Systemic Therapeutic Options for Carcinoid

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"Carcinoids" are mostly slow-growing neuroendocrine neoplasms (NENs) with low proliferative activity. A wide range of therapeutic options with variable efficacy exist, including locoregional ablative strategies. Thereafter, some patients may not require medical therapy for years depending on the rate of progression or recurrence. However, the majority of patients require systemic treatment and therein lies the dilemma, since no antiproliferative agent is currently approved for carcinoids. Somatostatin analogs (SSAs), and to a lesser extent interferon-alpha, are standard therapy for carcinoids associated with the carcinoid syndrome. These drugs have some antiproliferative efficacy. SSAs rarely lead to tumor remission but may modestly prolong time to tumor progression. Chemotherapy is of limited value in carcinoids with low proliferation indices but may be useful in higher grade tumors. Peptide receptor-targeted radionuclide therapy may be of benefit and is mostly used after medical therapies fail. However, it is considered an investigational modality. More recently, targeted drugs such as mammalian target of rapamycin (mTOR) inhibitors and anti-angiogenics have been investigated. Objective remissions are rare. Their value remains to be rigorously elucidated. Increased efficacy requires a better understanding of the underlying tumor biology and identification of molecular pathological criteria to allow appropriate preselection of candidates for targeted therapies.
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The term carcinoid (*Karzinoide*) was initially introduced in 1907 by the German pathologist Oberndorfer who described a series of diminutive cancers in the intestinal tract that he identified as benign tumors.[1] Over the succeeding half century, confusion regarding the cell of origin of these tumors was elucidated by Feyrter's delineation of the diffuse neuroendocrine system and Ciaccio's description of the enterochromaffin cells.[2] The identification of the pathology of the tumors and their neuroendocrine phenotype was provided by Masson.[3] The term "carcinoid" was subsequently applied by the pathologists Williams and Sandler in 1963 in referring to different tumors depending on their location (foregut, midgut, and hindgut) in the embryonic gut. They proposed that these locations characterized three distinct groups of tumors.[4] The term "carcinoid" was initially introduced within the World Health Organization (WHO) classification for gastro-entero-pancreatic (GEP) neuroendocrine tumors (NETs) in 1980. Thereafter, in 2000, this classification was modified and replaced by a pathological categorization recognizing three distinct histological groups of tumors (well-differentiated NET, well-differentiated neuroendocrine carcinoma [NEC], and poorly differentiated NEC) and defined by the organ-specific origin of the tumor. In the most recent WHO classification (2010), the term "neuroendocrine neoplasm" (NEN) has been used and the pathological grading has become one of the essential components. Based on immunostaining of Ki-67 or mitotic count, three groups of NENs are currently defined by the WHO/European Neuroendocrine Tumor Society (ENETS)—NET G1: <2%, NET G2: 3–20; NEC G3 >20% Ki-67 (Table 1).[5] In this classification, the term "carcinoid" is preserved for NET G1. Unfortunately, the terms "carcinoid" and "low-grade NET," or "well- and moderately differentiated NETs" are frequently used synonymously. It is rare that "carcinoids" arise in the pancreas. For NENs of pulmonary or thymic origin, a different classification is used that defines three distinct subgroups: typical carcinoid, atypical carcinoid, and large cell and small cell NEC (Table 1). In contrast to the classification for GEP-NETs, mitosis *and* necrosis are important for differentiating these groups.[6] The classification systems, as currently defined, are useful for clinical and pathological purposes. However, it is becoming apparent that they are simplistic in that they

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Table 1. The Different Classification Systems (1980–2010) for Gastro-entero-pancreatic NENs and the Classification System (2004) for Bronchopulmonary and Thymic NENs

	Classification of Gastro-entero-pancreatic NENs			Classification of Bronchial/Thymic NENs
WHO 1980	**WHO 2000**	**WHO 2010/ENETS**	**AJCC Classification**	**WHO 2004**
Carcinoid	Well-differentiated endocrine tumor	Neuroendocrine tumor G1 (Ki-67 ≤2%), (carcinoid)	Well differentiated - Low grade (carcinoid/islet cell tumors)	Typical carcinoid <2 mitosis/10 HPF, no necrosis
	Well differentiated endocrine carcinoma	Neuroendocrine tumor G2 (Ki-67 3%–20%)	Moderately differentiated - Intermediate grade (carcinoid/Islet cell tumors)	Atypical carcinoid 2–10 mitosis/10 HPF, necrosis
	Poorly differentiated endocrine carcinoma/ small cell carcinoma	Neuroendocrine carcinoma G3 (Ki-67 >20%) - Large cell - Small cell	Poorly differentiated - High grade	Neuroendocrine carcinoma >10 mitosis/10 HPF, vast necrosis - Large cell - Small cell

Abbreviations: WHO, World Health Organization; ENETS, European Neuroendocrine Tumor Society; AJCC, American Joint Committee on Cancer.

fail to incorporate molecular pathological criteria that will be necessary to specifically identify the precise characteristics of widely divergent individual tumors. It therefore has become evident that the complex and heterogeneous group of lesions are not adequately served by being grouped under the archaic term "carcinoid." Here, the term "NENs" is used when discussing the tumors as a group, but NETs/"carcinoids" is used as needed to be consistent with the terminology in the cited publication.[7] Similarly, the embryological nomenclature is used when this is included in the referenced publication. Use of both "carcinoid" and, for example, foregut tumor, should not be interpreted as acceptance of these archaic terms but rather as a pragmatic decision to facilitate discussion using the histomorphologic classifications.

