Medical Management of Pancreatic Neuroendocrine Tumors: Current and Future Therapy

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KEYWORDS

• Pancreatic neuroendocrine tumor • Somatostatin analogue • mTOR • Everolimus • Sunitinib • Temozolomide

KEY POINTS

- Low- and intermediate-grade pancreatic neuroendocrine tumors (NETs) are characterized by variable but most often indolent biological behavior.
- Somatostatin analogues decrease hormone production in functional NETs and improve progression-free survival.
- The tyrosine kinase inhibitor sunitinib and the mechanistic target of rapamycin inhibitor everolimus improve progression-free survival in patients with progressive pancreatic NETs.
- Pancreatic NETs may respond to alkylating agents, including streptozocin and temozolomide.
- Studies to evaluate the optimal timing, sequence, and combination of therapies and to identify predictors of response are warranted.

INTRODUCTION

Well-differentiated neuroendocrine tumors (NETs) are a rare and heterogeneous group of neoplasms that arise from neuroendocrine cells located throughout the body. These tumors can be broadly classified as either pancreatic NETs or carcinoid tumors, which include NETs arising in other sites, including the thymus, lung, and gastrointestinal (GI) tract. They are characterized by variable but most often indolent biological behavior and are also classically characterized by their ability to secrete peptides resulting in distinctive hormonal syndromes.

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Pancreatic NETs compose approximately 1% to 2% of all pancreatic neoplasms. Although NETs have been considered rare, recent studies suggest that they are more common than previously suspected. Analysis of the Surveillance, Epidemiology, and End Results database has demonstrated a significant increase in the incidence of NETs over time, with an age-adjusted annual incidence of pancreatic NETs in the United States of 0.3 cases per 100,000 population.[1] The increase in incidence is likely attributable to increasing awareness, improved diagnostic strategies, and possibly other undetermined environmental and genetic factors.

When pancreatic NETs are diagnosed at an early stage, surgical resection is often curative. Unfortunately, curative surgery is rarely an option for patients with metastatic disease. Until recently, systemic treatment options for patients with advanced pancreatic NETs were limited. However, improvements in our understanding of signaling pathways involved in the pathogenesis, growth, and spread of NETs have translated into an expansion of treatment options. Treatment approaches with somatostatin analogues, agents targeting the vascular endothelial growth factor (VEGF) signaling pathway and the mechanistic target of rapamycin (mTOR), provide therapeutic options for these patients. Cytotoxic chemotherapy may also benefit some patients, particularly those with high disease burden. The aim of this article is to summarize the current and future systemic therapy options for patients with advanced pancreatic NETs.

CLASSIFICATION OF PANCREATIC NEUROENDOCRINE TUMORS

Several histologic and anatomic classification systems for NETs have been proposed. Although there are differences in the specific criteria for grading tumors, the classification systems reflect the observation that NETs consist of a spectrum of diseases ranging from indolent well-differentiated, low-grade tumors to aggressive poorly differentiated, high-grade tumors (**Table 1**). In general, tumors with a high histologic grade represent aggressive neuroendocrine carcinomas that have a different natural history and response to treatment compared with low-grade, well-differentiated NETs.[2–4] In the 2010 World Health Organization (WHO) classification, neuroendocrine neoplasms of the digestive system are categorized as low grade (G1), intermediate grade (G2), and high grade (G3) based on the mitotic count and proliferative (Ki-67) index.[2] High-grade carcinomas have a more aggressive biology and are generally treated with platinum-based chemotherapy regimens used to treat small cell lung cancer. In contrast, well-differentiated, low- and intermediate-grade NETs have lower measures of cell proliferation and a more indolent biology.

