Targeted Therapy in Advanced Well-Differentiated Neuroendocrine Tumors

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Key Words. Neuroendocrine tumors • Targeted therapy • VEGF • mTOR • Temozolomide • Everolimus • Temsirolimus • Sunitinib • Bevacizumab • Sorafenib • Radionuclide

Disclosures: Chandrajit P. Raut: *Honoraria:* Novartis; Matthew H. Kulke: *Consultant/advisory role:* Pfizer, Novartis, Molecular Insight, Ipsen.

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the independent peer reviewers.

ABSTRACT

Treatments for advanced neuroendocrine tumors were, until recently, rather limited. Salvage surgery and liver-directed therapy both have relatively limited impact, and systemic cytotoxic chemotherapy has minimal efficacy. In the absence of other effective treatments, somatostatin analogs have been used for years to control disease and neuroendocrine symptoms, without cytotoxic intent. Advances in targeted therapy for neuroendocrine tumors

have opened several potentially new treatment paradigms in the management of these otherwise relatively drug-resistant neoplasms. Promising results have emerged from studies evaluating radiolabeled somatostatin analogs and inhibitors of the vascular endothelial growth factor and mammalian target of rapamycin pathways. This article reviews several of the more encouraging developments in this field. *The Oncologist* 2011;16:286–295

INTRODUCTION

Well-differentiated neuroendocrine tumors (NETs) are rare neoplasms that may be generally subclassified as carcinoids (arising in the gastrointestinal tract, lung, and thymus) and pancreatic NETs (arising in the pancreatic and peripancreatic tissue). The revised estimated annual incidence of clinically relevant carcinoids is 5.25 per 100,000 population, and the limited duration prevalence is >100,000 in the U.S. [1]. Advanced well-differentiated NETs may pursue a relatively indolent clinical course, in contrast to the potentially

more aggressive poorly differentiated NETs [2]. NETs may be functional, associated with symptoms of neuropeptide hypersecretion, or nonfunctional. Hypersecretion of serotonin and other vasoactive peptides may result in carcinoid syndrome. Hypersecretion of pancreatic neuropeptides may result in the heralding symptoms of insulinoma, vasoactive intestinal peptide (VIP)-oma, and gastrinoma.

Until recently, treatment options for patients with advanced NETs were limited to surgical debulking, local liver-directed therapy such as ablation or embolization, and

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somatostatin analogs. Cytotoxic chemotherapy, although active in patients with pancreatic NETs, has played only a minor role in the treatment of patients with advanced carcinoid tumors. Although surgery is the principal therapy for patients with localized NETs, surgery with cytoreductive intent has limited progression-free survival (PFS) benefit in patients with advanced disease. In a series of 170 patients undergoing hepatectomy for metastatic NETs, 84% experienced recurrent disease at 5 years [3]. The symptom control rate was high (>90%), but 59% of patients experienced recurrent symptoms at 5 years. The 5- and 10-year overall survival (OS) rates were 61% and 35%, respectively. Another retrospective study reported that patients undergoing cytoreductive surgery had a longer median OS time (43 months) than those undergoing embolization (24 months) [4]. Orthotopic liver transplantation (OLT) has been reported, but data are limited. In a series of 31 patients undergoing OLT for advanced NETs, the OS rate was higher in those with metastatic carcinoids (69% at 5 years) than in those with metastatic pancreatic NETs (8% at 4 years) [5].

Hepatic artery embolization exploits the observation that liver tumors typically derive their blood supply from the hepatic artery, whereas the normal hepatic parenchyma is generally supplied by the portal vein. Palliative embolization or chemoembolization may decrease hormonal secretion or induce radiographic regression. Patients with carcinoids have a better response rate (67% versus 35%) and longer PFS (23 months versus 16 months) and OS (34 months versus 23 months) times than those with pancreatic NETs [6].

This review evaluates the current state of targeted therapy options for patients with advanced well-differentiated NETs by summarizing recent trial data and briefly highlighting potential future directions. Patients with advanced poorly differentiated NETs are treated using regimens developed for small cell carcinoma and are beyond the scope of this article.

