Published in final edited form as:

Hematol Oncol Clin North Am. 2016 February ; 30(1): 119–133. doi:10.1016/j.hoc.2015.09.005.

Systemic Therapies for Advanced Pancreatic Neuroendocrine Tumors

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

Department of Medicine, Division of Solid Tumor Oncology, Gastrointestinal Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY

SYNOPSIS

Pancreatic neuroendocrine tumors are a rare tumor type, and comprise 1-2% of all pancreatic neoplasms. When nonfunctional (i.e. nonhormone secreting), these tumors generally cause few symptoms and often go unnoticed for several years; for this reason, they are rarely localized at presentation, and are typically diagnosed in the presence of metastatic disease, most commonly to the liver. Although pancreatic neuroendocrine tumors can be less aggressive than other tumor types, the management poses a significant challenge because of the heterogeneous clinical presentations and varying degrees of aggressiveness. The therapy of pancreatic neuroendocrine tumors includes a multimodality approach and can often include surgery, liver-directed therapies (i.e. embolization), as well as targeted and cytotoxic systemic treatments. A variety of systemic therapies have been developed for the management of pancreatic neuroendocrine tumors. These therapies include somatostatin analogs (octreotide or lanreotide), a select group of cytotoxic chemotherapy agents (alkylating, fluorouracil and platinum drugs), as well as targeted or biologic agents (everolimus and sunitinib). This chapter will review the available systemic therapy options for advanced pancreatic neuroendocrine tumors.

Keywords

neuroendocrine tumors; pancreatic neuroendocrine tumors; carcinoid tumors; octreotide; lanreotide; sunitinib; everolimus

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.[1] These tumors are subdivided into carcinoid tumors and pancreatic

CORRESPONDING AUTHOR Nitya Raj, MD, rajn@mskcc.org.

AUTHOR CONTACT INFORMATION 300 East 66th Street, 1039, New York, NY 10065, reidyd@mskcc.org

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

DISCLOSURE STATEMENT

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

neuroendocrine tumors (panNETs). Carcinoid tumors develop from the neuroendocrine tissues of the aerodigestive tract, and panNETs develop from the endocrine tissues of the pancreas (i.e. 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.[2] Epidemiological data from the last 30 years has demonstrated that the incidence of NETs continues to rise, while there have been no significant changes in survival from this disease.[3, 4]

panNETs are the second most common tumor of the pancreas, and represent 1-2% of all pancreatic neoplasms.[5, 6] Although the majority of panNETs are slow growing, after the development of metastatic disease (most commonly, in the liver), median survival ranges from 2 to 5 years, and most patients with liver metastases will die from disease.[7] 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 (VIPoma, secrete VIP and cause severe secretory diarrhea). [6, 8-10] Non-functional 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. [10] Metastatic disease is a common presentation for the majority of patients with panNETs, especially those with non-functioning tumors given the absence of clinical symptoms that would warrant earlier clinical evaluation.[7]

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.[8] 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 chapter will focus on the data and rationale supporting the use of systemic treatments for advanced, metastatic, well-differentiated panNETs.

Pathology

Since 2010, classification of panNETs has been based on revised WHO criteria which is defined by the cytological grade and the proliferative index (as assessed by the Ki-67 and/or mitotic count).[11] 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. While 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, and not surprisingly, tumor grade appears 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.[12] Unfortunately, this grading system is not universally incorporated into the majority of clinical trials investigating panNETs, and makes the interpretation of the published data somewhat challenging.

However, recent data also suggests that it may not be correct to consider all grade 3 GEP-NETs as a single entity. In specific, it has been suggested that some well differentiated grade 3 NETs may behave differently than poorly differentiated grade 3 NETs.[13] Furthermore, data on treatment outcomes suggests 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 <55% were less responsive to first-line platinum-based chemotherapy, though this subgroup achieved longer survival in comparison to grade 3 GEP-NETs with a Ki-67 proliferation index ≥55% (14 months versus 10 months).[14] Further corroborating this data, in an investigation of 45 patients specifically with grade 3 panNETs, studying survival and treatment response based on well or poorly differentiated status, differences were appreciated both in survival and response by therapy type.[15] Specifically, the well differentiated subgroup demonstrated improved OS in comparison to the poorly differentiated subgroup (52.0 months versus 10.1 months). Looking at responses to therapy, while both well and poorly 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 towards a better understanding of grade 3 NETs, both pancreatic and extra-pancreatic, as they appear to be a more heterogeneous group than originally thought.