Notably, there is a subset of patients with NETs that seem histologically well differentiated or moderately differentiated but have Ki-67 proliferation indices greater than 20% that fall into the high-grade range.[5] The most appropriate therapy for this heterogeneous subgroup of patients has not been well established. In a retrospective study of 305 patients with G3 neuroendocrine carcinomas of the GI tract (23% with pancreatic primary site), patients with a Ki-67 less than 55% had significantly longer median survival compared with patients with higher Ki-67 indices (14 months vs 10 months).[6] Response rates to platinum-based chemotherapy were lower in patients with a Ki-67 less than 55% (15% vs 42%). Because sensitivity to platinum-based chemotherapy seems to be associated with higher Ki-67 proliferation rates, other cytotoxic agents, such as temozolomide, or targeted agents, such as mTOR inhibitors or VEGF pathway inhibitors, may play a role in the management of well- to moderately differentiated high-grade disease.

Pancreatic NETs are also classified according to their functional status. Functional tumors, which account for approximately 30% of pancreatic NETs, are associated

Table 1
Nomenclature and classification for NETs

Differentiation	Grade	Mitotic Count[a]	Ki-67 Index[b] (%)	Traditional	ENETS,[65,66] WHO[2]
Well differentiated	Low grade (G1)	<2 per 10 HPF	≤2	Carcinoid, islet cell, pancreatic NET	NET, grade 1
	Intermediate grade (G2)	2–20 per 10 HPF	3–20	Carcinoid, atypical carcinoid[c], islet cell, pancreatic NET	NET, grade 2
Poorly differentiated	High grade (G3)	>20 per 10 HPF	>20	Small cell carcinoma	Neuroendocrine carcinoma, grade 3, small cell
				Large cell neuroendocrine carcinoma	Neuroendocrine carcinoma, grade 3, large cell

Abbreviations: ENETS, European Neuroendocrine Tumor Society; HPF, high power field.

[a] Counted in 10 high power fields. High power field = 2 mm^2 at least 40 fields (at 40× magnification) evaluated in areas of highest mitotic density. Cutoffs per AJCC seventh edition.[67]

[b] MIB1 antibody; percentage of 2000 tumor cells in areas of highest nuclear labeling. Cutoffs per AJCC seventh edition.[67]

[c] The term *atypical carcinoid* only applies to intermediate-grade NETs of the lung.

with clinical syndromes related to hormone secretion.[7] These tumors, including insulinoma, gastrinoma, glucagonoma, and vasoactive intestinal peptide (VIPoma), are named according to the hormone that is secreted. In contrast, nonfunctional tumors include those that are not associated with a specific clinical syndrome related to hormone secretion.

GENETIC BASIS OF NEUROENDOCRINE TUMORS

Inherited Neuroendocrine Tumor Syndromes

Most pancreatic NETs occur as nonfamilial (sporadic) tumors. However, several autosomal dominant genetic syndromes, including multiple endocrine neoplasia type 1 (MEN1), von Hippel-Lindau syndrome (VHL), neurofibromatosis type 1 (NF-1), and tuberous sclerosis (TS), have been associated with the development of NETs. MEN1 is caused by inactivating mutations of the *MEN1* gene. VHL results from germline mutations in the *VHL* gene, which functions as a tumor suppressor gene that regulates hypoxia-induced cell proliferation and angiogenesis. NF-1 and TS are caused by inactivating mutations in the tumor suppressor genes *NF1* and *TSC1* and *TSC2*, respectively.[8] *NF1* encodes the protein neurofibromin, which regulates *TSC1* and *TSC2*.[9] TSC1 and TSC2 form a tumor suppressor heterodimer that inhibits *mTOR*. Although most NETs are sporadic, the molecular genetics of these tumor susceptibility syndromes provide insight into the genetic mechanisms of this disease.

Recent efforts have also focused on the genetic basis of sporadic, nonfamilial pancreatic NETs. In a study involving exome sequencing of nonfamilial pancreatic NETs, Jiao and colleagues[10] found that the most frequently mutated genes encoded proteins involved in chromatin remodeling. Forty-four percent of tumors had somatic inactivating mutations in *MEN1*, and 43% had mutations in genes encoding either death-domain-associated protein (*DAXX*) or α thalassemia/mental retardation syndrome X-linked (*ATRX*). Mutations in genes in the mTOR pathway occurred in 14% of tumors. Furthermore, mutations in *MEN1* and *DAXX/ATRX* genes may identify a biologically distinct subgroup of pancreatic NETs with a favorable prognosis. Mutations in *MEN1, DAXX/ATRX*, or the combination of these genes were associated with improved survival; 100% of patients with mutations in both *MEN1* and *DAXX/ATRX* survived at least 10 years in contrast to death within 5 years of diagnosis for 60% of patients without these mutations.[10] Studies are ongoing to investigate whether the mutational profile is a predictive response to chemotherapy or targeted agents, including mTOR inhibitors.