SOMATOSTATIN ANALOGS

Octreotide

Somatostatin is a 14-amino-acid peptide that binds to five different somatostatin receptors (sst1, sst2, sst3, sst4, and sst5) expressed on most NETs. Octreotide is an eight-amino-acid somatostatin analog that includes the phenylalanine-tryptophan-lysine-threonine four-amino-acid sequence critical for receptor binding. Octreotide is administered initially as a s.c. injection (150 μ g three times per day) and subsequently (if tolerated) as a monthly i.m. injection (octreotide long-acting release [LAR], 20–30 mg). It may be titrated to ameliorate the hormonal symptoms of carcinoid

syndrome or functional pancreatic NETs such as insulinoma, glucagonoma, VIPoma, and gastrinoma. In an early study demonstrating its efficacy, s.c. octreotide improved the symptoms of carcinoid syndrome in 88% of patients [7].

Lanreotide

Lanreotide is a somatostatin analog available as a long-acting s.c. injection. In a randomized study, lanreotide slow release demonstrated similar rates of symptom control and reduction in biochemical markers as octreotide LAR [8].

Pasireotide

Pasireotide is another somatostatin analog demonstrating greater affinity for most somatostatin receptors than octreotide. It has 30 $\times$, 5 $\times$, and 40 $\times$ more binding affinity for sst1, sst3, and sst5, respectively, than octreotide, and similar affinity for sst2 [9]. It is administered as an s.c. injection 300 μ g twice per day and escalated to 1,200 μ g twice per day every 3 days until symptom control is achieved.

In a phase II study, pasireotide achieved symptom control in 27% of patients with metastatic carcinoids whose symptoms were inadequately controlled by octreotide LAR [10].

Recent Developments

Although the somatostatin analogs have been proven to be remarkably effective in controlling tumor-related hormonal symptoms, only recently have they been evaluated definitively for potential cytotoxic effects. In the recently published 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), patients with locally inoperable or metastatic well-differentiated NETs treated with octreotide LAR (30 mg i.m. per month) had a longer median time to progression than those treated with placebo (14.3 months, versus 6.0 months; hazard ratio, 0.33; $p = .00037$) [11]. There was no significant difference between patients with functional and nonfunctional tumors. Despite this difference, though, the most favorable clinical response was stable disease (SD), not partial response (PR). Because of the crossover design of the trial, no difference in OS was expected or observed.

Future Trials

Two ongoing industry-sponsored phase III trials evaluating somatostatin analogs are under way. In one trial, pasireotide is being compared with high-dose octreotide in patients with refractory carcinoid syndrome. The primary endpoint is symptom control. The other is a placebo-controlled trial

Table 1. Alkylating agents in advanced well-differentiated NETs

Regimen	Tumor type	<i>n</i> of patients	Response rate (%)	Median OS (mos)	Study
Prospective phase II/III trials					
Chlorozotocin	Pancreatic NET	33	30	18.0	Moertel et al. (1992) [17]
Streptozocin + 5-fluorouracil	Pancreatic NET	33	45	16.8	Moertel and Hanley (1979) [61]
Streptozocin + doxorubicin	Pancreatic NET	36	69	26.4	
Streptozocin + cyclophosphamide	Carcinoid	47	26	12.5	
Streptozocin + 5-fluorouracil	Carcinoid	42	33	11.2	Engstrom et al. (1984) [62]
Streptozocin + 5-fluorouracil	Carcinoid	80	22	14.9	
Doxorubicin	Carcinoid	81	21	11.1	
Streptozocin + 5-fluorouracil	Carcinoid	88	16	24.3	Sun et al. (2005) [19]
Doxorubicin + 5-fluorouracil	Carcinoid	81	21	11.1	Bukowski et al. (1994) [63]
Dacarbazine	Carcinoid	56	16	20	
Dacarbazine	Pancreatic NET	50	34	19.3	
Temozolomide + thalidomide	Carcinoid	14	7	NR	Kulke et al. (2006) [20]
Temozolomide + bevacizumab	Pancreatic NET	11	45	NR	Kulke et al. (2006) [21]
	Pancreatic NET	17	24	NR	
Retrospective studies					
Streptozocin + doxorubicin	Pancreatic NET	16	6	NR	Cheng and Saltz (1999) [65]
Streptozocin + doxorubicin	Pancreatic NET	16	6	20.2	McCollum et al. (2004) [66]
Streptozocin + 5-fluorouracil + doxorubicin	Pancreatic NET	84	39	37	Kouvaraki et al. (2004) [18]
Temozolomide + capecitabine	Pancreatic NET	17	59	8.9	Isacoff et al. 2006 [67]
Temozolomide	Carcinoid	24	17	NR	Ekeblad et al. (2007) [68]
	Pancreatic NET	12	8	NR	
Temozolomide + capecitabine	Pancreatic NET	17	71	NR	Strosberg et al. (2008) [69]
Temozolomide-based therapy	Carcinoid	44	2	NR	Kulke et al. (2009) [23]
	Pancreatic NET	53	34	NR	
Abbreviations: NET, neuroendocrine tumor; NR, not reported; OS, overall survival.					