Genetics

Inherited panNETs

Although panNETs often develop sporadically, inherited panNETs occur and are generally associated with four genetic disorders. These disorders include Multiple Endocrine Neoplasia type 1 (MEN1), von Hippel Lindau (VHL) disease, neurofibromatosis 1 (NF-1; 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.[10] The most frequent occurrence of panNETs is in MEN1, followed by VHL, then NF1, and finally TSC.[10]

Nonfamilial (Sporadic) panNETs

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).[16] 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 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 DAXX (death-domain-associated protein) and ATRX (alpha thalassemia/mental retardation syndrome X-linked), 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 PTEN, 8.8% in TSC2, and 1.4% in PIK3CA.

In the above study, all patients whose tumors were included were undergoing active therapy, and the patient population was comprised of individuals with potentially curative as well as 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 above 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 panNET patients that may demonstrate a more favorable response to the mTOR inhibitor everolimus; further studies to test this hypothesis are ongoing.

Systemic treatment of advanced panNETs

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 the unresectable patient, the goals of these therapies are to palliate tumor-related symptoms, and prolong lifespan.

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

Somatostatin analogs

Somatostatin and its synthetic analogs (i.e. octreotide and lanreotide) bind to G-protein couple receptors on the cell surface to exert their effects. There are five 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 analog scintigraphy (i.e. Octreoscan™).[17, 18] In octreotide positive disease, somatostatin analogs are often used first line, as they are well tolerated, treat functional symptoms (in those tumors that are hormone secreting), and have been demonstrated to have an anti-proliferative, cytostatic effect on the growth of tumor.

Somatostatin analogs 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 analogs appear 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 analogs appear to have a more limited role in controlling their hormone-related symptoms. In particular, when initiating somatostatin analog 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 analog therapy can blunt a compensatory glucagon response.[8] In gastrinomas, rather than somatostatin analogs, proton pump inhibitors are the preferred treatment to blunt the effects of excessive gastric acid production.

Somatostatin analogs 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 analogs included patients with many types of NETs, questioning the applicability to panNETs alone.[22, 23] The only randomized data to support an antiproliferative role for octreotide in the treatment of NETs came from the phase III PROMID study but this study only included midgut tumors and not pancreatic NETs.[24] In this study, 85 patients were randomized to either placebo or octreotide long-acting-release (LAR) 30 mg intramuscularly (IM) monthly until progression of disease or death. The primary endpoint 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 versus 6 months, $p=0.000072$). In clinical practice and by NCCN guidelines, physicians were extrapolating the use of octreotide in midgut tumors to use in pancreatic NETs but no prospective randomized data exist.[25]

The CLARINET study, however, confirmed the antiproliferative effect of somatostatin analogs in gastroenteropancreatic NETs (i.e. GEP-NETs). In this double-blind, placebo-controlled, multinational study in patients with low or intermediate grade, well or

moderately 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 endpoint was progression-free survival (PFS), defined as time to disease progression or death. The authors observed that lanreotide was associated with significantly prolonged PFS in comparison to placebo (median not reached versus median of 18 months, $p<0.001$). There were no significant differences between the two groups in 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 to placebo, lanreotide is safely tolerated and significantly prolongs PFS in patients with metastatic NETs; based on these findings, lanreotide is FDA approved to treat unresectable well differentiated GEP-NETs. Of note, lanreotide is the only somatostatin analog FDA approved for cytostatic tumor control in the treatment of NETs, however, octreotide is believed to have similar efficacy in controlling tumor growth.[26]