Overall, "carcinoids" (NENs–NET G1; poorly differentiated variants of NEN are, *per definition*, excluded from this grouping) exhibit a generally indolent clinical pattern of behavior. Unfortunately, systemic treatments have been explored in heterogeneous groups of patients (including both "carcinoids" of a variety of sites, as well as islet cell tumors/pancreatic NENs), although, more recently, a belated recognition of the differences in tumor biology between primary tumor sites (different cells of origin) has led to clinical trials in distinct subtypes of NEN, such as pancreatic or small intestinal NENs. While gastric, rectal, and lung NENs most frequently exhibit benign behavior, small intestinal lesions are more frequently malignant upon diagnosis (Table 2). As a consequence, data referable to systemic therapies are mostly related to small intestinal NENs. These lesions have been reported as metastatic in approximately 50% of patients at diagnosis.[8,9] This contrasts strikingly with an analysis of 780 cases with bronchopulmonary carcinoids, where 2% of the patients with typical carcinoids and 21% of the patients with atypical carcinoids present with stage IV disease, respectively.[10,11] Thus, data on therapeutic outcome of different systemic therapies are very limited for NENs of either lung, thymic, gastric, or rectal origin, and most data are based only on small case series. Given the lack of adequately powered studies and the heterogeneity of the data, the various therapeutic options are presented and discussed for the mixed group of "carcinoids."

In order to provide a representative overview of the current therapeutic status (despite the limitations), the PubMed database (January 1, 1980–August 6, 2012) was searched using "carcinoid" in combination with terms including 'systemic therapy' (n = 246), 'octreotide' (n = 861), 'lanreotide' (n = 90), 'chemotherapy' (n = 1624), 'interferon' (n = 284), 'peptide receptor radionuclide therapy' (n = 81), 'everolimus' (n = 24), 'sunitinib' (n = 17), 'targeted therapy' (n = 93), 'angiogenesis inhibitors' (n = 33), and 'bevacizumab' (n = 13). We included in our analysis all prospective trials, and retrospective studies only if large in size. Case reports were excluded, as were studies on poorly differentiated NENs or studies that focused on control of pancreatic NEN exclusively, since these are covered in other articles in this issue of *Seminars*. To provide a contemporary overview, American Society of Clinical Oncology (ASCO) abstracts detailing results of clinical trials within the last 5 years are included (n = 8). A total of 606 manuscripts were identified by this search; 58 (9.6%) were included in the final review.

TREATMENT OPTIONS—AN OVERVIEW

Systemic therapeutic options for "carcinoids"/NET G1 (the term carcinoid is also applied for NET G2) comprise a group of agents that have become referred to as targeted agents.[12] Inherent in this descriptive

Table 2. Biological and Clinicopathological Features of NENs ("Carcinoids") by Organ Site

Origin	Cell Type	Tumor Types (WHO)	Incidence (age-adjusted)*	Prevalence (all NENs)†	Secretory Products	Association With Hereditary Syndromes	Metastatic (%)*	5-Year Survival (SEER)‡
Small intestine	EC	NET G1 NET G2	0.67	19	Serotonin	(Familial?)	30–50	80
Thymus	EC	TC AC	0.02	1	ACTH NF	(MEN-1)	31	24
Colon	EC L	NET G1 NET G2	0.2	12	Serotonin/NF	—	30	45
Stomach	ECL EC G (Antrum)	NET G1 NET G2	0.3	7	Histamine/Serotonin Gastrin	MEN-I	9–15	30
Duodenum	EC D, G, L	NET G1 NET G2	0.19	2	Serotonin Gastrin/NF	MEN-I	9	54
Lung	EC	TC AC	1.35	29	Serotonin Histamine 5-OH-Tryptophan	MEN-I	5# 21#	19
Rectum	EC L	NET G1 NET G2	0.86	20	NF	—	0–5%	24
Pancreatic§	EC A,B,D,G, PP	NET G1 NET G2	0.32	7	Serotonin Calcitonin	MEN-I VHL	64	35

NOTE. The organ sites are tabulated in accordance with metastatic rate except for pancreas, which is included as a comparator.

Abbreviations: SEER, Surveillance, Epidemiology and End Results; AC, atypical "carcinoid"; EC, enterochromaffin cell; ECL, enterochromaffin-like cell; G, gastrin cell; L, enteroglucagon cell; MEN-I, multiple endocrine neoplasia type I; NET, neuroendocrine tumor; NF, nonfunctioning tumor; TC, typical "carcinoid"; VHL, von Hippel Lindau syndrome; ZES, Zollinger Ellison syndrome.

*Age-adjusted incidence = SEER 17 (1988–2004).[8]

†Prevalence of all NENs = SEER 17 (1973–2007).[9]

‡Five-year survival data, Modlin et al (unpublished data). Survival data relates to metastatic disease only and refers to "cause-specific" rather than "observed" survival.[8] The latter overestimates the mortality associated with the disease since it includes any cause of death. Cause-specific survival was obtained from the SEER 17 database and reflects "actual" survival from the diagnosed cancer which is more commensurate with clinical practice.

§Pancreas includes all tumors not only those currently termed "carcinoids" and is included as a comparison for other NENs. For pancreas-specific details see Kulke et al in this issue.

eponym, is the assumption that all NENs possess the specific target of interest and that the tumor of an individual patient expresses the target in a therapeutically susceptible fashion. Currently, apart from the pretherapeutic delineation of somatostatin receptors, there are little data to validate the presence of a putative drug "target" (receptor or signaling pathway) in a lesion. This limitation is likely reflected in the overall disappointing objective response rates to targeted drugs including SSAs in NENs ("carcinoids").

