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Gastrointestinal Cancer

A New Era for the Systemic Therapy of Neuroendocrine Tumors

JENNIFER R. EADS, NEAL J. MEROPOL

University Hospitals Seidman Cancer Center, Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, Ohio, USA

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the underlying biology of neuroendocrine tumors including pancreatic neuroendocrine tumors (PNETs) and carcinoids and the importance of these biologic features in the evolution of new drugs for these diseases.
2. Cite the historical data regarding the use of cytotoxic agents in the treatment of pancreatic neuroendocrine tumors and carcinoids.
3. Explain the significance of recent clinical trials utilizing biologic agents, in particular octreotide, the small molecule tyrosine kinase inhibitor, sunitinib and the mammalian target of rapamycin (mTOR) inhibitor, everolimus, and how these medications have altered the natural history of both pancreatic neuroendocrine tumors and carcinoids.

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ABSTRACT

Carcinoids and pancreatic neuroendocrine tumors are becoming increasingly common, with the majority of patients presenting with either lymph node involvement or metastatic disease. An improved understanding of the molecular mechanisms involved in these tumors has implicated several pathways that have led to new therapeutic approaches. In this manuscript, we describe the biology of neuroendocrine tumors and approaches to systemic therapy. We review early data regarding the use of cytotoxics and several recent studies employing more targeted approaches that promise to change the standard of care. Specifically, phase III studies indicate that pharmacologic inhibition of the vascular endothelial growth factor pathway with sunitinib, and of the mammalian target of rapamycin pathway with everolimus, appears to have altered the natural history of these diseases. These successes set the stage for further advances in the management of patients with neuroendocrine tumors. ***The Oncologist*** 2012; 17:326–338

Correspondence: Neal J. Meropol, M.D., 11100 Euclid Avenue, Wearn 145, Cleveland, Ohio, USA. Phone: 216-844-5220; Fax: 216-844-5234; e-mail: neal.meropol@case.edu Received October 19, 2011; accepted for publication January 3, 2012; first published online in ***The Oncologist*** *Express* on February 21, 2012. 1083-7159/2012/$20.00/0 http://dx.doi.org/10.1634/theoncologist.2011-0356

Introduction

Historically, neuroendocrine tumors (both carcinoids and pancreatic neuroendocrine tumors) have been thought to arise from neuroendocrine cells located throughout the body that are capable of undergoing neoplastic transformation. More recent data suggests that there may be a role for cancer stem cells in the pathogenesis of these tumors [1]. Neuroendocrine tumors (NETs) are characterized as functional or nonfunctional depending on whether they produce hormones, which in turn may result in specific symptoms. The majority of NETs are gastrointestinal in origin, arising in the foregut, midgut, or hindgut. The Surveillance, Epidemiology, and End Results (SEER) database approximates that 1%–4% of NETs arise within the pancreas, although case ascertainment may underestimate true incidence. An additional 75%–86% represent carcinoids from other gastrointestinal sites. Whereas most NETs follow a relatively indolent course, a small percentage (9.1%) are aggressive high-grade neoplasms with poor differentiation [2]. Here we review the medical management of well differentiated and moderately differentiated metastatic carcinoids and pancreatic neuroendocrine tumors (PNETs) and describe the impact of new targeted therapies on the natural history of these diseases.

Epidemiology, Clinical Presentation, and Staging

Although considered rare malignancies, the reported incidence of carcinoids and PNETs is increasing, due in part to improved classification systems and increased use of endoscopy [3]. A recent evaluation of the SEER database noted a significant rise in the age-adjusted annual incidence of both carcinoids and PNETs since 1973 with a two- to sixfold increase in the number of cases. Gastrointestinal carcinoids have increased from approximately 0.61/100,000 to 3.58/100,000 in 2004, whereas PNETs have risen from 0.17/100,000 to 0.32/100,000 [3]. Median age at the time of diagnosis is 60 years with most patients (60%–80%) presenting with metastatic disease [3, 4]. For patients presenting with localized disease, survival is reported from 9.3–18.6 years. However, patients with metastatic disease have an inferior prognosis with a median survival of only 39 months [3]. Of the 43,000 pancreatic neoplasms diagnosed annually [5], PNETs represent only 1%–10% while the remainder are ductal adenocarcinomas [6, 7].

At the time of presentation, patients may have symptoms related to tumor bulk or, in 20%–50% of cases, hormone production [6, 8, 9]. The likelihood of presenting with hormone-related symptoms depends on the site of tumor origin, with PNETs and midgut carcinoids (jejunum, ileum, appendix, and proximal colon) being more likely to present with symptoms than carcinoids arising from the foregut (lungs, thymus, stomach, and duodenum) or hindgut (distal colon and rectum). PNETs specifically involve pancreatic islet cells that produce various hormones and result in symptoms depending on the underlying cellular subtype involved (Table 1) [9]. In contrast, midgut carcinoids produce symptoms by virtue of having high levels of serotonin production. This may result in carcinoid syndrome, characterized by diarrhea, flushing, and, particularly in patients with liver involvement, cardiac carcinoid with fibrotic endocardial plaque formation, tricuspid insufficiency, and ultimately pulmonary hypertension [10].

The TNM staging system as outlined by the American Joint Committee on Cancer (AJCC) is recommended for both carcinoids and PNETs [11, 12], with staging based on the site of origin. Tumor histology ranges from well differentiated with a relatively indolent course to poorly differentiated with a very aggressive course similar to that of small cell lung cancer. Although not officially part of any standard staging system, histologic features including degree of differentiation, mitotic count, and Ki-67 level (Table 2) have prognostic significance and can guide therapy [4, 8, 12].