SYSTEMIC TREATMENT OF ADVANCED PANCREATIC NEUROENDOCRINE TUMORS

Multiple options are available for the management of patients with advanced, metastatic pancreatic NETs, including surgical resection, liver-directed therapies, and systemic therapy. Because of the heterogeneity of disease biology and presentation, a multidisciplinary approach to management is critical. The goals of therapy are to improve symptoms related to hormone hypersecretion, slow disease progression, and improve survival. Systemic therapy options include somatostatin analogue therapy, cytotoxic chemotherapy, and targeted agents, including everolimus and sunitinib.

Somatostatin Analogues

Somatostatin is a natural 14-amino acid peptide that binds to G-protein-coupled somatostatin receptors (SSTRs) that are expressed on most NETs.[11] Of the 5 different SSTR subtypes, SSTR-2 is expressed in approximately 80% of pancreatic NETs, with the exception of insulinomas, which express SSTR-2 in less the 50% of cases.[12]

By binding to somatostatin receptors, somatostatin analogues, including octreotide and lanreotide, have both antisecretory and antiproliferative effects.

Somatostatin analogues and control of symptoms from hormone secretion

Patients with metastases from functional pancreatic NETs often become symptomatic from hormone hypersecretion rather than from tumor bulk. Symptoms related to hormone secretion can often be well controlled with somatostatin analogues. The role of somatostatin analogues has been best established for patients with VIPoma and glucagonoma.[13,14] Overproduction of vasoactive intestinal peptide can result in severe secretory diarrhea and hypokalemia. These tumors are very responsive to administration of somatostatin analogues, which can reduce VIP levels and improve symptoms.[15,16] In patients with glucagonoma, reduction in glucagon levels and improvement in the characteristic rash (necrolytic migratory erythema) are observed in most patients with the use of somatostatin analogues.[17,18]

Although insulinomas and gastrinomas represent the most common types of functioning pancreatic NETs, the role of somatostatin analogues in controlling hormone-related symptoms for these tumor types is less well established. In patients with gastrinoma, high-dose proton pump inhibitors can effectively control hypergastrinemia-related gastric acid production and remain a mainstay of treatment in these patients. In patients with insulinoma, only 50% of patients express SSTR-2. In patients without SSTR-2 expression, hypoglycemia may paradoxically worsen because of inhibition of glucagon secretion caused by somatostatin analogue therapy. Therefore, patients with insulinoma need to be closely monitored when initiating therapy with somatostatin analogue therapy.

Somatostatin analogues and disease control

The antiproliferative effects of somatostatin analogues occur through both direct and indirect mechanisms. Binding of somatostatin analogues to SSTR-2 and SSTR-5 can lead to arrest of mitosis and cell cycle and may also induce apoptosis. The indirect antiproliferative effects of somatostatin analogues may be mediated through decreased production of circulating growth factors and inhibition of angiogenesis via reduction in production and release of proangiogenic factors.[19–21]

Although objective tumor shrinkage with somatostatin analogues is rare, tumor growth may be slowed. In the PROMID study, 85 patients with inoperable or metastatic well-differentiated midgut NETs were randomized to receive octreotide LAR 30 mg monthly or placebo.[22] Median time to tumor progression was significantly longer for patients receiving octreotide (14.3 vs 6.0 months). A limitation of this study, however, was that it did not include patients with pancreatic NETs.

