination and for patients without measurable tumor by imaging or examination; laboratory assays evaluating hormone production were used. Survival was short in both arms but favored the streptozocin arm (2.2 vs 1.4 years, \( P < 0.004 \)).

In further investigation, however, these findings from the ECOG trial could not be confirmed. In a retrospective review of 16 patients with advanced panNETs treated at a single institution with streptozocin and doxorubicin, only 1 of 16 (6%) achieved an objective response by standard computed tomography response criteria; 9 of 16 (56%) had stable disease and 6 of 16 (38%) had progression of disease as their best response during treatment. The investigators of this study were unable to confirm the high objective response rate previously appreciated, possibly because of the nonmodern response criteria (physical examination, laboratory biochemical parameters) used in the ECOG trial.

A retrospective study was subsequently conducted to investigate outcomes in 84 patients with metastatic panNETs treated with streptozocin, 5-FU, and doxorubicin; response evaluation criteria in solid tumors (RECIST) were used to evaluate response. In this study, the response rate to chemotherapy was 39%; the median duration of response was 9.3 months, and the 2-year PFS and OS rates were 41% and 74%, respectively.

**Alkylating Agents: Dacarbazine**

Dacarbazine (DTIC) is a nonclassic synthetic alkylating agent and has been investigated as a treatment option for panNETs. Early investigations of DTIC, first in carcinoid tumors, suggested a benefit in terms of tumor shrinkage in about half of treatment patients, along with an improvement in QOL; the most commonly appreciated side effect was nausea, with no major organ toxicities noted. Based on
these early data, a phase II study of DTIC in patients with advanced panNETs was conducted by ECOG (E6282). In this study, 50 patients with documented clinical or radiographic disease progression received DTIC every 4 weeks. In this patient cohort, the response rate was 34%, with chemotherapy-naive patients deriving the greatest benefit; the median OS was 19.3 months. Notable lethal toxicities were septic shock in one patient and myocardial infarction in one patient. The most common grade 4 toxicity was hematological (in 5 patients), and 13% of patients experienced grade 3 vomiting. Based on the results of this study, DTIC was thought to have activity in previously untreated, progressive, panNETs; but given the potential toxicities, as with streptozocin, widespread use of DTIC for panNET treatment has been limited.

**Alkylating Agents: Temozolomide**

Temozolomide is an oral alkylating agent developed to be a less toxic alternative to DTIC. The earliest data for a rationale for temozolomide in the therapy for panNETs came from a phase II trial in which 29 patients with metastatic NETs (including carcinoid tumors, pheochromocytoma, and panNETs) received a combination of temozolomide and thalidomide. In this study, temozolomide was given in a dose-intense regimen (150 mg/m² for 7 days, every other week). A 40% biochemical response rate (chromogranin A) and a 25% radiologic response rate were appreciated with the combination of temozolomide and thalidomide; when breaking the radiologic response rate down by tumor type, it was 45% in panNETs, 33% in pheochromocytomas, and 7% in carcinoid tumors. The median duration of response was 13.5 months, with 1-year and 2-year survival of 79% and 61% respectively. The most severe toxicity was grade 3 to 4 lymphopenia, seen in 69% of patients; the dose-intense regimen of temozolomide used in this study likely contributed to the high rates of lymphopenia observed. Of note, a separate single phase II study of thalidomide in 18 patients with NETs (5 with panNETs) showed no antitumor activity with thalidomide, with no patients achieving a complete or partial response. Taking these two studies together, temozolomide may have been the active drug in the combination study, and temozolomide seems to offer the greatest benefit in panNETs compared with other types of NETs.

The panNET treatment with monotherapy temozolomide was subsequently evaluated. In a retrospective analysis of 36 patients with metastatic NETs (12 patients with panNETs) treated with single-agent temozolomide (dosed at 200 mg/m² for 5 days, every 4 weeks), the medial overall time to progression was 7 months, with objective response appreciated in 14% of patients and stable disease in 53% of patients by RECIST criteria. The most common side effects were hematologic, with 14% of patients experiencing grade 3/4 thrombocytopenia. This small series suggested a role for single-agent temozolomide in panNETs.

Through small retrospective studies, the combination of capecitabine and temozolomide for panNET treatment has also been investigated. A retrospective review was undertaken of 18 patients with metastatic NETs to the liver (7 with panNETs), all who had progression on octreotide LAR and were then treated on a pilot study of capecitabine and temozolomide. Using RECIST, 1 patient (5.6%) had a complete response, 10 patients (55.5%) had a partial response, and 4 patients (22.2%) had stable disease; the median PFS was 14 months, with median OS from the diagnosis of liver metastases was 83 months. The most recent study to evaluate the combination of capecitabine and temozolomide was conducted retrospectively on 30 patients with metastatic panNETs who had not received any prior systemic therapy. Patients were treated with combination capecitabine and temozolomide; 21 of 30 (70%)
patients demonstrated an objective radiographic response, with a median PFS of 18 months and 2-year OS of 92%. Notable toxicities included grade 4 hematologic abnormalities in 2 patients. This study provided further support that these two oral drugs, used in combination, offer a high and durable response in metastatic pan-NETs. However, careful monitoring of blood counts is essential with the administration of temozolomide, given the potential hematologic toxicity. An ongoing ECOG study is randomizing patients to temozolomide single agent versus capecitabine plus temozolomide and is poised to ask the question of benefit of single versus combination therapy.