Neuroendocrine Tumor Biology

Several molecular mechanisms have been identified in the pathogenesis and behavior of neuroendocrine tumors (Fig. 1). This renders the treatment strategy for these tumors complex but also provides a basis for targeted approaches. In 80%–100% of PNETs and carcinoids, somatostatin receptors (SSTRs) are expressed of which there are five types (SSTR1–SSTR5). SSTR2 is the most common [13], but all five receptor types may be expressed with well differentiated tumors expressing higher levels and a wider variety of receptors than their poorly differentiated counterparts [14]. These are G protein coupled receptors that, upon binding somatostatin, are internalized as a receptor-ligand complex where they exert direct and indirect downstream effects. Direct effects on proliferation occur via inhibition of several pathways that differ depending on the receptor subtype, whereas indirect effects occur via suppression of growth factors such as insulin-like growth factor 1 (IGF-1) [13]. Binding of somatostatin (and thus its analogues) to somatostatin receptors also results in decreased hormone production by NETs, making it an attractive therapy for control of hormone-mediated symptoms.

Vascular endothelial growth factor (VEGF) is known to influence angiogenesis in PNETs and carcinoids [15, 16]. Additionally, several other growth factors and receptors including platelet-derived growth factor, platelet-derived growth factor receptors alpha and beta, stem-cell factor receptor (c-kit), VEGFR-2, VEGFR-3, insulin-like growth factor-1, insulin-like growth factor receptor, basic fibroblast growth factor, transforming growth factors alpha and beta, epidermal growth factor receptor, and stem-cell factor receptor have also been implicated in the cell signaling processes of NETs [15, 16]. Many of these pathways can be disrupted by small-molecule tyrosine kinase inhibitors and vascular endothelial growth factor inhibitors, which have led to clinical trials to evaluate the role of these agents in the treatment of NETs.

Mammalian target of rapamycin (mTOR) is an intracellular protein kinase involved in cell signaling and metabolism, which acts by mediating cell signaling via growth factor pathways [17–19]. One such growth factor is IGF-1, which has been shown to activate mTOR, resulting in cellular proliferation. Inhibition of mTOR has been shown to suppress neuroendocrine tumor growth [19, 20] and has recently proven to be a promising target for drug therapy.

Table 1. Subtypes of pancreatic neuroendocrine tumors with associated hormones and symptoms

Tumor type	Hormone produced	Clinical features
Gastrinoma	Gastrin	Recurrent peptic ulcers, diarrhea, steatorrhea
Insulinoma	Insulin	Hypoglycemia, catecholamine excess
Glucagonoma	Glucagon	Diabetes mellitus, migratory necrolytic erythema, weight loss, thromboembolism, panhypoaminoaciduria
VIPoma	VIP	Watery diarrhea, hypokalemia, achlorhydria, metabolic acidosis, hyperglycemia, flushing, hypercalcemia
Somatostatinoma	Somatostatin	Diabetes mellitus, diarrhea, steatorrhea, hypochlorhydria, weight loss, gallbladder disease
Pancreatic polypeptidoma	Pancreatic polypeptide	Hepatomegaly, abdominal pain, watery diarrhea

Abbreviation: VIP, vasoactive intestinal peptide.

Table 2. Histologic classification of neuroendocrine tumors

Differentiation	Grade	Mitotic count (per 10 hpf)	Ki-67 proliferative index	WHO classification
Well differentiated	Grade 1	<2	≤ 2	Neuroendocrine tumor, grade 1
Moderately differentiated	Grade 2	2–20	3–20	Neuroendocrine tumor, grade 2
Poorly differentiated	Grade 3	>20	>20	Neuroendocrine carcinoma, grade 3 (small cell or large cell)

Abbreviation: WHO, World Health Organization.

Multiple inherited syndromes associated with NETs exist including multiple endocrine neoplasia types 1 and 2, von Hippel–Lindau disease, neurofibromatosis 1, and tuberous sclerosis, although most NETs are sporadic [12]. Among PNETs, 10%–15% are part of an inherited disorder [21], whereas the hereditary aspect of carcinoid tumors is less well characterized but believed to be less common. Among PNETs, the finding that somatic mutations in the *MEN1*, *DAXX/ATRX*, and mTOR pathway genes are most common (44%, 43%, and 14%, respectively) was recently described, with tumors containing a *MEN1* or *DAXX/ATRX* mutation conferring a better prognosis [22]. Mechanisms including point mutations, deletions, DNA methylation, chromosomal loss, and chromosomal gains have been identified [23].

Treatment of NETs

The treatment approach for patients with NETs varies according to stage of disease. For localized disease, surgical resection is the standard of care. For patients with metastatic disease, goals of therapy include control of tumor growth and alleviation of hormone-mediated symptoms. Surgery may be appropriate in this setting for palliative debulking to decrease tumor burden or help control hormone production. Until recently, standard therapies for treatment of metastatic NETs included somatostatin analogues such as octreotide for hormonal control, hepatic-directed therapy for regional control, cytotoxic agents (including streptozocin, 5-fluorouracil, doxorubicin, capecitabine, dacarbazine, and temozolomide), or participation in a clinical trial. Over the last decade, development of targeted systemic therapies has resulted in significant impact as we understand more about the underlying biology of these tumors. Recently, two agents inhibiting relevant molecular targets have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of well differentiated PNETs with promising data also emerging for carcinoids. These include the mTOR inhibitor, everolimus, and the VEGF receptor tyrosine kinase inhibitor (TKI), sunitinib. Despite having low response rates because they are cytostatic rather than cytotoxic, significantly longer progression-free survival (PFS) has been reported as compared to placebo, leading to a new standard for treatment of PNETs [16, 19].

Advancements in hepatic-directed therapies have also taken place over the last decade. Although mainly small phase I and phase II studies, multiple treatment modalities including bland hepatic artery embolization, chemoembolization, radiofrequency ablation, and administration of 90-Yttrium labeled microspheres are showing promising results, particularly in PNETs [24–30]. Although the specifics of these treatment modalities are beyond the scope of this review, these approaches should be considered as part of the management of localized liver metastases.