Targeted Therapies

In recent years, targeted agents have been evaluated as therapy options for panNETs. All NETs are known to be highly vascular, and for this reason, targeted angiogenic inhibitors have been heavily investigated as a treatment option in the spectrum of NETs.[27] Specific biologic 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 VEGFR1-3 as well as PDGFR, c-KIT, RET, and FLT-3.[9] A phase II multicenter study investigated the efficacy of sunitinib in both carcinoid and panNETs (107 treated patients; 41 carcinoid and 66 panNET).[28] Patients were treated with sunitinib 50 mg for 4 weeks followed by a 2 week break. Overall objective response rate in panNETs was 16.7% (11/66 patients), and 68% (45/66 patients) had stable disease; in panNETs, median TTP was 7.7 months and one-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.[29] In this study, 171 patients were randomly assigned to either sunitinib 37.5 mg per day 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 arm. Specifically, median PFS was 11.4 months in the sunitinib group, compared with 5.5 months in the placebo group. Objective response rate was also improved with sunitinib in comparison to placebo (9.3% versus 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 ($p=0.11$). [30]

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.[31] In the phase II setting, everolimus demonstrated promising antitumor activity in both carcinoid tumors and panNETs.[32, 33] Based on these findings, RADIANT 3, a randomized double-blind placebo-controlled study of 410 patients with low- or intermediate-grade, progressive, and advanced panNETs was conducted.[34] In this study, patients were randomized to receive everolimus or placebo, and the authors observed a significantly improved median PFS of 11.0 months with everolimus, compared to 4.6 months with placebo. In the everolimus arm, 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.[16]

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 utilized 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 decrease in hepatic tumor burden while on therapy with streptozocin.[35] Then, in 1971, through a phase II study, a five-day, intensive course of streptozocin was evaluated and demonstrated to be active against panNETs.[36]

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 three treatment regimens: streptozocin plus 5-FU, streptozocin plus doxorubicin, or chlorozotocin alone.[37] In terms of tumor regression, streptozocin plus doxorubicin was superior to streptozocin plus 5-FU (69% versus 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 exam, laboratory assays evaluating hormone production were used. Survival was short in both arms but favored the streptozocin arm (2.2 versus 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 1/16 (6%) achieved an objective response by standard CT response criteria; 9/16 (56%) had stable disease and 6/16 (38%) had progression of disease as their best response during treatment.[38] The authors of this study were unable to confirm the high objective response rate previously appreciated, possibly because of the non-modern response criteria (physical exam, 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 utilized to evaluate response.[39] In this study, the response rate to chemotherapy was 39%; 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 non-classic synthetic alkylating agent and has been investigated as a treatment option for panNETs.[40, 41] 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.[42, 43] Based on this early data, a phase II study of DTIC in patients with advanced panNETs was conducted by ECOG (E6282).[41] 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-naïve patients deriving the greatest benefit; 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 felt 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.[44] The earliest data for a rationale for temozolomide in the therapy of panNETs came from a phase II trial in which 29 patients with metastatic neuroendocrine tumors (including

carcinoid tumors, pheochromocytoma, and panNETs) received a combination of temozolomide and thalidomide.[45] 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 79% and 61% respectively. The most severe toxicity was grade 3-4 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.[46]. Taking these two studies together, temozolomide may have been the active drug in the combination study, and temozolomide appears to offer the greatest benefit in panNETs, compared to other types of NETs.

panNET treatment with monotherapy temozolomide was subsequently evaluated. In a retrospective analysis of 36 patients with metastatic neuroendocrine tumors (12 patients with panNETs) treated with single agent temozolomide (dosed at 200 mg/m² for 5 days every 4 weeks), median 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.[47] 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. [48] 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; 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. [49] Patients were treated with combination capecitabine and temozolomide, and 21/30 (70%) patients demonstrated an objective radiographic response, with median PFS 18 months, and 2-year OS 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 panNETs. 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, 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. [50]

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). Amongst panNETs, the overall response rate was 38%; this study however also included patients with high grade, poorly differentiated tumors, which tend to be more chemo-sensitive, and it is unknown if the majority of responders were of higher grade.[51]

Additional experimental systemic treatments

Peptide receptor radiation therapy

Peptide receptor radiation therapy (PRRT), therapy that targets and treats NETs with radiolabeled somatostatin analogs, is based on the understanding that NETs highly expresses somatostatin receptors on their surface. In PRRT, a somatostatin analog 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.[52]

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

^{90}Y -DOTATOC—A phase II study of ^{90}Y -DOTATOC included 39 patients with progressive NETs (of gastrointestinal and lung origin) that received four intravenous injections at six week intervals. The investigators observed an objective response rate of 38%, and 5% of patients (2/39 patients) had complete remissions, 18% of patients (7/39 patients) had partial remissions, and 69% of patients (27/39 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.[52]

Building on this phase II data, the MAURITIUS trial was conducted.[53] 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 above studies, the authors did not appreciate any severe hematologic toxicity.