Most "carcinoid"/NET G1 (G2) therapy is termed as "targeted" and includes somatostatin analogs (SSAs), interferon-alpha, newer molecular targeted (signal pathway) therapies (eg, everolimus, vascular endothelial growth factor receptor [VEGFR] inhibitors) and peptide receptor radionuclide therapy (PRRT). The use of systemic chemotherapy is restricted to the more advanced and aggressive lesions (including NECs) (Figure 1). A wide variety of commutations and permutations of therapeutic strategies, especially related to the use of SSAs in hormone-secreting NENs (eg, small intestinal "carcinoids"), render it difficult to provide a precise determination of the antiproliferative effectiveness of a specific agent. In many instances, the exact efficacy of a therapy cannot be assessed since it may be administered in sequence with other modalities. These include locoregional approaches (embolization, chemoembolization) and/or cytoreductive surgery.

In the past, the endpoint in clinical trials was objective tumor remission. Currently, progression-free survival (PFS) or time to tumor progression (TTP) are often used as surrogate endpoints. None of the currently available drugs provides a cure, but stabilization of the disease associated with prolongation of PFS may be considered a therapeutic benefit since this may translate into an increase in overall survival. It has become accepted that any survival benefit related to one drug exclusively is unlikely given the generally favorable outcomes in many patients (>80% survival at 5 years is not atypical for, eg, midgut NENs).[8,9,13]

Parameters that impact therapeutic decision making include the functionality (hormone-secreting status of the lesion), tumor histology and grading, the site of the primary tumor, expression of somatostatin receptors based on the results of somatostatin receptor imaging, and the tumor burden, as well as the presence of extrahepatic disease.[14–19] The therapeutic options discussed here focus principally on the issue of inhibition of cell proliferation (tumor control) as opposed to inhibition of bioactive product secretion (symptom control).

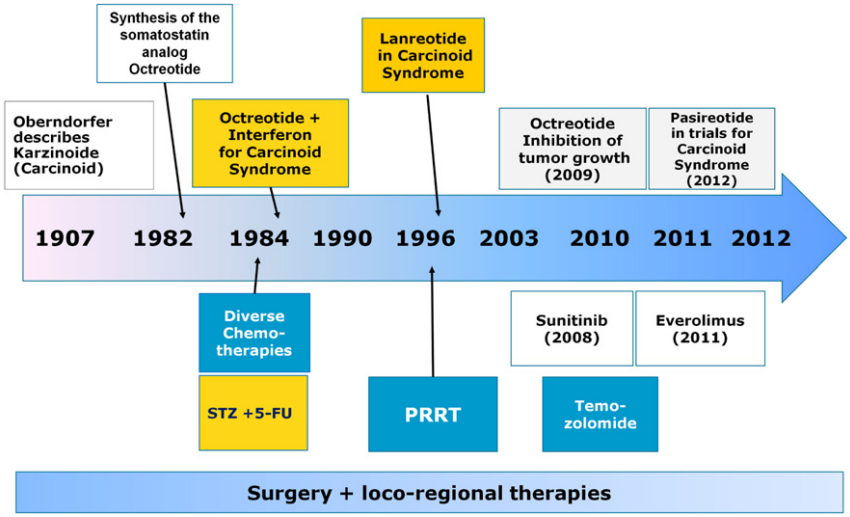

Figure 1. Evolution of therapy for NENs ("carcinoids"). Overview of the development of therapeutic agents, providing a general sense of NEN treatment as it pertains to "carcinoid" disease per se. Approved drugs are shown in yellow boxes (color figure may be viewed online). Dates in parenthesis indicate publication year.

THERAPEUTIC AGENTS

Somatostatin Analogs

NENs express a high density of somatostatin receptors (especially subtype 2) and, as a consequence, initial therapeutic strategies focused on the development of agents that targeted these receptors. SSAs have proven effective in the three decades since their introduction.[20] Two synthetic analogs of native somatostatin-14, octreotide and lanreotide, are approved standard therapies for control of symptoms of the carcinoid syndrome, such as flushing and diarrhea.[21–23] SSAs bind with high affinity to somatostatin receptor subtypes 2 and 5, which are expressed in high density on most GEP-NENs.[24,25] SSAs inhibit secretion of biogenic amines and other mediators, thus leading to complete or partial relief of flushing and/or diarrhea associated with the carcinoid syndrome in 40%–90% of the patients.[21,26–28] Octreotide is available as subcutaneous (SC) and long-acting intramuscular (IM) formulations (at 10-, 20-, and 30-mg dosages; Novartis), and lanreotide as a long-acting IM formulation (60-, 90-, and 120-mg Autogel; Ipsen). The dosages are selected and adapted depending on the severity of the syndrome and the extent of disease. Patients on long-acting SSAs may require additional SC injections of octreotide for breakthrough symptoms. Dose escalation with either SC or IM SSAs may provide further improvement of syndrome control.[29–31] Lanreotide is currently not approved in the United States for the treatment of carcinoid disease.

Based on the data from prospective and retrospective studies and from a single prospective, placebo-controlled trial (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) of 85 patients, octreotide LAR is considered a therapeutic option for tumor growth control. The mechanisms underlying the antiproliferative action of SSAs remain poorly understood and include direct and indirect effects, such as G1 cell cycle arrest and induction of apoptosis, as well as the inhibition of the release of growth factors (eg, insulin-like growth factor-1 [IGF-1], epidermal growth factor [EGF], insulin, gastrin) from tumor cells and the extracellular tumor surrounding matrix.[32,33] The PROMID study demonstrated a prolongation of median TTP in metastatic, non-resectable midgut NENs. The median TTPs were 14.3 and 6.0 months in patients treated with octreotide LAR 30 mg and placebo, respectively. Patients with functionally active and inactive tumors were noted to have a similar benefit.[34] Consistent with these results are data from the placebo arm of a large trial investigating the efficacy of octreotide ± everolimus in NENs[35]; the median PFS for octreotide in the placebo arm of therapy-naïve patients was 13.6 months (Table 3). Several trials, including the PROMID study, have indicated low objective response rates (0%–8%), with disease stabilization occurring in 50%–67% of patients.[26,34,36] However, it should be noted that the rigorous delineation of disease stabilization is a difficult and complex situation given the current limitations in sensitivity of the assessment techniques available.