In evaluating results of treatment clinical trials for NETs, it is important to note that most trials conducted have been noncomparative phase II studies. Given the prolonged and variable natural history of NETs, nonrandomized studies must be interpreted with caution. Additionally, recent studies assessing targeted, cytostatic therapies have highlighted that a significant progression-free survival can be seen in the absence of a radio-

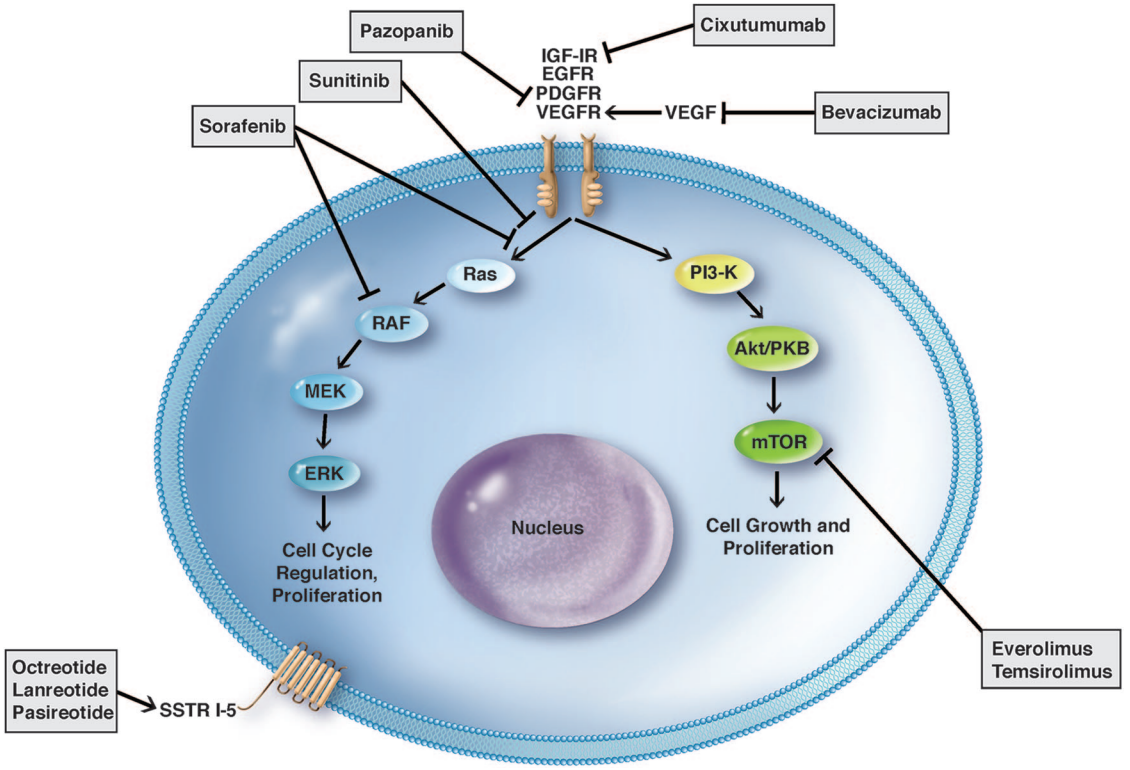

Figure 1. Molecular pathways implicated in neuroendocrine tumors and targets of action for therapeutic agents. Arrows represent activation whereas lines with a perpendicular block represent inhibition.

Abbreviations: EGFR, endothelial growth factor receptor; IGF-1R, insulin-like growth factor 1 receptor; mTOR, mammalian target of rapamycin; PDGFR, platelet-derived growth factor receptor; SSTR, somatostatin receptor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

graphic response, suggesting that response rate may be a suboptimal primary end point. This is not altogether surprising given that the indolent nature of these tumors often leads to stable disease both with and without treatment. Thus, small, single-arm, early studies with response end points are difficult to compare with more recent clinical trials. Table 3 summarizes results from selected trials discussed below.

Cytotoxic Agents

PNETs

In 1973, streptozocin was reported to have a 37% objective response rate and a 54% biochemical response rate in patients with metastatic PNETs [31]. This led to subsequent studies further investigating the role of streptozocin as well as doxorubicin and 5-fluorouracil in PNETs and carcinoids. A randomized phase III study of 84 patients with PNETs evaluated streptozocin versus streptozocin plus fluorouracil and reported an improved response rate of 63% with combination therapy as compared to 36% with streptozocin alone; however, a significant survival advantage was not observed (24 months versus 17 months) [32]. Combination therapy with streptozocin and doxorubicin versus streptozocin and fluorouracil versus chlorozotocin was compared in a randomized phase III trial of 102 PNET patients with significantly higher response rates and overall survival in the streptozocin plus doxorubicin group (69%, 2.2 years) as compared to the streptozocin plus fluorouracil group and chlorozotocin group (45%, 1.4 years and 30%, 1.5 years, respectively) [33]. It is important to note that all of these studies evaluated response using a combination of measurable tumor on physical exam, decrease in size of hepatomegaly, and improvement in endocrine parameters, which are not used as standard measurements in modern studies. Two retrospective studies assessed response to streptozocin plus doxorubicin using modern radiographic response criteria. A total of 32 patients were evaluated between the two studies, and a radiographic response rate of only 6% was seen [34, 35]. A retrospective study of 84 patients with metastatic PNETs who received streptozocin, fluorouracil, and doxorubicin evaluated efficacy and survival using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria and showed a response rate of 39% and median overall survival of 37 months [36]. Unfortunately, no prospective studies have been conducted in the modern era using standard radiologic response criteria to determine outcome of these regimens in PNETs. Cisplatin shows activity in poorly differentiated NETs and thus has been assessed in PNETs and carcinoids. A phase II study of cisplatin and etoposide in 14 PNET patients showed disappointing results with a 0% response rate as assessed by change in tumor size on exam or imaging, hepatomegaly, or change in endocrine func-