More recently, however, support for the antiproliferative effect of somatostatin analogues in pancreatic NETs was provided by the phase III CLARINET trial, which compared lanreotide versus placebo in 204 patients with advanced well- or moderately differentiated, nonfunctioning GI and pancreatic (45%) NETs.[23] Patients were randomly assigned to receive either 120 mg lanreotide Autogel or placebo every 4 weeks for 96 weeks or until progressive disease or death. All patients had avid disease on SSTR scintigraphy. Most patients (96%) had no tumor progression in the 3 to 6 months before randomization. Compared with placebo, lanreotide was associated with significantly prolonged progression-free survival (PFS), with a similar effect seen across major subgroups. At a time point of 2 years following initiation of treatment, the median PFS was not reached with lanreotide compared with 18 months with placebo (hazard ratio [HR] for progression or death 0.45; 95% confidence interval [CI] 0.30–0.73). Based on these data, lanreotide has been approved in the United

States for the treatment of patients with unresectable, well- or moderately differentiated, locally advanced or metastatic gastroenteropancreatic NETs.

TARGETED THERAPY

Mechanistic Target of Rapamycin Inhibitors

The mTOR (also referred to as mammalian target of rapamycin) is an intracellular serine/threonine kinase that regulates key cell functions involved in cell survival, proliferation, and metabolism. Signaling through the PI3K (phosphatidylinositide 3-kinase)/AKT/mTOR pathway leads to increased translation of proteins regulating cell cycle progression and metabolism.[24] mTOR mediates downstream signaling from several pathways, including VEGF and insulin-like growth factor (IGF), that are implicated in NET growth.[25] Several observations support the importance of the mTOR pathway in the pathogenesis of NET. First, although most NETs arise sporadically, NETs can arise within the context of several familial cancer syndromes, including NF-1 and TSC, that are due to inactivating mutation in tumor suppressor genes leading to activation of the mTOR pathway. Additionally, gene expression analyses have demonstrated altered expression of genes in the mTOR pathway, and recent gene sequencing studies of pancreatic NETs have revealed mutations in genes in the mTOR pathway in 14% of tumors.[10,26]

Everolimus monotherapy was compared with best supportive care alone in the placebo-controlled RADIANT-3 trial, which included 410 patients with advanced pancreatic NETs (**Table 2**).[27] Approximately 40% of patients also received somatostatin analogue therapy. Everolimus was associated with a significant prolongation in median PFS (11.0 vs 4.6 months, HR for progression 0.35, 95% CI 0.27–0.45). Confirmed objective partial radiographic responses were observed in 5% of patients receiving everolimus compared with 2% of those receiving placebo. The rate of tumor stabilization was high, 73% among patients receiving everolimus versus 51% in the placebo group. Based on this result, everolimus was approved by the Food and Drug Administration (FDA) for patients with progressive pancreatic NETs.

Table 2
Clinical trials of mTOR inhibitors in pancreatic NET tumors

Study	Agent	No. Patients	Tumor Response Rate (%)	Median TTP (^{T}) or PFS (^{P})	Reference
Phase II studies					
RADIANT-1	Everolimus	115	9	9.7 mo^{P}	Yao et al,[61] 2010
	Everolimus + octreotide	45	4	16.7 mo^{P}	
	Temsirolimus[a]	15	7	10.6 mo^{T}	Duran et al,[68] 2006
	Temsirolimus + bevacizumab	58	41	13.2 mo^{P}	Hobday et al,[58] 2014
Phase III studies					
RADIANT-3	Everolimus	207	5	11.0 mo^{P}	Yao et al,[27] 2011
	Placebo	203	2	4.6 mo^{P}	
CALGB 80701	Everolimus	75	12	14.0 mo^{P}	Kulke et al,[59] 2015
	Everolimus + bevacizumab	75	31	16.7 mo^{P}	

Abbreviations: CALGB, Cancer and Leukemia Group B; PFS, progression-free survival; TTP, time to progression.

[a] Data from the subset of patients with pancreatic NET in this phase II study of unselected patients with NET are presented.