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evaluating lanreotide in patients with carcinoids and pancreatic NETs. The primary endpoint is PFS.

INTERFERON

Interferon (IFN)- α is a cytokine with reported efficacy in controlling symptoms of carcinoid syndrome refractory to somatostatin analogs [12, 13]. Both tumor regression and biochemical responses have been observed with low-dose IFN- α therapy [14].

A prospective study randomizing patients to octreotide alone or octreotide plus IFN- α demonstrated no difference in OS, but a lower rate of tumor progression was noted with combination therapy [15]. In a trial randomizing treatment-naïve patients to lanreotide, interferon, or both, similarly low rates of PR were observed in all three arms (4%, 4%, and 7%, respectively) [16]. Stable disease was noted in a

larger percentage of patients (28%, 26%, and 18%, respectively). Nevertheless, the response rates were lower than those noted in nonrandomized studies. There were no differences between patients with functional and nonfunctional NETs. These results, plus the potential for significant side effects from interferon, such as myelosuppression, fatigue, and depression, have diminished the enthusiasm for this as a treatment agent.

CYTOTOXIC SYSTEMIC CHEMOTHERAPY

Alkylating Agents

Streptozocin

Streptozocin has been used in combination with doxorubicin, 5-fluorouracil (5-FU), or both for patients with ad-

vanced pancreatic NETs based on a phase III trial reported by Moertel and colleagues (1992) (Table 1) [17]. That trial demonstrated a survival advantage associated with streptozocin–doxorubicin treatment, and streptozocin was approved for use for this indication. The response rates noted in that trial (45% for streptozocin and 5-FU, 69% for streptozocin and doxorubicin) were greater than those observed in other studies. This may be a result of the use of nonstandard response criteria, evaluating both biochemical and radiographic criteria. A subsequent single-institution retrospective study of 84 patients with locally advanced or metastatic pancreatic NETs treated with streptozocin, 5-FU, and doxorubicin reported an overall response rate of 39% [18].

Streptozocin has shown more modest response rates for patients with metastatic carcinoids. In a phase II/III trial comparing 5-FU plus doxorubicin with 5-FU plus streptozocin, the PR rates were 15.9% and 16%, respectively [19]. The median PFS times were 4.5 months and 5.3 months, respectively. There was a difference in the median OS times, 15.7 months and 24.3 months, respectively ($p = .0267$), favoring streptozocin. However, the survival advantage was offset by a 35% renal toxicity rate noted in the streptozocin arm. Consequently, streptozocin-based regimens are only rarely used in patients with advanced carcinoid.

Temozolomide

The routine use of streptozocin-based regimens in patients with NETs has been limited by concerns regarding their potential for toxicity. Temozolomide is an orally available alkylating agent that is similar to streptozocin in its mechanism of action. Temozolomide was evaluated in two prospective trials and several retrospective studies in both advanced carcinoid and pancreatic NET patients (Table 1). In one study of temozolomide and thalidomide, PRs were observed in 7% of patients with carcinoids and 45% of patients with pancreatic NETs [20]. In a second study evaluating temozolomide and bevacizumab, the PR rates were 0% and 24% in carcinoid and pancreatic NET patients, respectively [21].

This observed difference in response between carcinoid and pancreatic NET patients may be a result of differences in expression of O-6-methylguanine DNA methyltransferase (MGMT). The cytotoxicity of alkylating agents such as temozolomide has been attributed to the induction of DNA methylation at the O-6 position of guanine [22]. In the absence of MGMT, DNA mismatch repair is futile, leading to apoptosis and subsequent tumor cell death. However, MGMT restores such abnormally methylated DNA to its normal form. Thus, MGMT mitigates the effect of the alkylating agent, allowing the tumor cell to survive. The sensitivity of tumor cells to alkylating agents is associated with

MGMT deficiency, which in turn is more common in pancreatic NETs than in carcinoids.