Table 3. Clinical trials of systemic treatment of pancreatic neuroendocrine tumors (PNETs) and carcinoids

Drug/Study	No. patients	Response rate	Stable disease	Survival endpoint
PNETs				
Broder, 1973 (phase II)* [31]				
Streptozocin	52	37%		
Moertel, 1980 (phase III)* [32]	84			
Streptozocin	42	36%		Med OS = 16.5 mo(s)
Streptozocin/5-FU	42	63%		Med OS = 26 mo(s)
		$p < .01$		p = NS
Moertel, 1992 (phase III)*[a] [33]	105			
Streptozocin/5-FU	34	45%		Med OS = 1.4 years, 6.9 mo(s)
Streptozocin/doxorubicin	38	69%		Med OS = 2.2 years, TTP = 20 mo(s)
		$p = .05$		p = .004, .001, respectively
Moertel, 1991 (phase II)* [37]				
Cisplatin/etoposide	14	0%		
Turner, 2010 (phase II) [38]				
Cisplatin/5-FU/streptozocin	47	38%		
Ramanthan, 2001 (phase II)* [39]				
Dacarbazine	50	34%		Med OS = 19.3 mo(s)
Kulke, 2006 (phase II) [40]				
Temozolomide/thalidomide	11	45%	68%[b]	2-year OS = 61%[c]
Kulke, 2006 (phase II) [42]				
Temozolomide/bevacizumab	18	24%	70%	
Saltz, 1994 (phase II)* [50]				
Alpha-interferon/5-FU	7	14%	57%	
Kulke, 2008 (phase II) [15]				
Sunitinib	66	16.7%	68%	TTP = 7.7 mo(s) 1-year survival = 81.1%
Hobday, 2007 (phase II) [81]				
Sorafenib	43	10%		PFS = 11.9 mo(s)
Raymond, 2011 (phase III) [16]	171			
Sunitinib	86	9.3%		PFS = 11.4 mo(s)
Placebo	85	0%		PFS = 5.5 mo(s) (HR = 0.42, $p < .001$)
Phan, 2010 (phase II) [85]				
Pazopanib/octreotide	29	17%		PFS = 11.7 mo(s)
Yao, 2008 (phase II) [17]				
Everolimus/octreotide	30	27%	60%	PFS = 50 wk(s)
Yao, 2010 (nonrandomized phase II) [18]				
Everolimus	115	9.6%	67.8%	PFS = 9.7 mo(s)
Everolimus/octreotide	45	4.4%	80%	PFS = 16.7 mo(s)
Yao, 2011 (phase III) [19]	410			
Everolimus	207	5%	73%	PFS = 11 mo(s)
Placebo	203	2%	51%	PFS = 4.6 mo(s) (HR = 0.35, $p < .001$)

(continued)

Table 3. (Continued)

Drug/Study	No. patients	Response rate	Stable disease	Survival endpoint
Duran, 2006 (phase II) [20]				
Temsirolimus	15	6.7%	58.3%	TTP = 6 mo(s)
Carcinoids				
Engstrom, 1984 (phase II/III)* [45]	172			
Streptozocin/5-FU	86	22%		Med OS = 64 wk(s)
Doxorubicin	86	21%		Med OS = 48 wk(s)
				p = NS
Sun, 2005 (phase II/III)*[d] [46]	176			
Streptozocin/5-FU	88	16%		Med OS = 24.3 mo(s)
Streptozocin/doxorubicin	88	15.9%		Med OS = 15.7 mo(s)
		p = NS		p = .03
Moertel, 1991 (phase II)* [37]				
Cisplatin/etoposide	13	15%		
Turner, 2010 (phase II) [38]				
Cisplatin/5-FU/streptozocin	32	25%		
Bukowski, 1994 (phase II)* [47]				
Dacarbazine	56	16%		Med OS = 20 mo(s)
Kulke, 2006 (phase II) [40]				
Temozolomide/thalidomide	15	7%	68%[b]	2-year OS = 61%[c]
Kulke, 2006 (phase II)* [42]				
Temozolomide/bevacizumab	16	0	92%	
Bajetta, 1993 (phase II)* [49]				
Recombinant interferon-alpha 2a	49	10%		
Saltz, 1994 (phase II)* [50]				
Alpha-interferon/5-FU	14	7%	57%	
Andreyev, 1995 (phase II)* [51]				
Interferon-alfa 2b/5-FU	15	47%	33%	
Kolby, 2003 (phase II) [55]	68			
Octreotide	35			5-year survival = 36.6%
Octreotide/interferon-alpha	33			5-year survival = 56.8%
				p = NS
				Decreased risk of progressive disease with combination therapy (HR = 0.28, p = .008)
Rinke, 2009 (phase III) [59]	85			
Octreotide	42	2.4%	66.7%	TTP = 14.3 mo(s)
Placebo	43	2.4%	37.2%	TTP = 6 mo(s)
				(HR = 0.34, p = .000072)
Yao, 2008 (phase II) [56]	44			
Bevacizumab/octreotide	22	18%	77%	PFS rate at 18 wk(s) = 95%
Interferon/octreotide	22	0%	68%	PFS rate at 18 wk(s) = 68%
				p = .02
Kulke, 2008 (phase II) [15]				
Sunitinib	41	2.4%	83%	TTP = 10.2 mo(s)
				1-year survival = 83.4%

(continued)

Table 3. (Continued)