While octreotide LAR 30 mg was used in the PROMID trial, and the antiproliferative activity of lanreotide AG 120 mg is currently under clinical investigation (an ongoing trial of lanreotide *v* placebo [Controlled study of Lanreotide Antiproliferative Response in NET or CLARINET] addresses the value of lanreotide in intestinal and pancreatic NETs), the optimal antiproliferative

Table 3. Efficacy Details of Targeted Therapies in Prospective NENs ("Carcinoids") Trials

Agent	No. of Patients	Design	Type of NEN	PR (%)	SD (%)	PD (%)	Median PFS	Reference
Octreotide LAR 30 mg *v* placebo	42 43	PCT	Midgut	2 2.3	67 37	23.8 53	14.3† 6	*Rinke et al, 2009[34]
Octreotide LAR 30 mg (therapy-naïve)	43	PCT	NENs with CS	2	81	12	13.6	Pavel et al, 2011[35]
^{90}Y-edotreotide	90	MCT	NENs with CS	4	70	26	16.3	Bushnell et al, 2010[43]
^{90}Y-DOTATOC	265	Phase II	Midgut NENs	26.8**	ND	ND	ND	Imhof et al, 2011[44]
IFN *v* STZ/5-FU#	64	MCT Phase III	NENs‡	9 3	63 56	9 31	14.1 5.5	Dahan et al, 2010[59]
Sunitinib (+ SSA in 54%)	41	Phase II	NENs	2.4	83	14.6	10	Kulke et al, 2008[75]
Everolimus + octreotide	30	Phase II	NENs	17	80	3	15.7	Yao et al, 2008[62]
Everolimus + octreotide	216	PCT	NENs with CS§	2	84	14	16.4	Pavel et al, 2011[35]
Placebo + octreotide	213			2	81	12	11.3	

Abbreviations: CS, carcinoid syndrome; MCT, multicenter trial; NEN, neuroendocrine neoplasms; PCT, placebo-controlled trial; PD, progressive disease; PR, partial response; SD, stable disease (all objective responses as assessed by radiological imaging).
*Objective response at 6 months as assessed by WHO criteria.
†TTP not PFS.
‡Pancreatic NENs included.
§Midgut 51%; lung 15%, colon 7%, pancreas 5%, liver 3% and others.
#Although 5-FU/STZ is not considered a targeted therapy, for comparative purposes and completeness, this has been included.
**Any morphological response. PRRT data cited do not provide adequate information for rigorous analysis or direct comparison but are presented as a general comparator for the therapy. Only data from the midgut group are presented.

dose for octreotide and lanreotide still requires rigorous delineation. There are also no data to determine the appropriate time point for initiation of SSAs. This reflects a number of issues, including the inability to define for a specific tumor the natural tumor biology, the overall indolent tumor growth pattern, and the possibility of spontaneous tumor growth arrest. Since there are no data on improvement of overall survival associated with the early use of SSAs, it remains an unanswerable question as to when treatment should be initiated. While the PROMID study was performed in therapy-naïve patients to prevent tumor progression, observation with imaging and tumor markers may be an alternative approach to SSAs, especially in asymptomatic patients with low tumor burden. While the majority of tumors may express the target (demonstrated, eg, by somatostatin receptor scintigraphy), this may not necessarily correlate with objective responses or duration of disease control. Biomarkers to preselect patients that may benefit from therapy are currently unavailable. Positive somatostatin receptor imaging was not required for inclusion in the PROMID study.

Octreotide is only approved by the US Food and Drug Administration (FDA) for symptom control. The original application was not designed to assess the drug as an antiproliferative agent and to date octreotide has not been approved as an antiproliferative agent in NET therapy by the FDA. Despite this, a number of neuroendocrine tumor societies have supported the use of octreotide as an antiproliferative agent and this recommendation is included in a variety of national guidelines (National Comprehensive Cancer Network [NCCN], North American Neuroendocrine Tumor Society [NANETS], and ENETS). The NCCN guidelines specifically recommend octreotide in patients with "clinically significant" tumor burden without prior observation.[37] The basis for the inconsistency between the FDA and the recommendations of the various societies is unclear but may reflect recognition of the lack of other approved therapies.

Relevant clinical data on the efficacy of SSA are lacking for specific subtypes of NENs, such as lung, thymic or rectal "carcinoids." The ENETS guidelines indicate that SSAs may be considered a therapeutic option not only in midgut but also in NENs of other sites if slowly progressive or categorized as G1 NETs.[16] Several studies support efficacy of SSA in gastric type I and II NENs associated with chronic atrophic gastritis. SSAs may lead to complete remission of these lesions.[33,38-40]; these, however, recur after withdrawal of therapy.[41] Since these tumors are very rarely metastatic (<5%), it remains unclear if SSAs improve long-term outcome, but use may facilitate follow-up investigations and be helpful in complex cases with high numbers of lesions. Overall, however, the use of an expensive agent with some adverse effects that requires monthly lifelong injection for a benign, usually asymptomatic disease, such as type I gastric "carcinoid" seems to offer little, clinical advantage and cannot be recommended based on the available data.

Peptide Receptor Radionuclide Therapy

This form of therapy (PRRT) embodies the combination of two agents: a target directed SSA linked to an isotope capable of providing cytotoxic radiation emis-

sions. Using this principle, a number of radiolabeled SSAs have been investigated in a limited number of prospective and retrospective studies. Most studies include heterogeneous patient populations comprising different primary tumor sites and functionality and have been undertaken using either ^{90}Y-DOTA-Phe1-Tyr3-Octreotide (^{90}Y-DOTATOC) or ^{177}Lu-DOTA-Tyr3-octreotate (^{177}Lu-DOTATATE). Objective response rates range between 0%–34%.[42–44] Some studies report high rates of disease stabilization but did not require disease progression prior to PRRT therapy. Some also included patients with stable disease.[42] Different designs and criteria of response assessment have thus been applied and individual studies are often not comparable.