If this is the case, then MGMT expression, as measured by immunohistochemical staining, may serve as a predictor of temozolomide response. In a recent analysis of 97 archival NETs and 101 consecutive NET patients, 51% of 37 archival and 34% of 53 patient pancreatic NETs were MGMT deficient, whereas none of the 60 archival and only 2% of the 44 patient carcinoids were [23]. Four of five patients with MGMT-deficient tumors (all pancreatic NETs) and none of the 16 patients with tumors expressing MGMT responded to temozolomide. These data suggest that the absence of MGMT may correlate with the sensitivity of pancreatic NETs to temozolomide therapy.

Future Directions

The correlation between MGMT deficiency and temozolomide sensitivity needs validation in larger studies. Prior to doing so, techniques assessing MGMT status in tumor tissue need to be standardized. If confirmed, then MGMT status may help identify which patients with NETs are likely to respond to alkylating agent therapy.

TARGETED THERAPY

Radiolabeled Peptides

Radiolabeled somatostatin analogs have been developed to target tumors positive for somatostatin receptors. A variety of synthetic somatostatin analogs with varying affinities for different somatostatin receptors have been conjugated to different radionuclides. The most extensively evaluated radionuclides, indium-111 (^{111}In), yttrium-90 (^{90}Y), and lutetium-177 (^{177}Lu), differ from each other in particles emitted, particle energy, and tissue penetration [24, 25]. In general, β -radiation-emitting radionuclides have a therapeutic advantage because the emitted particle has a longer range of tissue penetration [26].

Results of relevant studies evaluating the therapeutic efficacy of the various radiolabeled somatostatin analogs are listed in Table 2. In general, ^{111}In -labeled octreotide has demonstrated minimal objective tumor responses [27, 28]. The various ^{90}Y -labeled somatostatin analogs may be more efficacious, with response rates in the range of 7%–37% [25, 29–34]. However, they may cause renal and hematologic toxicity. Perhaps the largest experience involves ^{177}Lu -labeled [Tyr^3]octreotate, a somatostatin analog with very high affinity for sst2. This agent has been administered to >600 patients, with a response rate of approximately 30% reported in evaluable patients [35, 36]. The selective targeting of somatostatin receptors exploited in this treat-

Table 2. Radiolabeled somatostatin analogs in advanced well-differentiated neuroendocrine tumors

Agent	Emitted particle	Receptor ^a	n of patients	Response rate (%)	Study
[¹¹¹ In-DTPA]octreotide	β -particle, Auger electron		26	0	Valkema et al. (2002) [28]
			26	8	Anthony et al. (2002) [27]
[⁹⁰ Y-DOTA,Tyr ³]octreotide	High-energy β -particle	sst2 ↑	29	7	Otte et al. (1999) [30]
			30	23	Paganelli et al. (2001) [31]
			41	24	Waldherr et al. (2001) [33]
			39	34	Waldherr et al. (2002) [34]
			32	9	De Jong et al. (2002) [29]
[⁹⁰ Y-DOTA]lanreotide	High-energy β -particle	sst5 ↑	39	20	Virgolini et al. (2002) [32]
[⁹⁰ Y-DOTA,Tyr ³]octreotate	High-energy β -particle	sst2 ↑ ↑	75	37	Teunissen et al. (2005) [25]
[¹⁷⁷ Lu-DOTA,Tyr ³]octreotate	Low-energy β -, γ -particle	sst2 ↑ ↑	125	28	Kwekkeboom et al. (2005) [35]
			310	30	Kwekkeboom et al. (2008) [36]

Table modified from [70].