Drug/Study	No. patients	Response rate	Stable disease	Survival endpoint
Hobday, 2007 (phase II) [81]				
Sorafenib	50	10%		PFS = 7.8 mo(s)
Yao, 2007 (phase II) [82]				
Imatinib	27	4%	63%	PFS = 24 wk(s)
Phan, 2010 (phase II) [85]				
Pazopanib/octreotide	22	0%		PFS = 12.7 mo(s)
Yao, 2008 (phase II) [17]				
Everolimus/octreotide	30	17%	80%	PFS = 60 wk(s)
Pavel, 2011 (phase III) [86]	429			
Everolimus/octreotide	216	2.3%	84%	Med PFS = 16.4 mo(s)
Placebo/octreotide	213	1.9%	81%	Med PFS = 11.3 mo(s) (HR = 0.77, p = .026)
Duran, 2006 (phase II) [20]				
Temsirolimus	21	4.8%	58.3%	TTP = 6 mo(s)
NETs (Combined PNETs and Carcinoids)[e]				
Frank, 1999 (phase II)* [52]				
Interferon-alpha/octreotide	21	5%	67%	
Arnold, 2005 (phase III)* [53]	105			
Octreotide	51	2%	15.7%	Med OS = 35 mo(s)
Octreotide/interferon-alpha	54	9.3%	14.8%	Med OS = 51 mo(s)
		p = NS		p = NS
Faiss, 2003 (phase III) [54]	80			
Interferon-alfa	27	3.7%	25.9%	
Lanreotide	25	4%	28%	
Interferon-alfa/lanreotide	28	7.1%	17.9%	
		p = NS		

The asterisk (*) indicates that the response criteria may include tumor markers and physical exam.
[a]Study also included a chlorozotocin arm.
[b]Stable disease including PNETs and carcinoids.
[c]2-year OS including PNETs and carcinoids.
[d]Both regimens were then followed by dacarbazine.
[e]Studies did not distinguish between PNETs and carcinoids.
Abbreviations: 2-yr OS, 2-year overall survival; 5-FU, 5-fluorouracil; HR, hazard ratio; Med OS, median overall survival; Med PFS, median progression-free survival; NET, neuroendocrine tumor; NS, not significant; PFS, progression-free survival; PNET, pancreatic neuroendocrine tumor; TTP, time to progression.

tion [37]. A second phase II study of cisplatin, fluorouracil, and streptozocin in 47 PNET patients yielded a response rate of 38% as assessed by the RECIST criteria—however, this study also included poorly differentiated tumors, which are known to be much more chemosensitive than well differentiated or moderately differentiated tumors [38]. The poor chemotherapeutic response seen with well differentiated and moderately differentiated tumors further confirms the biologic differences observed as compared to their poorly differentiated counterparts.

Dacarbazine has shown promising results in patients with PNETs with a phase II study of 50 patients reporting a response rate of 34% [39]. Follow-up trials using temozolomide (an inhibitor of nucleoside incorporation and an oral alternative to dacarbazine) were then conducted in light of these positive results. When used with thalidomide (which is thought to have disease-stabilizing effects in metastatic NETs secondary to its antiangiogenic effect via inhibition of VEGF and basic fibroblast growth factor), a response rate of 45% was seen, but this regimen was associated with significant toxicity including neuropathy and lymphopenia and resulted in opportunistic infections in 10% of patients [40]. The relative contribution of each agent could not be evaluated in this study, but a retrospective evaluation of temozolomide in patients with advanced NETs showed a response rate of 14% [41]. The response rate in PNETs and carcinoids specifically, however, could not be assessed from this study because both were included. Combina-

tion studies including temozolomide/bevacizumab [42] and temozolomide/capecitabine [43] appear promising with response rates of 24% and 70%, respectively, although the latter was a retrospective study. The mechanism of sensitivity to temozolomide is unclear but may be related to a deficiency in the enzyme methylguanine methyltransferase (MGMT). Immunohistochemical analysis of MGMT in archived NETs revealed that 51% of PNETs and 0% of carcinoids were MGMT deficient [44]. Furthermore, of 21 temozolomide-treated patients with tissue available for immunohistochemical evaluation, 80% of MGMT-deficient tumors responded to therapy (all PNETs) while no tumors with normal MGMT expression responded [44]. This difference in MGMT expression further suggests the existence of underlying molecular differences between PNETs and carcinoids. To date, temozolomide has not been compared to any streptozocin-containing regimen, nor have the various temozolomide regimens been compared head-to-head. Further studies are needed to determine if temozolomide is superior to streptozocin-containing regimens.

Carcinoids

In general, cytotoxic agents have less activity against carcinoid tumors than against PNETs. After positive results were seen with streptozocin in PNETs, a phase II/III study was conducted in 210 carcinoid patients (172 randomized, 38 directly assigned) who were treated with streptozocin plus fluorouracil or single-agent doxorubicin. A response rate of 22% and 21% was observed in the two groups, respectively, with no significant difference in overall survival [45]. A phase II/III study randomizing patients to either streptozocin/fluorouracil or streptozocin/doxorubicin showed a response rate of only 16% in both groups, but there was an improved median overall survival in the streptozocin/fluorouracil group (24.3 months versus 15.7 months, $p = .03$) [46]. It is again important to note that these studies also evaluated response using methods not currently considered as standard in modern studies.

Cisplatin-containing regimens have also been evaluated in carcinoids. A phase II study of cisplatin/etoposide in 13 patients yielded a response rate of only 15% as assessed by change in tumor size on physical exam or imaging, hepatomegaly, or change in endocrine function [37]. A phase II study of cisplatin/fluorouracil/streptozocin in 32 patients yielded a response rate of 25% [38]. As of now, cisplatin is not considered as a standard therapy in the treatment of carcinoid tumors.

Dacarbazine and temozolomide show less activity against carcinoids than in PNETs. A phase II study of 56 patients with carcinoid treated with dacarbazine reported a response rate of 16% [47], whereas two smaller phase II studies of temozolomide/thalidomide (15 patients) and temozolomide/bevacizumab (16 patients) reported response rates of 7% and 0%, respectively [40, 42].