Drug-related adverse events included stomatitis, rash, diarrhea, and fatigue.[27] The most common grade 3 or 4 drug-related adverse events were stomatitis (7%), anemia (6%), and hyperglycemia (5%). Although rare, everolimus has been associated with serious adverse events, including pneumonitis.

Everolimus causes hyperglycemia, particularly in those with preexisting hyperglycemia. In the RADIANT-3 trial, the frequency of severe (grade 3 or 4) hyperglycemia was higher in those with preexisting diabetes mellitus or baseline hyperglycemia (15% vs 3% in those without diabetes or baseline hyperglycemia).[28] Because of this effect, everolimus may be of particular value in patients with hypoglycemia related to insulinoma.[29,30] An objective tumor response may lead to improvements in insulin secretion, and it is also possible that everolimus may have a direct effect on insulin production and/or release or an effect on peripheral insulin sensitivity.

Vascular endothelial growth factor pathway inhibitors

A key role for angiogenesis and VEGF pathway signaling in NET is suggested by clinical observations that NETs are vascular tumors. Expression of VEGF has been demonstrated in carcinoid and pancreatic NETs.[31,32] Increased expression of VEGF receptor-2 (VEGFR-2) has been demonstrated in tissue from GI carcinoid tumors and a carcinoid cell line.[33,34] Additionally, pancreatic NETs show widespread expression of VEGFR-2 and -3 in addition to platelet-derived growth factor receptors α and β, stem-cell factor receptor (c-kit).[35–37]

Sunitinib was evaluated in a multi-institutional phase II study enrolling 109 patients with advanced NETs (**Table 3**).[38] Partial responses were observed in 16% of the pancreatic neuroendocrine cohort. Based on evidence of activity in this study, an international randomized phase III study to confirm the activity of sunitinib in pancreatic NETs was undertaken. After enrolling 171 patients, the study was halted before a planned interim analysis. Treatment with sunitinib was associated with a median PFS of 11.4 months, as compared with 5.5 months for placebo (HR 0.42, 95% CI 0.26–0.66).[39] Based on this result, sunitinib was approved by the FDA for patients with progressive pancreatic NETs. The most common grade 3 or 4 drug-related adverse events were neutropenia (12%), hypertension (10%), fatigue (5%), and diarrhea (5%).

Table 3
Clinical trials of VEGF pathway inhibitors in pancreatic NET tumors

Study	Agent	No. Patients	Tumor Response Rate (%)	Median TTP or PFS	Reference
Phase II studies	Sunitinib[a]	66	17	7.7 mo^{T}	Kulke et al,[38] 2008
	Sorafenib[a]	43	11	11.9 mo^{P}	Hobday et al,[40] 2007
	Pazopanib[a]	32	22	14.4 mo^{P}	Phan et al,[41] 2015
	Bevacizumab	22	9	13.6 mo^{P}	Hobday et al,[42] 2015
	Temsirolimus + bevacizumab	58	41	13.2 mo^{P}	Hobday et al,[58] 2014
Phase III studies	Sunitinib	86	9	11.4 mo^{P}	Raymond et al,[39] 2011
	Placebo	85	0	5.5 mo^{P}	
CALGB 80701	Everolimus	75	12	14 mo^{P}	Kulke et al,[59] 2015
	Everolimus + bevacizumab	75	31	16.7 mo^{P}	

Abbreviations: P, median PFS; PFS, progression-free survival; T, median time to progression; TTP, time to progression.

[a] Data from the subset of patients with pancreatic NET in these phase II studies of unselected patients with NET are presented.

Other tyrosine kinase inhibitors with activity against VEGFR have been evaluated in prospective trials of patients with advanced pancreatic NETs (see **Table 3**). In a preliminary report of a phase II study examining the activity of sorafenib in the treatment of NETs, responses were seen 11% of 43 patients with pancreatic NETs.[40] Pazopanib has been evaluated in a phase II study that enrolled 52 patients with advanced NETs, including 32 with pancreatic NETs. Seven (22%) of the patients with pancreatic NETs achieved an objective response. Notably, 6 (29%) of the 21 patients with pancreatic NETs who had progressive disease at study entry showed objective responses. The median PFS and overall survival (OS) in the cohort with pancreatic NETs were 14.4 months and 25.0 months, respectively.[41]