^aArrows indicate affinity of somatostatin analog for specific somatostatin receptor indicated relative to octreotide.**Table 3.** Vascular endothelial growth factor pathway inhibitors in advanced well-differentiated NETs

Agent	Target	Tumor type	n of patients	Partial response (%)	Median PFS/TTP (wks)	Study
Sorafenib	VEGFR, PDGFR, B-raf	Carcinoid	50	7	34 (PFS)	Hobday et al. (2007) [45]
		Pancreatic NET	43	11	52 (PFS)	
Bevacizumab versus pegylated IFN- α 2b	VEGF	Carcinoid	22 (each)	18 versus 0	66 (PFS)	Yao et al. (2008) [40]
Sunitinib	VEGFR, PDGFR, KIT, RET, Flt-3	Carcinoid	41	2	42 (TTP)	Kulke et al. (2008) [43]
		Pancreatic NET	66	16	33 (TTP)	
Sunitinib	VEGFR, PDGFR, KIT, RET, Flt-3	Pancreatic NET	171		11.4 mos (PFS)	Raymond et al. (2010) [44]
Placebo					5.5 mos (PFS)	
Pazopanib	VEGFR, PDGFR, KIT	Carcinoid	22	0	12.7 mos (PFS)	Phan et al. (2010) [46]
		Pancreatic NET	29	17	11.7 mos (PFS)	

Abbreviations: Flt-3, FMS-like tyrosine kinase-3; IFN- α , interferon- α ; NET, neuroendocrine tumor; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; TTP, time to progression; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

ment approach is promising, but its position in the treatment algorithm for NETs remains undefined.

Vascular Endothelial Growth Factor and Vascular Endothelial Growth Factor Receptor Inhibitors

Observations of the highly vascular nature of NETs have led investigators to evaluate the vascular endothelial growth factor (VEGF) pathway as a therapeutic target. Both carcinoids and pancreatic NETs overexpress VEGF and VEGF receptor (VEGFR)-1 and VEGFR-2 [37–39]. Four agents targeting the VEGF pathway have been evaluated in phase II and phase III trials (Table 3): bevacizumab, sunitinib, sorafenib, and pazopanib.

Bevacizumab

Bevacizumab is a monoclonal antibody directed against the VEGF ligand. It is used as first-line therapy in combination with cytotoxic chemotherapy for patients with advanced colorectal cancer, non-small cell lung cancer, and breast cancer. In a randomized phase II trial versus pegylated-IFN- α 2b in patients with carcinoids, patients treated with bevacizumab had higher rates of radiographic PR (18% versus 0%) and 18-week PFS (96% versus 68%; $p = .02$) [40]. In the bevacizumab arm, functional computed tomography (CT) scans also demonstrated decreased tumor blood flow, blood volume, and permeability surface. However, because of the small number of patients studied, it is difficult to correlate clinical outcomes and functional CT findings. Based

on the results of this study, the Southwest Oncology Group launched a phase III study randomizing patients with progressive carcinoids to bevacizumab or IFN (with or without octreotide LAR). The primary endpoint is PFS.

Bevacizumab has also been evaluated in combination with other agents. In another phase II study, combination therapy with bevacizumab and temozolomide was found to produce a PR rate of 14% and an SD rate of 79% in 34 patients with advanced disease [21]. All patients experiencing PRs had pancreatic NETs.

Bevacizumab is being further evaluated in combination with capecitabine and oxaliplatin [41], 5-FU, leucovorin, and oxaliplatin [42], methoxyestradiol (ClinicalTrials.gov identifier, NCT00328497), everolimus (ClinicalTrials.gov identifier, NCT00607113), and 5-FU, doxorubicin, and streptozocin (ClinicalTrials.gov identifier, NCT00609765) in patients with advanced NETs.

Sunitinib

Sunitinib is a small molecule multitargeted tyrosine kinase inhibitor (TKI) with antiproliferative and antiangiogenic properties. It has activity against VEGFR-1, VEGFR-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR)- α , PDGFR- β , KIT, RET, FMS-like tyrosine kinase-3, and colony-stimulating factor receptor-1R. It is employed as second-line therapy for patients with advanced gastrointestinal stromal tumors (GISTs) and first-line therapy for patients with advanced renal cell cancer (RCC). After demonstrating efficacy in a phase II trial [43], a phase III study in advanced pancreatic NET patients was undertaken. As a result of significant differences in efficacy in favor of the sunitinib arm, the trial was stopped after 171 of a planned 340 patients had been enrolled. In preliminary data reported at the 2010 American Society of Clinical Oncology Gastrointestinal Cancers Symposium, sunitinib showed a greater response rate, PFS time, and OS time than placebo [44]. The median PFS interval was 11.4 months in patients on sunitinib, versus 5.5 months for patients on placebo. In the aforementioned phase II study, the authors identified soluble VEGFR-3 as a possible biomarker of sunitinib activity and interleukin-8 as a potential predictor of response to sunitinib [43].