^{177}Lu -DOTATATE— ^{177}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 four treatment cycles, with treatment intervals of 6 to 10 weeks.[54] Amongst 310 evaluable patients, the authors appreciated complete tumor remission in 2% of patients, and partial tumor remission in 28% of patients. Median TTP was 40 months, and from start of treatment, 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.[55] The majority of studies of bevacizumab in NETs have investigated a role for bevacizumab in patients with advanced carcinoid tumors.[56, 57] However subsequently, a role for bevacizumab has been studied in panNETs. In a phase II study of bevacizumab plus temozolomide in patients with advanced neuroendocrine tumors, 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/m² on days 1 through 7 and days 15 through 21.[58] The authors observed an overall radiographic response of 15% (5/34), however when broken down by subgroup, response rate was 33% in panNETs (5/15) and 0% (0/19) in carcinoid tumors. Median PFS was 11 months (14.3 months for panNETs and 7.3 months for carcinoid tumors) and median OS was 33.3 months (41.7 months for panNETs and 18.8 months for carcinoid tumors).

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.[59] 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, and 6 of these 7 patients (85.7%) had panNETs.[60] 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 RR was 41% (23/56), median PFS was 13.2 months, and median OS was 34 months.[61] The findings from this study suggested possible activity for the combination of mTOR and VEGF pathway inhibitors.

Based on the findings of the above 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 ASCO 2015 convention.[62] The study met its primary endpoint. 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% versus 12%). This 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 3-4 events. The toxicity therefore calls combination therapy into question.

A phase II study of single agent bevacizumab for progressive well or moderately differentiated panNETs was also recently reported.[63] In this study of 22 patients, partial response rates were 9% (2/22). In a heavily treated patient population, median PFS was 13.6 months. Notably, 36% of patients did experience grade 3 hypertension. The findings from this study were felt 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.

Conclusions and future directions

As discussed in this chapter, there are multiple types of systemic therapy options to manage and treat panNETs, including somatostatin analog therapy, targeted therapy, and chemotherapy. Surgery remains the mainstay of treatment for patients with limited and localized disease and offers the potential for cure. However, as discussed, the majority of patients with panNETs present with advanced disease, and goals of therapy in the metastatic setting are directed towards control of symptoms (both due to tumor bulk and hormone hypersecretion in functional tumors), halting growth of disease, and prolonging lifespan, 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 analogs are typically started as first-line therapy; these analogs are also sometimes administered upon 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, and 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 progression free survival although response rates are generally less than 10%.

After decades of stagnation, in the past five 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 for patients. In addition, tumor mutational analysis will hopefully 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 appear 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