In a large phase II study with ^{90}Y-DOTATOC (3.7 GBq/m^2; median, 2 cycles) including among others, small intestinal NENs (n = 265), bronchial "carcinoids" (n = 84) and unknown primaries (n = 67), a "morphological" response, defined as any measurable decrease in the sum of the longest diameters of all pre-therapeutically detected tumor lesions, was reported in 26.8%, 28.6%, and 34% of the groups, respectively. The overall response rate in this trial (>1,100 patients) was 34%.[44] In a prospective, open-label, multicenter trial, in 90 patients with NENs associated with the carcinoid syndrome refractory to octreotide who received treatment with three cycles of 4.4 GBq (120 mCi) ^{90}Y-edotreotide, partial tumor remissions were much lower (4%), but disease stabilization was achieved in 74%. Median PFS was favorable given the 16.3 month time frame (Table 3). This study provides more reliable data on tumor response with PRRT due to its inclusion requirements. These included at least one measurable tumor lesion that demonstrated disease progression prior to enrollment and used an assessment of response according to the criteria proposed by the Southwest Oncology Group (SWOG). The radiopeptide also exhibited some efficacy in syndrome control, which was the primary endpoint of the trial. The median duration of improvement of diarrhea and hot flushes was rather short (13.8 and 9.7 weeks, respectively) but lasted for up to 21 weeks in some patients.[43]

PRRT is, in general, well tolerated. However, some significant adverse outcomes have been described. Based on the analysis of more than 1,000 patients treated with ^{90}Y-DOTATOC, a permanent renal toxicity of grade 4–5 was observed in 9.2%, and 12.8% developed grade 3 to 4 transient hematologic toxicities.[44] Two patients had severe bone marrow disease including myelodysplastic syndrome after two cycles and acute myeloid leukemia after four cycles.[44] The latter adverse event also has been described in other studies in individual patients.[45] In contrast, the study with ^{90}Y-edotreotide reported a lower rate of kidney toxicity (3%) that was also reversible. Careful consideration of medical history (arterial hypertension, diabetes mellitus) is important for selection of patients for PRRT.[46]

According to ENETS guidelines, PRRT is a recommended treatment after failure of medical therapies. However, both NCCN and ENETS consider PRRT as investigational, and stress the need for further randomized trials to evaluate the benefit and potential toxicities. An international study comparing treatment with ^{177}Lu-DOTA0-Tyr3-octreotate to high-dose octreotide long-acting release (LAR) (60 mg/mo) in patients with inoperable, progressive, somatostatin receptor-positive midgut NENs is currently underway (www.clinical.trials.gov).

Interferon-Alpha

Interferon receptors are expressed in NENs and therefore provide a putative target for therapeutic intervention.[47] Interferons bind to a common receptor at the surface of tumor cells and, via induction of the JAK-STAT pathway, initiate transcription of interferon-inducible genes.[48] Inhibition of secretion and proliferation is mediated via direct and indirect effects. Interferon-alpha (IFN) is standard treatment for syndrome control of the carcinoid syndrome albeit frequently used as second-line therapy if SSAs are either not tolerated or patients are refractory to SSAs over time. Symptom control is achieved in 40%–70% of the patients.[21,49,50] The recommended dose of IFN is 3–5 $\times$ 10^6 U SC thrice weekly. The use of IFN is limited by its side effects such as influenza-like symptoms, fatigue, and weight loss, among others. Alternatively, for better tolerability, pegylated IFN (80–150 μg/week SC) may be considered, although data in patients with NENs are limited[51,52] and pegylated IFN is not yet approved for this indication.

As with SSAs, the use of IFN is associated with disease stabilization in 50%–60% of patients, while significant tumor shrinkage only occurs in approximately 10%–15%.[21,49,53] These results stem from limited studies representing heterogeneous primary tumor sites and functionality, and different endpoints (either biochemical and/or radiological). There is no evidence from two prospective, randomized controlled trials that the combination therapy of a SSA and IFN increases tumor response or TTP when used as first-line treatment in progressive NENs, although both studies were underpowered.[54,55] The study by Faiss et al was a three-arm study that assessed the antiproliferative efficacy of IFN-α2b (5 $\times$ 10^6 U, three times per week SC) in comparison to lanreotide (1 mg, three times per day SC) and to the combination of both lanreotide and IFN-α2b as first-line therapy in 80 patients with progressive GEP-NENs. The study included foregut (n = 36), midgut (n = 30), hindgut (n = 3), and unknown (n = 11) tumors. Both drugs were equally effective with respect to objective response (3.7% *v* 4% partial remission rate

and 26% and 28% stable disease rate at 12 months), while the combination was not superior to monotherapy, and was associated with more side effects.[54] Patients with midgut NENs had significantly longer TTP compared with foregut lesions. However, this may reflect the natural tumor biology of midgut NETs rather than drug efficacy per se. The trial by Arnold et al was a two-arm prospective trial in 105 patients with GEP-NENs including 43% midgut tumors. The study was constructed to assess the antiproliferative efficacy of octreotide (3×200 μg/d) + interferon-α2a (4.5×10^6 U thrice weekly) versus octreotide alone. It failed to demonstrate a significantly different outcome (objective response and TTP) between combination and monotherapy. Treatment failures occurred in 50% of patients within 6 months in each treatment arm.[55] In contrast, in a randomized trial in 68 patients with metastatic midgut NENs, the risk of progression was reduced by addition of IFN to octreotide compared to octreotide alone, but this was not associated with a survival benefit.[56] Although the use of early combination therapy of SSA and IFN is not supported by these trials, it has been proposed that in selected patients the addition of IFN to SSA may be useful for more effective symptom control (flushing and/or diarrhea), or improved tumor growth control.[56–58]