Interferon

Leukocyte interferon was first reported to be of benefit in treating carcinoid syndrome in 1983 [48]. Several subsequent phase II studies of recombinant interferon-alpha-2a, alone or in combination with 5-fluorouracil, reported symptomatic improvement and variable response rates in patients with NETs [49–51]. Combination studies of interferon-alpha plus a somatostatin analogue as compared to somatostatin analogue monotherapy have shown response rates of 5%–6% with one of three studies favoring an improved overall survival with combination therapy [52–54]. In each of these studies, carcinoids and PNETs were evaluated together. A small randomized study of octreotide with or without interferon-alpha in 68 patients with midgut carcinoids only showed a reduced risk of tumor progression with combination therapy but no difference in overall survival [55]. Recent clinical data regarding the combination of bevacizumab with depot octreotide [56] has led to an ongoing national, randomized phase III study of octreotide and interferon-alpha-2b versus octreotide and bevacizumab (SWOG 0518). Most recently, a small randomized phase III study of 64 patients receiving either 5-fluorouracil/streptozocin or recombinant interferon-alpha-2a showed no significant difference between the two treatment arms in terms of response rate or progression-free or overall survival; however, there was a trend for improved PFS in the interferon arm of 14.1 months versus 5.5 months in the chemotherapy arm [57]. A definitive role for interferon therapy in treating NETs, particularly carcinoids, is still under investigation.

Somatostatin Analogues

Somatostatin is a hormone originally identified as produced by the hypothalamus and inhibiting the release of growth hormone [13]. It has since been found to also be produced by the endocrine pancreas and the gastrointestinal tract [58]. The presence of somatostatin receptors on the surface of most NETs makes targeting these receptors a natural therapeutic approach. Although a targeted approach may suggest inhibiting somatostatin receptors, the natural activity of somatostatin is to inhibit the release of hormones and, in some cases, inhibit cellular proliferation. As such, somatostatin analogues were originally approved for controlling hormone production by functional NETs but recently were shown to have antitumor effects as well [59]. Natural somatostatin is rapidly degraded and therefore is of limited pharmaceutical potential [13]. Instead, several synthetic somatostatin analogues have been produced including octreotide, lanreotide, and pasireotide.

Octreotide is the most widely studied of the somatostatin analogues and acts primarily upon the SST2 receptor. Multiple studies show benefit in the treatment of hormone-mediated symptoms from functional PNETs and carcinoids [60–65], and the first early evidence of an antitumor effect was seen in 1993 when 50% of patients were noted to have disease stabilization with a possible survival advantage [66]. However, until recently there was substantial controversy regarding whether octreotide had benefit beyond symptom management. Rinke et al. recently published results of a phase III trial (the PROMID study) confirming the antitumor effect of octreotide in functional and nonfunctional well differentiated metastatic midgut NETs. Patients receiving octreotide long-acting repeatable (LAR) as compared to placebo had an 8.3 month improvement in time to progression (14.3 months versus 6 months), and a greater percentage of patients achieved disease stability

(66.7% versus 37.2%) [59]. This study has established octreotide as a standard option for patients with midgut carcinoids, both functional and nonfunctional. The antitumor activity of somatostatin analogue treatment in PNETs has not been fully characterized; however, a nonrandomized phase II study of everolimus that was stratified for concurrent octreotide use suggested a potential prolongation of progression-free survival in patients receiving octreotide (16.7 months versus 9.7 months) [18].

Pasireotide (SOM 230) is a somatostatin analogue with affinity for four of five somatostatin receptors (SSTR1, SSTR2, SSTR3, and SSTR5) [13]. In a study assessing control of carcinoid-associated symptoms in patients refractory to octreotide, pasireotide provided symptomatic benefit in 25% [67]. A phase II study (the COOPERATE-2 study) using pasireotide in combination with everolimus in the treatment of PNETs is ongoing.

Therapy with radiolabeled somatostatin analogues for metastatic PNETs and carcinoids is under investigation. Although multiple small phase I and II studies have been conducted using a variety of radiolabels [68–78], the largest phase II study thus far included 1,109 patients with carcinoids, PNETs, rare neuroendocrine tumors, and neuroendocrine tumors of unknown primary who were treated with 2,472 cycles of [^{90}Y-DOTA]-TOC (^{90}yttrium-labeled tetraazacyclododecane tetraacetic acid modified Tyr-octreotide). A "morphologic" response (any radiologic improvement) was observed in 34.1%, a biochemical response (any improvement in tumor markers) was observed in 15.5%, and a clinical response (decrease in hormonal symptoms) was observed in 29.7% of patients, respectively. Response was associated with prolonged overall survival—44.7 months versus 18.3 months for morphologic ($p < .001$), 35.3 months versus 25.7 months for biochemical ($p = .023$), and 36.8 months versus 23.5 months ($p < .001$) for clinical response groups [79]. Although promising, given the variable natural history of NETs, the activity of [^{90}Y-DOTA]-TOC requires further prospective evaluation using standard response criteria in randomized clinical trials of homogeneous patient populations.

Table 4. Treatment options for pancreatic neuroendocrine tumors and carcinoids

Pancreatic neuroendocrine tumors (PNETs)	
Hormonal symptoms	Octreotide
	Surgical resection/debulking
Liver-only metastases	Surgical resection (if feasible)
	Hepatic-directed therapy
Unresectable metastatic disease	Cytotoxic therapy (STZ or TMZ regimen)
	Everolimus
	Sunitinib
	Consider octreotide
Carcinoids	
Hormonal symptoms	Octreotide
	Surgical resection/debulking
Liver-only metastases	Surgical resection (if feasible)
	Hepatic-directed therapy
	Octreotide
Unresectable metastatic disease	Octreotide
	Consider everolimus
	Cytotoxic therapy (STZ-containing regimen)
	Interferon-alpha

Abbreviations: STZ, streptozocin; TMZ, temozolomide.