1. Kunz PL, et al. Consensus guidelines for the management and treatment of neuroendocrine tumors. *Pancreas*. 2013; 42(4):557–77. [PubMed: 23591432]
2. Moertel CG, et al. Treatment of Neuroendocrine Carcinomas with Combined Etoposide and Cisplatin - Evidence of Major Therapeutic Activity in the Anaplastic Variants of These Neoplasms. *Cancer*. 1991; 68(2):227–232. [PubMed: 1712661]
3. Modlin IM, et al. Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncology*. 2008; 9(1):61–72. [PubMed: 18177818]
4. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer*. 2003; 97(4):934–959. [PubMed: 12569593]
5. Dumlu EG, Karakoc D, Ozdemir A. Nonfunctional Pancreatic Neuroendocrine Tumors: Advances in Diagnosis, Management and Controversies. *Int Surg*. 2015
6. Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. *Gastroenterology*. 2008; 135(5):1469–92. [PubMed: 18703061]
7. Yao JC, et al. One hundred years after “Carcinoid”: Epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *Journal of Clinical Oncology*. 2008; 26(18):3063–3072. [PubMed: 18565894]
8. Reidy-Lagunes DL. Systemic Therapy for Advanced Pancreatic Neuroendocrine Tumors: An Update. *Journal of the National Comprehensive Cancer Network*. 2012; 10(6):777–783. [PubMed: 22679119]
9. Castellano D, et al. Expert consensus for the management of advanced or metastatic pancreatic neuroendocrine and carcinoid tumors. *Cancer Chemother Pharmacol*. 2014
10. Jensen RT, et al. Inherited pancreatic endocrine tumor syndromes: advances in molecular pathogenesis, diagnosis, management, and controversies. *Cancer*. 2008; 113(7 Suppl):1807–43. [PubMed: 18798544]
11. Bosman FT.; World Health Organization., and International Agency for Research on Cancer.. World Health Organization classification of tumours. 4th ed.. International Agency for Research on Cancer; Lyon: 2010. WHO classification of tumours of the digestive system.; p. 417
12. Strosberg JR, et al. Prognostic validity of a novel American Joint Committee on Cancer Staging Classification for pancreatic neuroendocrine tumors. *J Clin Oncol*. 2011; 29(22):3044–9. [PubMed: 21709192]
13. Basturk O, et al. The high-grade (WHO G3) pancreatic neuroendocrine tumor category is morphologically and biologically heterogeneous and includes both well differentiated and poorly differentiated neoplasms. *Am J Surg Pathol*. 2015; 39(5):683–90. [PubMed: 25723112]
14. Sorbye H, et al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): The NORDIC NEC study. *Annals of Oncology*. 2013; 24(1):152–160. [PubMed: 22967994]
15. Raj NP. Treatment response and outcomes of grade 3 (G3) pancreatic neuroendocrine carcinomas (HGNEC) based on pathologic differentiation. *J Clin Oncol (Meeting Abstracts)*. 2015; 33(suppl) abstr e15185.
16. Jiao Y, et al. DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. *Science*. 2011; 331(6021):1199–203. [PubMed: 21252315]
17. Reubi JC, Waser B. Concomitant expression of several peptide receptors in neuroendocrine tumours: molecular basis for in vivo multireceptor tumour targeting. *Eur J Nucl Med Mol Imaging*. 2003; 30(5):781–93. [PubMed: 12707737]
18. Oberg KE, et al. Role of somatostatins in gastroenteropancreatic neuroendocrine tumor development and therapy. *Gastroenterology*. 2010; 139(3):742–53. 753, e1. [PubMed: 20637207]