Platinum Agents

Platinum chemotherapy drugs have also been evaluated as a treatment option for panNETs; however, the benefit may be more limited to patients with higher-grade tumors. In a phase II trial of cisplatin and etoposide in 45 patients with metastatic NETs, the tumor response was restricted to the patients with higher-grade, more aggressive tumors; among 18 patients classified with anaplastic neuroendocrine carcinomas, there were 9 partial responses and 3 complete responses. In comparison, among the 27 patients with well-differentiated carcinoid tumors or panNETs, there were only 2 partial responses observed, both in carcinoid tumors.

In a separate study, the combination of cisplatin, 5-FU, and streptozocin was investigated in 79 patients with metastatic or locally advanced NETs (47 patients with panNETs). Among panNETs, the overall response rate was 38%; this study, however, also included patients with high-grade, poorly differentiated tumors, which tend to be more chemosensitive, and it is unknown if most responders were of higher grade.

ADDITIONAL EXPERIMENTAL SYSTEMIC TREATMENTS

Peptide Receptor Radiation Therapy

Peptide receptor radiation therapy (PRRT), therapy that targets and treats NETs with radiolabeled somatostatin analogues, is based on the understanding that NETs highly express somatostatin receptors on their surface. In PRRT, a somatostatin analogue is linked to a therapeutic beta-emitting radioisotope, with the goal of the radiation emitted from the radiolabeled peptide binding to the surface of a tumor cell to both kill the tumor cell as well as neighboring cells, as the path length of beta particles extends across many cells.

Several studies have demonstrated a role for PRRT in the treatment of advanced, metastatic NETs. Multiple radioisotopes have been investigated, including yttrium-90 (90Y), indium-111, and lutetium-177 (177Lu); these radioisotopes are linked to a somatostatin analogue to exert their therapeutic effects.

Yttrium-90-DOTATOC

A phase II study of 90Y-DOTA-d-Phe(1)-Tyr(3)-octreotide (DOTATOC) included 39 patients with progressive NETs (of gastrointestinal and lung origin) who received 4 intravenous injections at 6-week intervals. The investigators observed an objective response rate of 38%, and 5% of patients (2 of 39 patients) had complete remissions, 18% of patients (7 of 39 patients) had partial remissions, and 69% of patients (27 of 39 patients) had stable disease. There was a similar reduction in clinical symptoms, including diarrhea, flushing, wheezing, and pellagra. The most severe grade 3 or 4 toxicities were hematologic.

Building on this phase II data, the Multicenter Analysis of a Universal Receptor Imaging and Treatment Initiative, a European Study (MAURITIUS) trial was conducted. In
MAURITIUS, 154 patients were treated with $^{90}$Y-DOTA-lanreotide; stable disease was observed in 63 patients (41%), and tumor regression was seen in 22 patients (14%). In contrast to the aforementioned studies, the investigators did not appreciate any severe hematologic toxicity.

**Lutetium-177–DOTATATE**

$L^t$Lu-DOTATATE has also been studied, with results demonstrating a benefit in terms of reduction in tumor size as well as QOL.

In the largest study of $^{177}$Lu-DOTATATE, 504 patients with advanced NETs were treated with 4 treatment cycles, with treatment intervals of 6 to 10 weeks. Among 310 evaluable patients, the investigators appreciated complete tumor remission in 2% of patients and partial tumor remission in 28% of patients. Median TTP was 40 months; from the start of treatment, the median OS was 46 months (128 months from diagnosis). Using historical controls, a survival benefit of 40 to 72 months from diagnosis was observed. In terms of adverse events, 3 patients did develop myelodysplastic syndrome and temporary liver toxicity was seen in 2 patients.

**Other Experimental Targeted Treatments**

**Bevacizumab-containing regimens**

Bevacizumab is a humanized monoclonal antibody that binds to soluble VEGF and inhibits tumor growth by preventing endothelial cell proliferation. Most of the studies of bevacizumab in NETs have investigated a role for bevacizumab in patients with advanced carcinoid tumors. However, subsequently, a role for bevacizumab has been studied in panNETs. In a phase II study of bevacizumab plus temozolomide in patients with advanced NETs, 34 patients (44% with panNETs, 56% with carcinoid) received bevacizumab 5 mg/kg on day 1 and 15 of a 28-day cycle and temozolomide 150 mg/m$^2$ on days 1 through 7 and days 15 through 21. The investigators observed an overall radiographic response of 15% (5 of 34); however, when broken down by subgroup, the response rate was 33% in panNETs (5 of 15) and 0% (0 of 19) in carcinoid tumors. The median PFS was 11 months (14.3 months for panNETs and 7.3 months for carcinoid tumors), and the median OS was 33.3 months (41.7 months for panNETs and 18.8 months for carcinoid tumors).