TKIs

Sunitinib malate is a small molecule that inhibits multiple targets including platelet-derived growth factor receptor alpha (PDGFRα), PDGFRβ, VEGFR1, VEGFR2, VEGFR3, stem cell factor receptor (KIT), FML-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor type I, and the glial cell-line derived neurotrophic factor receptor (RET). A phase II study showed an overall response rate of 16.7% in PNET patients and 2.4% in carcinoid patients [15], prompting a phase III randomized study in patients with PNETs. Here, 171 patients were randomized to receive 37.5 mg of sunitinib daily or placebo. Patients randomized to the sunitinib arm showed improved PFS compared with those in the placebo arm (11.4 months versus 5.5 months, hazard ratio [HR] 0.42, $p < .001$), and a response rate of 9.3% was observed [16]. Patients were allowed to receive a somatostatin analogue as well, but in a subgroup analysis this did not affect PFS. Patients with disease progression while receiving placebo were permitted to enter an open-label sunitinib extension protocol. The most commonly seen adverse events with sunitinib included diarrhea, nausea, vomiting, asthenia, and fatigue, with the most severe adverse events being neutropenia and hypertension. The use of sunitinib did not adversely affect quality of life. Of note, this study was terminated early by the data safety and monitoring committee due to a greater number of deaths and serious adverse events noted in the placebo group in addition to the favorable progression-free survival seen in the sunitinib group. As a result of early termination as well as multiple unplanned interim analyses, there is potential for overestimation of the benefit of sunitinib in prolonging PFS. Furthermore, with additional follow-up, a significant difference in overall survival has not been observed. Nevertheless, these promising findings led to FDA approval of sunitinib in May, 2011, for treatment of metastatic PNETs. Although the exact mechanism of action is still under investigation, it is thought that this is mediated by sunitinib's effect on PDGFRα, PDGFRβ, c-kit, VEGFR2, or VEGFR3, as these are all known to be expressed by PNETs [16].

Sorafenib is a small-molecule TKI that inhibits both intracellular and cell surface kinases (BRAF, CRAF, KIT, FLT-3, RET, VEGFR1, VEGFR2, VEGFR3, and PDGFRβ) [80]. In 50 patients with well differentiated carcinoids and 43 patients with PNETs, a 10% response rate was observed in each group [81]. Among PNETs, the response rates and PFS were similar

Table 5. Ongoing clinical trials in pancreatic neuroendocrine tumors and carcinoids

NCT number and sponsor	Treatment regimen	Tumor type	Phase of study	No. patients	Primary end point
NCT00569127 (SWOG)	Octeotide and interferon-alfa 2b versus octreotide and bevacizumab	Carcinoid	III	400	PFS
NCT01374451 (Novartis)	Everolimus alone versus everolimus and pasireotide	PNET	II	150	PFS
NCT01229943 (CALGB)	Everolimus and octreotide versus everolimus, octreotide, and bevacizumab	PNET	II	138	PFS
NCT00576680 (DFCI)	Everolimus and temozolomide	PNET	II	12	RR
NCT00055809 (MD Anderson)	Bevacizumab and PEG interferon-alpha 2b	Carcinoid	II	44	RR
NCT00416767 (FFCD)	5-Fluorouracil, leucovorin, and irinotecan	Duodenal NET, PNET	II	20	6-month PFS
NCT00602082 (CUH NHS Foundation Trust)	Capecitabine and streptozocin versus capecitabine, streptozocin, and cisplatin	NET, PNET	II	84	RR
NCT00781911 (ImClone LLC)	Cixutumumab and octreotide	Carcinoid, PNET	II	43	PFS
NCT01253161 (HL Moffitt CC)	Pasireotide LAR	Carcinoid, PNET	II	30	PFS
NCT01465659 (Northwestern University)	Temozolomide and pazopanib	PNET	I/II	39 (for I/II combined)	RR (phase II only)
NCT01024387 (DFCI)	AMG 479 (anti-IGF1 receptor)	Carcinoid, PNET	II	60	RR
NCT00084461	Romidepsin (histone deacetylase inhibitor)	Carcinoid, PNET	II	16–25	RR
NCT00427349 (ECOG)	AMG 706 (multikinase inhibitor) and octreotide	NET	II	44	4-month PFS, TTP
NCT01169649 (MSKCC)	MK-2206 (Akt inhibitor)	Carcinoid, PNET	II	8	RR

Abbreviations: CALGB, Cancer and Leukemia Group B; CUH, Cambridge University Hospitals; DFCI, Dana Farber Cancer Institute; ECOG, Eastern Cooperative Oncology Group; FFCD, Federation Francophone de Cancerologie Digestive; IGF1, insulin-like growth factor 1; MSKCC, Memorial Sloan Kettering Cancer Center; NET, neuroendocrine tumor; PFS, progression-free survival; PNET, pancreatic neuroendocrine tumor; RR, response rate; SWOG, Southwest Oncology Group; TTP, time to progression.

to those seen with sunitinib; however, no phase III studies have compared sunitinib to sorafenib. Imatinib inhibits Abelson tyrosine kinase (ABL), platelet-derived growth factor receptor (PDGFR), and stem cell ligand receptor (c-kit), the latter two of which have been identified on NETs. In a small study of 27 patients with advanced carcinoid tumors treated with imatinib, the response rate (4%) and PFS (24 weeks) appear inferior [82] as compared to those for sunitinib or sorafenib. Cixutumumab is a fully human monoclonal antibody targeting insulin-like growth factor receptor 1. In a phase I study, 2 of 5 patients with carcinoid tumors showed tumor regression (one partial response and one minor response) [83]. A follow-up phase II study of cixutumumab in combination with octreotide in patients with carcinoids and PNETs is underway [84]. Pazopanib is a selective small-molecule TKI that inhibits the VEGFR-1, VEGFR-2, VEGFR-3, PDGF-α, PDGF-β, and c-kit tyrosine kinases. A phase II study of 29 patients with PNETs and 22 patients with carcinoids treated with a combination of pazopanib and octreotide LAR showed a response rate of 17% in the PNET group with a median PFS of 11.7 and 12.7 months in the PNET and carcinoid groups, respectively [85]. A combination study of pazopanib with temozolomide is currently underway.