19. Kraenzlin ME, et al. Long-term treatment of a VIPoma with somatostatin analogue resulting in remission of symptoms and possible shrinkage of metastases. *Gastroenterology*. 1985; 88(1 Pt 1): 185–7. [PubMed: 2856877]
20. Nikou GC, et al. VIPomas: an update in diagnosis and management in a series of 11 patients. *Hepatogastroenterology*. 2005; 52(64):1259–65. [PubMed: 16001675]
21. Frankton S, Bloom SR. Gastrointestinal endocrine tumours. Glucagonomas. *Baillieres Clin Gastroenterol*. 1996; 10(4):697–705. [PubMed: 9113318]
22. Saltz L, et al. Octreotide as an antineoplastic agent in the treatment of functional and nonfunctional neuroendocrine tumors. *Cancer*. 1993; 72(1):244–8. [PubMed: 8389666]
23. Arnold R, et al. Somatostatin analog sandostatin and inhibition of tumor growth in patients with metastatic endocrine gastroenteropancreatic tumors. *World J Surg*. 1993; 17(4):511–9. [PubMed: 8395752]
24. Rinke A, et al. 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: A Report From the PROMID Study Group. *Journal of Clinical Oncology*. 2009; 27(28):4656–4663. [PubMed: 19704057]
25. Clark OH, et al. NCCN Clinical Practice Guidelines in Oncology: neuroendocrine tumors. *J Natl Compr Canc Netw*. 2009; 7(7):712–47. [PubMed: 19635226]
26. Caplin ME, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med*. 2014; 371(3):224–33. [PubMed: 25014687]
27. Turner HE, et al. Angiogenesis in endocrine tumors. *Endocr Rev*. 2003; 24(5):600–32. [PubMed: 14570746]
28. Kulke MH, et al. Activity of sunitinib in patients with advanced neuroendocrine tumors. *J Clin Oncol*. 2008; 26(20):3403–10. [PubMed: 18612155]
29. Raymond E, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med*. 2011; 364(6):501–13. [PubMed: 21306237]
30. Vinik A, et al. Updated results from a phase III trial of sunitinib versus placebo in patients with progressive, unresectable, well-differentiated pancreatic neuroendocrine tumor (NET). *J Clin Oncol (Meeting Abstracts)*. 2012; 30(suppl) abstr 4118.
31. O'Donnell A, et al. Phase I pharmacokinetic and pharmacodynamic study of the oral mammalian target of rapamycin inhibitor everolimus in patients with advanced solid tumors. *J Clin Oncol*. 2008; 26(10):1588–95. [PubMed: 18332470]
32. Yao JC, et al. Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low- to intermediate-grade neuroendocrine tumors: results of a phase II study. *J Clin Oncol*. 2008; 26(26): 4311–8. [PubMed: 18779618]
33. Yao JC, et al. Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. *J Clin Oncol*. 2010; 28(1):69–76. [PubMed: 19933912]
34. Yao JC, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med*. 2011; 364(6):514–23. [PubMed: 21306238]
35. Murray-Lyon IM, et al. Treatment of multiple-hormone-producing malignant islet-cell tumour with streptozotocin. *Lancet*. 1968; 2(7574):895–8. [PubMed: 4176152]
36. Moertel CG, et al. Phase II study of streptozotocin (NSC-85998) in the treatment of advanced gastrointestinal cancer. *Cancer Chemother Rep*. 1971; 55(3):303–7. [PubMed: 5115851]
37. Moertel CG, et al. Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. *N Engl J Med*. 1992; 326(8):519–23. [PubMed: 1310159]
38. Cheng PN, Saltz LB. Failure to confirm major objective antitumor activity for streptozocin and doxorubicin in the treatment of patients with advanced islet cell carcinoma. *Cancer*. 1999; 86(6): 944–8. [PubMed: 10491519]
39. Kouvaraki MA, et al. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. *J Clin Oncol*. 2004; 22(23): 4762–71. [PubMed: 15570077]