The combination of 5-FU, oxaliplatin, and bevacizumab was also studied in panNETs. In one study, there was a 33% response rate in 6 patients with progressive panNETs who received short-term infusional 5-FU, leucovorin, oxaliplatin, and bevacizumab. In another study, 40 patients (20 panNETs) were treated with capecitabine, oxaliplatin, and bevacizumab; of 31 evaluable patients, 7 patients (23%) were observed to have partial responses; 6 of these 7 patients (85.7%) had panNETs. A phase II study has also been conducted in patients with panNETs investigating the combination of the mTOR inhibitor temsirolimus and bevacizumab; in this study of 58 patients (56 evaluable), confirmed response rate (RR) was 41% (23 of 56), median PFS was 13.2 months, and median OS was 34 months. The findings from this study suggested possible activity for the combination of mTOR and VEGF pathway inhibitors.

Based on the findings of the aforementioned study, there has been continued investigation of the combination of mTOR and VEGF inhibition. CALGB 80701 (NCT01229943) was a randomized phase II trial of octreotide LAR, bevacizumab, and everolimus versus octreotide LAR and everolimus in 150 patients with metastatic panNETs; data analysis was just recently reported at the American Society of Clinical Oncology 2015 convention. The study met its primary end point. PFS was
16.7 months in the combination arm versus 14 months in the single-agent everolimus arm. Response rates were higher in the combination arm (31% vs 12%). It is a paradigm shift to see targeted therapies cause such a high response rate. However, toxicity was significantly greater; 84% of patients on the combination bevacizumab/everolimus arm experienced serious grade 3 to 4 events. The toxicity, therefore, calls combination therapy into question.

A phase II study of single-agent bevacizumab for progressive moderately or well-differentiated panNETs was also recently reported. In this study of 22 patients, partial response rates were 9% (2 of 22). In a heavily treated patient population, the median PFS was 13.6 months. Notably, 36% of patients did experience grade 3 hypertension. The findings from this study were thought to be promising, given that patients were required to have disease progression by RECIST within 7 months of study enrollment and patients overall experienced minimal systemic toxicity. Further investigation is warranted.

SUMMARY AND FUTURE DIRECTIONS

As discussed in this article, there are multiple types of systemic therapy options to manage and treat panNETs, including somatostatin analogue therapy, targeted therapy, and chemotherapy. Surgery remains the mainstay of treatment of patients with limited and localized disease and offers the potential for cure. However, as discussed, most patients with panNETs present with advanced disease; goals of therapy in the metastatic setting are directed toward control of symptoms (both due to tumor bulk and hormone hypersecretion in functional tumors), halting growth of disease, and prolonging life spans, all while preserving QOL.

For grade 1 and grade 2 metastatic panNETs, in the absence of symptoms and with low tumor volume, a trial of observation is generally encouraged to better understand the pace of disease growth. In the setting of disease progression, somatostatin analogues are typically started as first-line therapy; these analogues are also sometimes administered on patient presentation to control hormone-related symptoms from functional tumors.

Subsequently, the order of treatment varies and is individualized to each patient. Multimodality therapy is essential for the management of panNETs; over time, patients will receive several types of therapy, potentially including surgical debulking, liver-directed therapies, as well as systemic treatments to control their disease. As has been discussed, chemotherapy is generally reserved for use in the presence of rapid tumor growth or heavy disease burden. Targeted agents are another option to consider, which improve PFS, although response rates are generally less than 10%.

After decades of stagnation, in the past 5 years, an improved understanding of this rare disease has led to more treatment options. As noted, the appropriate selection and sequencing of treatment approaches for patients with advanced pancreatic NETs is unknown and currently depends on clinical judgment. The hope is that increased understanding of the disease will lead to a more personalized individualized treatment of patients. In addition, it is hoped that tumor mutational analysis will identify biomarkers that can serve as predictors of response and/or resistance to the different agents.

When designing clinical trials in the future, it will be essential that these trials separate panNETs from NETs originating in other locations; from the knowledge to date, panNETs seem to respond differently to the available systemic therapies and need to be studied in isolation. Randomized trials are also clearly needed to test the role of combination therapies to assess toxicity and confirm their efficacy compared with our currently available agents.
REFERENCES


61. Kulke MH, Niedzwiecki D, Foster NR, et al. Randomized phase II study of everolimus (E) versus everolimus plus bevacizumab (E+B) in patients (Pts) with locally advanced or metastatic pancreatic neuroendocrine tumors (pNET), CALGB 80701 (Alliance) [Meeting Abstracts]. J Clin Oncol 2015;33(suppl) [abstract: 4005].