Vascular Endothelial Growth Factor Inhibitors

Bevacizumab has been evaluated in unresectable and metastatic carcinoid tumors. A small phase II study randomizing 44 patients to octreotide plus bevacizumab versus octreotide plus interferon alfa-2b showed improved response rates and PFS in the bevacizumab arm as compared to interferon [56]. An ongoing large confirmatory cooperative group study (SWOG 0518) is comparing octreotide and bevacizumab to octreotide and interferon alfa-2b in 400 carcinoid patients with a primary outcome of PFS. Data assessing bevacizumab in patients with

PNETs has not been reported, but a phase II study (CALGB 80701) of everolimus ± bevacizumab is currently ongoing.

Mammalian Target of Rapamycin Inhibitors

Recently, two phase II studies reported that the orally administered small-molecule mTOR inhibitor everolimus (RAD001) has promising anti-tumor activity in PNETs and carcinoids [17, 18]. Response rates were low in these studies, but progression-free survival was similar to values seen with the tyrosine kinase inhibitors sunitinib and sorafenib. A follow-up phase III randomized placebo-controlled trial of 410 patients with PNETs showed a response rate of only 5% but demonstrated a significantly improved PFS with everolimus as compared to placebo (11.0 months versus 4.6 months, HR 0.35, $p < .001$) [19], and in May 2011, the FDA approved everolimus for treatment of metastatic PNETs. In a nonrandomized phase II study, PFS in a patient cohort receiving octreotide in addition to everolimus (16.7 months) was superior to those treated with everolimus alone (9.7 months) [18].

Although not FDA approved for use in carcinoid tumors, the RADIANT-2 trial, a randomized, placebo-controlled, phase III study assessing everolimus plus octreotide versus placebo plus octreotide in patients with metastatic carcinoid tumors showed a PFS of 16.4 months versus 11.3 months in the two arms, respectively. Although the improvement did not reach statistical significance per central radiology review, local investigator assessment found improved PFS with combination therapy as compared to octreotide therapy alone [86]. Although these results are promising, further phase III studies will be needed to evaluate the role of everolimus both as a single agent and in combination with other therapies in the treatment of well differentiated, advanced carcinoid tumors.

A phase II study assessing temsirolimus, an intravenous mTOR inhibitor, in patients with advanced carcinoids and PNETs showed similar response rates to those seen with everolimus (4.8% in carcinoid patients, 6.7% in PNET patients) [20]. Median time to progression was estimated to be 6.0 months.

Recommendations

Treatment selection for metastatic PNETs and carcinoids is difficult given the paucity of comparative trials assessing various approaches in these diseases. On the basis of the data reviewed above, suggested treatment options are provided in Table 4. For patients with localized or fully resectable metastatic disease, surgical excision of both the primary tumor and metastatic foci is appropriate. Surgical resection should also be considered for debulking metastatic lesions, particularly for symptomatic carcinoids because there are limited effective systemic treatment options. In considering cytotoxic therapies, patients with PNETs should be considered for treatment with a streptozocin- or temozolomide-based regimen because response rates of up to 69% have been observed. Recent evidence from phase III randomized clinical trials also supports the use of everolimus and sunitinib as initial treatment of patients with metastatic PNETs. At this point, prospective comparative studies of cytotoxics and these pathway inhibitors have not been completed. Although not yet approved for use by the FDA in the treatment of carcinoids, we recommend consideration of everolimus in combination with octreotide for patients with carcinoid in light of the recently published RADIANT-2 trial. This is in stark contrast to cytotoxic efficacy in carcinoids, which is poor. In regard to somatostatin analogues, once metastatic disease is present, we favor initiation of octreotide in all midgut carcinoid patients and both carcinoid and PNET patients with hormone-mediated symptoms. Finally, hepatic-directed therapy may be considered an option for control of liver-only metastases, particularly those that are symptomatic. Unfortunately, there are no large or randomized studies evaluating the various hepatic-directed treatment modalities to guide the timing or selection of these interventions.

Conclusions

Recent phase III studies of octreotide, everolimus, and sunitinib suggest that these targeted approaches can alter the natural history of neuroendocrine tumors. It is apparent that carcinoids and PNETs are indeed two separate diseases that must be approached differently. It has also become evident that utilizing response rate as a primary end point for treatment trials is suboptimal. These tumors are typically quite indolent, and even without treatment, stable disease may be observed in a significant proportion of cases. Indeed, a National Cancer Institute GI Steering Committee Clinical Trials Planning meeting report recommends that further trials in carcinoids and PNETs utilize progression-free survival as a primary end point [12].

The discovery of multiple molecular mechanisms associated with PNETs and carcinoids, combined with clinical data to support drug efficacy against these targets, makes this a very exciting time in the investigation and clinical management of NETs. Clinical trials assessing various combinations of somatostatin analogues, mTOR inhibitors, tyrosine kinase inhibitors, and cytotoxic agents are ongoing (Table 5), and there is substantial promise that a multitargeted approach to therapy will translate into improved patient outcomes.

Author Contributions

Conception/Design: Jennifer R. Eads, Neal J. Meropol
Collection and/or assembly of data: Jennifer R. Eads, Neal J. Meropol
Data analysis and interpretation: Jennifer R. Eads, Neal J. Meropol
Manuscript writing: Jennifer R. Eads, Neal J. Meropol
Final approval of manuscript: Jennifer R. Eads, Neal J. Meropol

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