40. Loo TL, et al. Mechanism of action and pharmacology studies with DTIC (NSC-45388). *Cancer Treat Rep.* 1976; 60(2):149–52. [PubMed: 1260772]
41. Ramanathan RK, et al. Phase II trial of dacarbazine (DTIC) in advanced pancreatic islet cell carcinoma. Study of the Eastern Cooperative Oncology Group-E6282. *Ann Oncol.* 2001; 12(8): 1139–43. [PubMed: 11583197]
42. Altamari AF, et al. DTIC therapy in patients with malignant intra-abdominal neuroendocrine tumors. *Surgery.* 1987; 102(6):1009–17. [PubMed: 2825370]
43. Kessinger A, Foley JF, Lemon HM. Use of DTIC in the malignant carcinoid syndrome. *Cancer Treat Rep.* 1977; 61(1):101–2. [PubMed: 861955]
44. Stevens MF, et al. Antitumor activity and pharmacokinetics in mice of 8-carbamoyl-3-methylimidazo[5,1-d]-1,2,3,5-tetrazin-4(3H)-one (CCRG 81045; M & B 39831), a novel drug with potential as an alternative to dacarbazine. *Cancer Res.* 1987; 47(22):5846–52. [PubMed: 3664486]
45. Kulke MH, et al. Phase II study of temozolomide and thalidomide in patients with metastatic neuroendocrine tumors. *J Clin Oncol.* 2006; 24(3):401–6. [PubMed: 16421420]
46. Varker KA, Campbell J, Shah MH. Phase II study of thalidomide in patients with metastatic carcinoid and islet cell tumors. *Cancer Chemother Pharmacol.* 2008; 61(4):661–8. [PubMed: 17589846]
47. Ekeblad S, et al. Temozolomide as monotherapy is effective in treatment of advanced malignant neuroendocrine tumors. *Clin Cancer Res.* 2007; 13(10):2986–91. [PubMed: 17505000]
48. Fine RL, et al. Capecitabine and temozolomide (CAPTEM) for metastatic, well-differentiated neuroendocrine cancers: The Pancreas Center at Columbia University experience. *Cancer Chemother Pharmacol.* 2013; 71(3):663–70. [PubMed: 23370660]
49. Strosberg JR, et al. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. *Cancer.* 2011; 117(2):268–75. [PubMed: 20824724]
50. Moertel CG, et al. Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. Evidence of major therapeutic activity in the anaplastic variants of these neoplasms. *Cancer.* 1991; 68(2):227–32. [PubMed: 1712661]
51. Turner NC, et al. Chemotherapy with 5-fluorouracil, cisplatin and streptozocin for neuroendocrine tumours. *Br J Cancer.* 2010; 102(7):1106–12. [PubMed: 20234360]
52. Waldherr C, et al. Tumor response and clinical benefit in neuroendocrine tumors after 7.4 GBq (90)Y-DOTATOC. *J Nucl Med.* 2002; 43(5):610–6. [PubMed: 11994522]
53. Virgolini I, et al. In- and Y-DOTA-lanreotide: results and implications of the MAURITIUS trial. *Semin Nucl Med.* 2002; 32(2):148–55. [PubMed: 11965610]
54. Kwekkeboom DJ, et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. *J Clin Oncol.* 2008; 26(13):2124–30. [PubMed: 18445841]
55. Ranieri G, et al. Vascular endothelial growth factor (VEGF) as a target of bevacizumab in cancer: from the biology to the clinic. *Curr Med Chem.* 2006; 13(16):1845–57. [PubMed: 16842197]
56. Yao JC, et al. Targeting vascular endothelial growth factor in advanced carcinoid tumor: a random assignment phase II study of depot octreotide with bevacizumab and pegylated interferon alpha-2b. *J Clin Oncol.* 2008; 26(8):1316–23. [PubMed: 18323556]
57. Kulke MH, et al. A prospective phase II study of 2-methoxyestradiol administered in combination with bevacizumab in patients with metastatic carcinoid tumors. *Cancer Chemother Pharmacol.* 2011; 68(2):293–300. [PubMed: 20960192]
58. Chan JA, et al. Prospective study of bevacizumab plus temozolomide in patients with advanced neuroendocrine tumors. *J Clin Oncol.* 2012; 30(24):2963–8. [PubMed: 22778320]
59. Venook AP, et al. Phase II trial of FOLFOX plus bevacizumab in advanced, progressive neuroendocrine tumors. *J Clin Oncol (Meeting Abstracts).* 2008; 26(15_suppl):15545.
60. Kunz PL, et al. A phase II study of capecitabine, oxaliplatin, and bevacizumab for metastatic or unresectable neuroendocrine tumors. *J Clin Oncol (Meeting Abstracts).* 2010; 28(15_suppl):4104.
61. Hobday TJ, et al. Multicenter Phase II Trial of Temsirolimus and Bevacizumab in Pancreatic Neuroendocrine Tumors. *J Clin Oncol.* 2015; 33(14):1551–6. [PubMed: 25488966]

62. Kulke MH, 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). J Clin Oncol (Meeting Abstracts). 2015; 33(suppl) abstr 4005.
63. Hobday TJ, et al. Multicenter prospective phase II trial of bevacizumab (bev) for progressive pancreatic neuroendocrine tumor (PNET). J Clin Oncol (Meeting Abstracts). 2015; 33(suppl) abstr 4096.

KEY POINTS

1. Pancreatic neuroendocrine tumors are genetically and clinically different than extrapancreatic neuroendocrine tumors (i.e. carcinoid tumors) and often respond to cytotoxic and targeted treatments.
2. 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.
3. Somatostatin analogs (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.
4. Sunitinib and everolimus are two targeted therapies approved for progressive pancreatic neuroendocrine tumors and are generally reserved for use in tumors that have progressed on somatostatin analog therapy.
5. Pancreatic neuroendocrine tumors can respond to cytotoxic chemotherapy, and the most commonly used agents include alkylating, fluorouracil, and platinum drugs.