One ongoing industry-sponsored phase II study is evaluating the sequential combination of selective hepatic artery embolization and sunitinib in patients with metastatic pancreatic NETs with measurable liver metastases (ClinicalTrials.gov identifier, NCT00434109).

Sorafenib

Sorafenib is another multitargeted TKI with activity against Raf kinase, VEGFR-2, and PDGFR- β used as second-line

therapy for RCC patients and approved for use in patients with hepatocellular carcinoma. It demonstrated a modest response in one phase II study [45]. Another multicenter phase II study was suspended (ClinicalTrials.gov identifier, NCT00131911). There are presently no ongoing phase II or phase III studies with this agent.

Pazopanib

Pazopanib is yet another multitargeted TKI active against VEGFR-1, VEGFR-2, VEGFR-3, PDGFR- α , PDGFR- β , and KIT that has been approved for use in RCC patients. Pazopanib was evaluated in a prospective, phase II trial enrolling carcinoid and pancreatic NET patients in two independent cohorts. No Response Evaluation Criteria in Solid Tumors–defined PRs were observed among 22 carcinoid patients. Among 29 pancreatic NET patients, five (17%) experienced PRs. The median PFS times were encouraging in both cohorts (12.7 months in the carcinoid cohort and 11.7 months in the pancreatic NET cohort) [46].

mTOR Inhibitors

Another class of promising agents is the inhibitors of the mammalian target of rapamycin (mTOR), a serine–threonine kinase that functions downstream of a number of receptor tyrosine kinases (including VEGF) and is involved in cell growth, proliferation, and apoptosis [47]. Aberrant activation of the pathway upstream of mTOR via increased signaling through growth factor receptors, activating mutations or amplification of kinase, or loss of the tumor receptor phosphatase and tensin homologue deleted on chromosome ten leads to greater downstream translation of proteins involved in regulating progression through the cell cycle and metabolism [48, 49]. Rapamycin is an immunosuppressant that is a very specific inhibitor of mTOR. Two macrolide rapamycin derivatives, temsirolimus and everolimus, have been evaluated in NET patients (Table 4).

Temsirolimus

Temsirolimus, approved for use in advanced RCC patients, was evaluated in one phase II study in patients with advanced carcinoids or pancreatic NETs [50]. However, it was demonstrated to have only a modest response rate (5%–7%), and there are presently no ongoing trials with this agent.

Everolimus

Everolimus was demonstrated to have somewhat greater activity in an initial phase II study in both carcinoid (17%) and pancreatic NET (27%) patients [51]. Based on that study, everolimus was further evaluated in a multinational phase II study enrolling patients with pancreatic NETs who

Table 4. mTOR pathway inhibitors in advanced well-differentiated NETs

Agent	Target	Tumor type	n of patients	Partial response (%)	Median PFS/TTP (wks)	Study
Temsirolimus	mTOR	Carcinoid	21	5	26 (TTP)	Duran et al. (2006) [50]
		Pancreatic NET	15	7	46 (TTP)	
Everolimus + octreotide	mTOR	Carcinoid	30	17	63 (PFS)	Yao et al. (2008) [51]
		Pancreatic NET	30	27	50 (PFS)	
Everolimus	mTOR	Pancreatic NET	115	9.6	9.7 (PFS)	Yao et al. (2010) [52]
Everolimus + octreotide			45	4.4	16.7 (PFS)	
Everolimus	mTOR	Pancreatic NET	410		11.0 (PFS)	Yao et al. (2010) [53]
Placebo					4.6 (PFS)	

Abbreviations: mTOR, mammalian target of rapamycin; NET, neuroendocrine tumor; PFS, progression-free survival; TTP, time to progression.

had failed prior cytotoxic chemotherapy (Randomized, Double-Blind Trial in Adjuvant NSCLC With Tarceva [RADIANT]-1).