A French multicenter trial in 64 patients with advanced NENs of different sites addressed the question of the antiproliferative efficacy of IFN-α2a (3×10^6 U three times per week SC) in comparison to streptozotocin/5-fluorouracil (5-FU) chemotherapy. Median PFS was the primary endpoint; PFS was longer with IFN-α2a but not significantly different from STZ/5-FU (14.1 months *v* 5.5 months). In the chemotherapy arm, one patient (3%) with a small intestinal primary tumor had a partial response, while three patients (9%), two with small intestinal and one with an unknown primary, exhibited a partial tumor response with IFN. The rates of stable disease were not different (chemotherapy 56% and IFN 63%, respectively) (Table 3).[59] A limitation of this study is that it included a variety of primary tumor sites including pancreatic NENs. Hematologic toxicities were more frequent with IFN, whereas nausea and renal toxicity were more frequent in the chemotherapy arm, but these were mostly mild (grade 1–2 proteinuria).[59] Data for IFN from other disease sites are rare. A small study in patients with typical bronchial "carcinoids" demonstrates that IFN ± octreotide treatment resulted in stable disease in a low number of patients (15%; 4/27 patients) and this lasted for a median of 15 months.[60]

NCCN and ENETS guidelines advise that IFN can be considered as a treatment option in metastatic progressive NENs, although the data for this recommendation, as we describe, are less than optimal.

Mammalian Target of Rapamycin Inhibitors

Mammalian target of rapamycin (mTOR) represents a major regulatory component of a number of cellular metabolic events, including energy usage and proliferation. Theoretically, it therefore provides access to an ideal therapeutic node necessary for cell function. Temsirolimus and everolimus are two mTOR inhibitors that have been investigated in advanced NENs. Thirty-seven patients with progressive tumors including 21 patients with midgut NENs were treated with 25 mg/wk intravenous (IV) temsirolimus. In this group, the partial remission rate was 4.8%, while 57% achieved stable disease after prior disease progression within 6 months. The median TTP was 6 months in these patients.[61]

In a phase II trial, everolimus was evaluated in combination with octreotide in 30 patients. The high disease control rate (partial remissions in 17%, stable disease in 80%) along with a median PFS of 15.7 months was promising.[62] In a large placebo-controlled phase III trial in 429 patients with progressive NENs, patients were randomized to receive octreotide LAR with everolimus or placebo. The primary endpoint of the study, PFS according to central radiological reading, was 16.4 months in the everolimus arm and 11.3 months in the placebo/octreotide-only arm (Table 3). However, the predefined threshold for statistical significance was not reached.[35] Multivariate analysis and local radiological analysis support some efficacy of everolimus,[63] it remains unclear, however, which patient subgroups (primary tumor site and grading) might have a preferential benefit. A subgroup analysis identified some potential primary tumor sites that might particularly benefit. Median PFS was with 13.6 months in favor of the everolimus arm compared to 5.6 months in the placebo/octreotide arm in bronchial/lung NENs (n = 44), while in a subgroup of colonic NENs (n = 28), the median PFS was more than double that of the placebo arm (29.9 *v* 13 months). Despite these observations, the precise role of everolimus as a therapeutic agent remains to be defined.

Predictive biomarkers are not yet available for preselection of patients for mTOR inhibitor treatment. However, expression of mTOR and downstream signaling components (including p-4EBP1, p-S6K and p-eIF4E) has been reported in NENs.[64,65] Expression levels were higher in foregut than in midgut tumors, while mTOR positivity was significantly higher in tumors with higher proliferative activity.[64] In the temsirolimus trial, paired baseline and post-treatment biopsies were analyzed to address this issue in a small number of samples (n = 13). Interestingly, higher baseline levels of phosphorylated mTOR were predictive of tumor response, and increases in the expression of phosphorylated AKT and decreases in phosphorylated mTOR after 2 weeks on treatment were asso-

ciated with an increased TTP.[61] However, the predictive value of these biomarkers requires confirmation in other studies.

While everolimus has been approved for pancreatic NENs, the data for its efficacy in other NENs are regarded as controversial. Thus, the RADIANT-2 (RAD001 in advanced neuroendocrine tumors, second trial) study, which included mostly (51%) small intestinal "carcinoids," failed to achieve its primary endpoint. More recently a placebo-controlled trial in progressive gastrointestinal and lung "carcinoids" (RADIANT-4) has been initiated to assess the antiproliferative efficacy of everolimus as a monotherapy (www.clinical.trials.gov). Nevertheless, the current NCCN guidelines recommend the use of everolimus in clinically significant progressive disease as one of several therapeutic options. The ENETS guidelines recommend everolimus in non-pancreatic NETs after failure of all other medical therapies.

Angiogenesis Inhibitors

A feature of NENs is the evidence of angiogenesis and increased vascularity in comparison to other tumor types.[66] Consideration of this biological variable as a therapeutic target has led to the development of agents that inhibit tumor vessel development.[67] Anti-angiogenic drugs have recently been evaluated in small phase II trials in NENs, including midgut and pancreatic NENs. Drugs targeting VEGF (the monoclonal antibody bevacizumab), small molecules that inhibit the receptor tyrosine kinases of VEGFR and/or platelet-derived growth factor receptor (PDGFR; vatalanib, sunitinib) or VEGFR, PDGFR, c-KIT and Raf kinases (sorafenib), and other compounds with different anti-angiogenic mechanisms (eg, thalidomide, endostatin) have been investigated. In these studies (which included heterogeneous patient populations), no objective remissions were achieved with vatalanib, thalidomide, or endostatin.[68–70] Although high rates of disease stabilization were observed, in the absence of a placebo or observational arm, it remains unclear whether this was related to the natural tumor biology or the study drugs. These drugs are not investigated in current clinical trials.