Bevacizumab, a monoclonal antibody against VEGF, has also been evaluated as monotherapy in patients with advanced pancreatic NETs. In a phase II study of 22 patients with progressive well- or moderately differentiated pancreatic NETs, treatment with bevacizumab was associated with a confirmed partial response rate of 9% and median PFS of 13.6 months.[42]

Cytotoxic Chemotherapy

Various studies have demonstrated that pancreatic NETs are responsive to cytotoxic chemotherapy. Because of the higher response rates associated with chemotherapy compared with somatostatin analogues and targeted agents, chemotherapy is often used in patients who are symptomatic from tumor bulk or who have more rapidly progressive disease.

Streptozocin-containing regimens

In an early randomized trial, streptozocin plus doxorubicin had a combined biochemical and radiologic response rate of 69% and a median survival of 2.2 years.[43] The FDA subsequently approved streptozocin as a treatment of patients with pancreatic NETs. The very high response rates reported in this study may derive in part from the use of nonstandard response criteria. A large retrospective analysis of 84 patients with either locally advanced or metastatic pancreatic endocrine tumors receiving a 3-drug regimen of streptozocin, fluorouracil, and doxorubicin showed that this regimen was associated with an overall response rate of 39% and a median survival duration of 37 months.[44] Despite the demonstrated efficacy of streptozocin-based regimens, concerns about toxicity, together with a cumbersome 5-consecutive-day infusion schedule, has precluded their more widespread use.

Dacarbazine- and temozolomide-containing regimens

Like streptozocin, dacarbazine is an alkylating agent with activity against pancreatic NETs. In an Eastern Cooperative Oncology Group (ECOG) phase II trial of dacarbazine in 42 patients with advanced pancreatic NETs, the objective response rate was 33%.[45] As with streptozocin, concerns regarding toxicity have limited use of dacarbazine. Temozolomide is a less toxic orally active analogue of dacarbazine. Recent prospective and retrospective studies have suggested that temozolomide-based regimens may be comparable in efficacy with streptozocin-based regimens and that these regimens may also be more tolerable (**Table 4**). In retrospective series, temozolomide-based therapy has been associated with overall response rates of 8% to 70%.[46–48] Temozolomide has been evaluated prospectively in combination with thalidomide, bevacizumab, and everolimus, with overall response rates of 33% to 45%.[49–51] In a retrospective series of 30 patients who were treated with temozolomide plus capecitabine, the response rate was 70%.[48] Although temozolomide-based therapy is clearly active in pancreatic NETs, neither the optimal dosing regimen nor the relative benefits of combination

Table 4
Clinical trials of temozolomide-based therapy in pancreatic NET tumors

Regimen	N	Tumor Response Rate (%)	PFS (mo)	Reference
Retrospective studies				
Temozolomide	12	8	NR	Ekeblad et al,[46] 2007
Temozolomide + capecitabine	30	70	18.0	Strosberg et al,[48] 2011
Temozolomide (various regimens)	53	34	13.6	Kulke et al,[47] 2009
Prospective trials				
Temozolomide + thalidomide	11	45	NR	Kulke et al,[49] 2006
Temozolomide + bevacizumab	15	33	14.3	Chan et al,[50] 2012
Temozolomide + everolimus	40	40	15.4	Chan et al,[51] 2013

Abbreviations: PFS, progression-free survival; NR, not reported.
[a] Data shown are limited to results for pancreatic NET in studies that may have included both pancreatic NET and carcinoid.

therapy has been clearly established. An ongoing trial by ECOG is evaluating the activity of the combination of temozolomide plus capecitabine compared with temozolomide alone (National Clinical Trial [NCT] NCT01824875).