Although the objective tumor response rates in that trial were modest (9.6% in patients receiving everolimus alone and 4.4% in patients receiving concurrent octreotide), the PFS times were encouraging (9.7 months in patients receiving everolimus alone and 16.7 months in patients receiving concurrent octreotide) [52]. Based on these results, everolimus was taken forward in a multicenter study in which 410 patients with advanced pancreatic NETs were randomly assigned to receive either everolimus or placebo (RADIANT-3). Patients receiving treatment with everolimus experienced a significantly longer PFS duration (11.0 months versus 4.6 months; $p < .0001$) [53]. A second placebo-controlled study (RADIANT-2) is further evaluating the activity of everolimus in patients with advanced carcinoid tumors.

Everolimus may also have an additional impact in patients with symptomatic hypoglycemia from insulinoma. In a report of four patients with insulinoma, treatment with everolimus achieved glycemic control with normalization of glucose levels and discontinuation of diazoxide, nocturnal feedings, glucose tablets, and/or nocturnal dextrose infusions [54].

OTHER AGENTS

Several other agents have been evaluated, but do not have the demonstrated response rates to warrant further larger studies. Endostatin is an antiangiogenic peptide that showed no evidence of biochemical regression or even a cytostatic effect in a phase II study [55].

Imatinib is a well-tolerated, orally available TKI targeting KIT and PDGFR- α . Although it has been approved by the U.S. Food and Drug Administration (FDA) for use in

both chronic myelogenous leukemia and GIST patients, there are no compelling data to support its use in NET patients [56, 57].

Gefitinib, an inhibitor of the epidermal growth factor receptor, has demonstrated minor responses [58], and a phase II study is ongoing at the Mayo Clinic (ClinicalTrials.gov identifier, NCT0075439).

Thalidomide, an orally available immunomodulator that targets tumor necrosis factor- α production and may exert antiangiogenic effects by also targeting VEGF and basic fibroblast growth factor, was evaluated in a phase II study with temozolomide [20]. The efficacy observed in that study was likely a result of temozolomide rather than thalidomide. There is one ongoing phase II trial evaluating thalidomide (ClinicalTrials.gov identifier, NCT00027638).

More recently, the antifolate pemetrexed was evaluated but was demonstrated to have poor activity while having toxicity similar to that of other cytotoxic agents [59].

One promising agent targets insulin-like growth factor-1 receptor (IGF-1R). AMG479 is a human monoclonal antibody that antagonizes IGF-1R by blocking interaction with its ligands IGF-1 and IGF-2. Carcinoids express IGFs and IGF-1R. A recently reported phase I trial evaluating AMG479 included five patients with carcinoids [60]. One patient experienced a PR and the other four experienced SD.

Additional agents under investigation include an Src kinase inhibitor (AZD0530), histone deacetylase inhibitor (FR901228), 26S proteasome inhibitor (bortezomib), and protease inhibitor (nelfinavir).

CONCLUSION

Treatment for patients with advanced well-differentiated NETs remains challenging. Octreotide and the newer soma-

tostatin analogs are generally considered first-line therapy for patients with advanced well-differentiated NETs. They are effective in controlling symptoms of hormonal hypersecretion. However, their antineoplastic effect is generally limited to inducing SD.

There is little consensus on a standard treatment approach for patients with refractory tumors. Alkylating agents, radiolabeled nuclides, VEGF pathway inhibitors, and mTOR inhibitors all show promising results, though response rates are generally modest at best. The greater efficacy of alkylating agents in pancreatic NET patients than in carcinoid patients may be related to MGMT deficiency in the former. Of the effective alkylating agents, streptozocin is approved for use in NET patients by the U.S. FDA. However, the high incidence of renal toxicity limits enthusiasm for its routine use. The oral alkylating agent temozolomide may prove to be an active and potentially more easily tolerated alternative to streptozocin-based therapy in pancreatic NET patients.

Data from recent studies of agents targeting the VEGF and mTOR pathways are encouraging in both carcinoid tumor and pancreatic NET patients. Randomized, placebo-controlled studies of sunitinib and everolimus have now confirmed the activity of these agents in patients with pancreatic NETs and will likely change the pattern of care. Studies of these and similar agents in advanced carcinoid tumors are ongoing or planned. Future studies are likely to build on these promising results by exploring molecular correlates of response to these targeted agents and through the development of combination regimens to further enhance antitumor activity and prolong survival.

AUTHOR CONTRIBUTIONS

Conception/Design: Chandrajit P. Raut, Matthew H. Kulke
Collection and/or assembly of data: Chandrajit P. Raut, Matthew H. Kulke
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