While there are no studies on monotherapy of bevacizumab in NENs, the drug has been evaluated in combination with several other compounds, including octreotide, chemotherapeutic agents (5-FU or capecitabine/oxaliplatin, temozolomide), 2-methoxyestradiol (a metabolite of estradiol with antiangiogenic properties including inhibition of hypoxia-inducible factor [HIF]-1α), sorafenib or everolimus.[52,71–74] A phase II trial of octreotide with either bevacizumab (15 mg/kg every 3 weeks) or pegylated IFN (0.5 μg/kg/wk) in 44 patients identified a higher response rate in the bevacizumab arm compared to IFN (18% *v* 0%).[52] This provides the basis for an ongoing SWOG phase III randomized trial in advanced NENs, comparing bevacizumab + octreotide to IFN + octreotide. In all other combination therapies with bevacizumab, it remains unclear if the addition of the antibody improves efficacy since the benefit of the investigated single drugs or drug combinations has not been fully elucidated, and heterogeneous patient populations have been studied. In most instances, objective remissions have been lacking with these combinations with a few exceptions.

While sunitinib is an approved therapy in pancreatic NENs, data on sunitinib in midgut or NENs from other sites (carcinoids) are limited to a single phase II trial including 40 patients. Fourteen patients had lung or stomach (foregut) primary tumors. In this trial, every second patient received SSAs along with sunitinib. The objective response rate was low (2.4%) (Table 3),[75] and the median PFS (10 months) was not longer than might have been expected with SSA alone. Neither the size of the study nor the outcome supports the use of sunitinib in these tumors. Preliminary results of a phase II study with sorafenib identified partial responses in 10% of the patients. The inclusion of those patients with minor responses provided a 17% response rate. However, the drug was associated with toxicity (skin and gastrointestinal symptoms, fatigue) in 43% of patients.[76] The initial results of a Spanish multicenter trial with a combination of sorafenib and bevacizumab demonstrated a similar response rate (10%) to that obtained with sorafenib alone.[77] The potential benefit of a higher disease control rate with combination therapies including anti-angiogenic drugs may, overall, be limited by the potential adverse events associated with these agents. Given the lower toxicity, bevacizumab is currently the preferred drug in clinical trials with anti-angiogenics.

CHEMOTHERAPY-BASED PROTOCOLS

Systemic Chemotherapy

While most commonly used in non-neuroendocrine tumors, there has been a recent re-evaluation of chemotherapy in NENs. Objective response rates range between 0%–33% for chemotherapeutic drugs including 5-FU, streptozotocin, and dacarbazine, when used as monotherapy or in combination.[78–82] While cisplatin-based chemotherapy is standard therapy in poorly differentiated NENs, this treatment is associated with low response rates in "carcinoids" and is associated with high toxicity.[83,84] At present, it is therefore not recommended in well-differentiated NENs or "carcinoids." However, oxaliplatin-based chemotherapy has been investigated in NENs after the failure of other medical therapies. The largest trials evaluated the combination therapy of streptozotocin or doxorubicin and 5-FU. The results are included in Table 4.

Streptozotocin-Based Regimens

The efficacy of systemic chemotherapy in well-differentiated advanced (G1) NENs is limited. Although widely used,[71,82,85] its precise role is not well-defined. There are

Table 4. Systemic Chemotherapy in NENs ("Carcinoids")

Agent(s)	No. of Patients	Type of NEN	Enrollment Criteria	Objective Response (%)	Duration of Response (mo)	PFS/TTP	Overall Survival (mo)	Reference
STZ+5-FU *v* DOXO	172	NENs	Progression	22 *v* 21	7.75 *v* 6.5	ND	16 12	Engstrom et al, 1984[84]
STZ + 5-FU *v* DOXO + 5-FU	78 85	Mixed NENs (carcinoids)	Mixed: Symptoms, biochem./radiol.	16 *v* (15.4% SD) 15.9 (15.3% SD)	5.3 *v* 4.5	ND	24.3 15.7	Sun et al, 2005[80]
STZ+5-FU	32	Mixed, most midgut NENs	PD radiological and/or biochemical	3 (56% SD)	ND	5.5/8.5	30.4	Dahan et al, 2009[59]
STZ + 5-FU + cisplatin (72% first line)	79	Pancreas GI Other NENs	PD radiol. or biochem.	38/25†	ND	9.1	31.5	Turner et al, 2010[81]
Temozolomide*	24 (lung n = 12)	Lung NENs Thymic NENs	Advanced disease	31 (31% SD) 0 (71% SD)	ND	ND	ND	Ekeblad et al, 2007[93]
Temozolomide*	17 (small intestinal n = 10)	Small intestinal Other	Progression	0 (SD 70%) 0 (SD 100%)	ND	ND	ND	Maire et al, 2009[94]
Temozolomide + bevacizumab	19	NEN	ND	0	ND	7.3	18.8	Chan et al, 2012[71]
Temozolomide thalidomide	29 ("carcinoid" n = 14)	NEN	ND	7	ND	ND	ND	Kulke et al, 2009[95]

Abbreviations: DOXO, doxorubicin; STZ, streptozotocin; 5-FU, 5-fluorouracil; ND, no data; PD, progressive disease; SD, stable disease.
*Retrospective studies.
†Pancreatic/GI and other NEN.