FUTURE DIRECTIONS

Peptide Receptor Radionuclide Therapy

The high rate of SSTR expression in NETs provides the rationale for peptide receptor radionuclide therapy (PRRT) as a treatment modality for patients with inoperable or metastatic disease. Somatostatin analogues with high receptor affinity are conjugated with chelators and a radionuclide to deliver a tumoricidal dose of radiation. The most frequently used radionuclides include the β-emitting radionuclide ^{90}yttrium (^{90}Y) and β- and γ-emitting ^{177}lutetium (^{177}Lu).[52,53] Differences in patient characteristics, tumor types, radionuclides, and cumulative administered doses have made it difficult to compare studies that have reported on the efficacy of PRRT.

In a prospective, phase II study of 90 patients with metastatic carcinoid tumor and symptoms refractory to octreotide treated with ^{90}Y-DOTA-Tyr^3-octreotide, more than 50% of patients had improvement in symptom control. Modest tumor responses were noted, including 4% of patients with a partial radiographic response and 70% stable disease following treatment.[54] In another single-center phase II study of ^{90}Y-DOTA-Tyr^3-octreotide that included 1109 patients, 378 (34%) experienced morphologic response; 172 (16%), biochemical response; and 329 (30%), clinical response. Longer survival was associated with morphologic, biochemical, and clinical responses.[55] Overall, 142 patients (13%) developed severe transient grade 3 to 4 hematologic toxicities. Two patients developed myeloproliferative diseases, and 2 experienced tumor lysis syndrome.

A retrospective analysis of ^{177}Lu-DOTA-Tyr^3-octreotate in the treatment of more than 500 patients with metastatic NET reported efficacy results for 310 patients. Complete and partial tumor remissions were demonstrated in 2% and 28% of patients, respectively. Minor tumor response (decrease in size >25% and <50%) occurred in 16%. The median time to progression was 40 months. The median OS from the start of treatment was 46 months, and the median OS from diagnosis was 128 months.[56] An assessment of toxicity in 504 patients demonstrated acute toxicity, including nausea (25%), vomiting (10%), and abdominal pain (10%). Serious delayed toxicity occurred

in 9 patients, including renal insufficiency (n = 2), temporary liver function test abnormalities (n = 3), and myelodysplastic syndrome (n = 4).

Randomized, prospective studies better defining the antitumor activity and long-term toxicity of radiolabeled somatostatin analogues are anticipated. The NETTER-1 study, a multinational randomized phase III study of ^{177}Lu-DOTA-Tyr^3-octreotate compared with high dose octreotide LAR (60 mg monthly) in patients with midgut NET with progressive disease on standard-dose octreotide, completed accrual in early 2015. Results of this study (NCT01578239) will provide additional information on efficacy and safety of PRRT.

Combination therapy

Targeting multiple signaling pathways may provide better tumor control and overcome resistance mechanisms. Combining an mTOR inhibitor of the VEGF pathway, somatostatin analogues, and cytotoxic chemotherapy have been evaluated as treatment strategies for NETs.

Combining mechanistic target of rapamycin inhibitor and vascular endothelial growth factor pathway inhibitor

Several recently completed and ongoing studies have evaluated the combination of an mTOR inhibitor with inhibitors of the VEGF pathway. Combining everolimus with tyrosine kinase inhibitors of VEGFR and other growth factor receptors may be limited by toxicity. In a phase I study of everolimus in combination with sorafenib, dose-limiting toxicity precluding escalation to full doses of each agent was observed.[57] However, combinations of an mTOR inhibitor and bevacizumab seem to be better tolerated and have demonstrated higher levels of activity than would have been expected with single-agent therapy. In a phase II trial of temsirolimus plus bevacizumab in 58 patients with progressive pancreatic NETs, confirmed partial responses were documented in 23 of 56 patients eligible for response assessment (41%) with a median PFS of 13.2 months.[58] Additionally, the Cancer and Leukemia Group B (CALGB) 80701, a randomized phase II trial of 150 patients with advanced pancreatic NETs who received standard-dose octreotide LAR and everolimus with or without bevacizumab, demonstrated superior PFS with everolimus plus bevacizumab compared with everolimus (16.7 vs 14.0 months; HR 0.80, 95% CI 0.55–1.17; $P = .12$).[59] Combination therapy also was associated with a significantly higher response rate (RR) of 31% compared with 12% with everolimus alone ($P = .005$). It should be noted that patients receiving combination therapy had a higher incidence of grade 3/4 adverse events, including hypertension, proteinuria, diarrhea, and electrolyte abnormalities.

Combining mechanistic target of rapamycin inhibitor and somatostatin analogue

Because octreotide has been shown to decrease IGF-1 levels and PI3K/Akt signaling in vitro, it has been postulated that combining an mTOR inhibitor with a somatostatin analogue might result in enhanced antitumor activity.[60] Clinical trial data, however, have not demonstrated a definite benefit. Everolimus has been evaluated in combination with octreotide in several studies, including patients with pancreatic NETs in stratum 2 of the phase II RADIANT-1 trial and patients with carcinoid tumors in the phase III RADIANT-2 trial. In the RADIANT-1 trial, patients with pancreatic NETs receiving octreotide and everolimus had longer PFS compared with patients receiving everolimus monotherapy (**Table 2**).[61] However, the study was not randomized or designed to make this comparison. In the RADIANT-2 trial, although combined therapy with everolimus and octreotide was associated with a significantly longer PFS duration compared with everolimus and placebo based on local investigator radiology review, the improvement in PFS was not statistically significant according to central radiology review.[62]

Pasireotide is a novel somatostatin analog that binds to a broader range of somatostatin receptor subtypes than octreotide. Compared with octreotide, pasireotide has a greater binding affinity to SSTR-1, SSTR-3, and SSTR-5 and less affinity to SSTR-2.[63] The COOPERATE-2 study, a multicenter randomized phase II study, examined the efficacy of everolimus alone or in combination with pasireotide LAR in patients with advanced, progressive pancreatic NETs.[64] The results of this study showed no benefit for the addition of pasireotide with regard to tumor control. Further investigation is needed to determine whether there are specific subsets of patients with advanced NETs who benefit most from combination therapy with somatostatin analogues and targeted agents.

Combining mechanistic target of rapamycin inhibitor and chemotherapy

The combination of temozolomide and everolimus has been evaluated in a phase I/II study of patients with advanced pancreatic NETs.[51] Treatment was associated with known side effects of each drug without evidence of synergistic toxicity. Encouraging evidence of antitumor activity with this combination was observed. Among 40 evaluable patients, 16 (40%) experienced a partial response. The median PFS duration was 15.4 months, which is superior to the reported PFS observed with everolimus alone in the randomized, placebo-controlled RADIANT-3 study. However, these results need to be interpreted with caution because this was a single-arm study. Furthermore, disease progression before study enrollment was not a requirement in this study, as it was in the RADIANT-3 study. Future studies evaluating the relative efficacy of combining chemotherapy with an mTOR inhibitor compared with treatment with either agent alone are warranted.

SUMMARY

Advances in our understanding of the biology of NETs have translated into an expansion of treatment options for patients. Because of the heterogeneity of disease biology and presentation, a multidisciplinary approach to management is critical. Surgical resection remains the mainstay of the treatment of patients with localized disease. Several treatment options are available for patients with advanced pancreatic NETs. These options include hepatic-directed therapies, including surgical resection and hepatic artery embolization. Systemic treatment options include the use of somatostatin analogues for control of hormonal hypersecretion and also disease control. The tyrosine kinase inhibitor sunitinib and the mTOR inhibitor everolimus improve PFS in patients with pancreatic NETs. In patients with low-volume, low- and intermediate-grade disease without symptoms, a period of observation to better understand disease biology can be considered. In the setting of disease progression or development of symptoms related to disease, somatostatin analogue therapy is often initiated as the first-line therapy. Cytotoxic chemotherapy with alkylating agents, including streptozocin and temozolomide, can lead to tumor shrinkage and can be particularly useful for patients with symptoms related to bulk of disease. The optimal timing, sequence, and benefits of combination therapy are not known. Studies to examine these issues and to identify predictors of response may allow us to better tailor personalized treatment of individual patients in the future.

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