inconsistencies between the various clinical studies with respect to response rate and response criteria (ie, endpoint analysis of biochemical response versus tumor response). Phase III comparative trials are lacking or very limited in both gut and lung NENs. The largest study reported is a comparative trial of 5-FU/doxorubicin versus streptozotocin/5-FU.[81] There were no differences in the objective response rates (15.9% *v* 16%) and PFS (4.5 *v* 5.3 months) between the treatment arms. The study reported a benefit in median survival for the streptozotocin arm with 24.3 months compared to 15.7 months for doxorubicin, and may thus be considered in selected patients where chemotherapy is considered a therapeutic option.[81] A variety of primary tumor sites (25% small intestine, followed by other, unknown, lung and rectum) were included. In contrast, in a prospective French multicenter trial with 32 patients with progressive NENs including a higher percentage of small intestinal primary tumors (63%), the objective response rate was only 3% (one patient with a small intestinal NEN), while stable disease was achieved in 59%. Median PFS was 5.5 months and thus similar to the other trial.[59,81] Subgroups were too small to assess any preferential response in either study. A series of small case studies indicate that objective response in bronchial "carcinoids" is lacking. In seven patients, the use of streptozotocin and 5-FU was associated with progressive disease in all patients; stable disease was, however, initially observed in two patients treated with streptozotocin and doxorubicin for 8 and 10 months, respectively.[60]

In a retrospective analysis including 33 NENs, the objective response rate was 25% with a three-drug regimen of streptozotocin/5-FU and cisplatin.[82] Although this study is small and based on heterogeneous primary tumor sites (lung [n = 8], gastrointestinal [n = 9], ovarian [n = 1], unknown primary [n = 15]), there was a suggestion that chemo-sensitivity increased with increasing mitotic count; response rates of 15% were noted with 0–1 mitosis/10 high-power fields (HPF), and 29% with 2–4 mitosis/10 HPF, respectively.[82] Other small series support that response to chemotherapy is dependent on the proliferative activity.[86] In a prospective trial of 86 patients with GEP-NENs (including 20% foregut, 33% unknown, and 48% pancreatic NENs) comparing a three-drug (capecitabine, streptozotocin, and cisplatin) and two-drug regimen (capecitabine, streptozotocin), the disease control rates and PFS did not differ between the regimens.[87] There are therefore no data supporting the idea that three-drug regimens are superior to two drugs (without platinum). Metronomic chemotherapy may provide an attractive alternative approach. This strategy facilitates dose reduction, which has the advantage of limiting adverse effects but in addition, allowing combinations of other drugs. The metronomic use of 5-FU in combination with octreotide was associated with partial responses in 24% and a high rate of disease stabilization (69%). This regimen was well tolerated and may warrant further investigation.[88]

Alkylating Agents (Dacarbazine, Temozolomide)

Early reports suggested a high tumor control rate with dacarbazine in metastatic midgut NENs.[89] Combination chemotherapy did not appear to increase the objective response rates. Only one of nine patients developed a partial response on combination therapy with dacarbazine and 5-FU.[90] In two prospective trials with multidrug treatment (dacarbazine, 5-FU, and epirubicin), a partial tumor remission was achieved in two of 20 and one of nine NENs, respectively.[91,92] In a separate study, the response rate with dacarbazine was 8.2% after failure of streptozotocin-based chemotherapy.[81] Thus, objective remissions remain a rare event with dacarbazine and range between 8%–11%.

More recently, temozolomide, an oral alkylating agent sharing the same metabolite with dacarbazine, has been explored either as mono- or combination therapy. Retrospective analysis of temozolomide as monotherapy suggests efficacy in treating bronchial and pancreatic NENs.[93,94] Ekeblad et al noted an objective remission rate of 30% in bronchial "carcinoids" (n = 13) with advanced disease stages, suggesting this agent may warrant additional study in larger trials. Although objective responses are lacking in NENs with temozolomide (± bevacizumab), a high rate of disease stabilization was noted in small intestinal, thymic, and NENs of other origin in a variety of small trials and a case series (Table 4).[71,94,95] Absence of methyl guanine methyl transferase (MGMT) expression, a DNA repair enzyme involved in induction of cancer cell resistance to some alkylating agents, eg, temozolomide, appears to be an important biological requirement to achieve tumor remission. MGMT staining has been examined in NENs.[96] Expression correlated with tumor responses; only one of 44 patients (2%) experienced an objective response; this patient was MGMT-negative.[96]

Platinum-Based Chemotherapy

While cisplatin and etoposide is standard treatment for poorly differentiated NEC, it has no efficacy in well differentiated NENs[83] and is associated with significant toxicity such as bone marrow suppression and polyneuropathy. More recently, oxaliplatin-based systemic chemotherapy has been explored in NENs either in combination with 5-FU (FOLFOX [folinic acid + 5-fluorouracil + oxaliplatin]) or capecitabine (XELOX [capecitabine + oxaliplatin]) ± bevacizumab (Table 5). Based on small patient numbers, objective responses have been observed mainly in foregut NENs, including pancreatic (18%–33%), bronchial (up to 60%), and thymic tumors, while only stable disease was noted in small intestinal NENs.[73,97–101] When used as second-line therapy after failure of SSA, stabilization of the disease may be achieved in 60%–100% of NENs, including small intestinal tumors (Table 5).

Overall, systemic chemotherapies have a very limited role in the management of NENs. Chemotherapy should be considered in individual patients once there is evidence of failure with other therapies, such as locoregional therapies, SSAs and IFN or PRRT in the absence of alternative antiproliferative drugs. Additional, well-constructed studies evaluating the benefit of these toxic chemotherapeutic regimens therefore should be considered to clarify which additional subgroups of patients may benefit. Currently, based on the observed toxicity (polyneuropathy, ototoxicity, nephrotoxicity, bone marrow suppression), oxaliplatin-based chemotherapy should be reserved for patients with NENs that display a high proliferative activity (Ki-67 >10%–15%) or rapid tumor growth over a 3- to 6-month period.

THERAPY OF THE UNKNOWN PRIMARY

In patients with "carcinoids" of unknown primary (CUP), imaging and pathology should be used to seek to identify the location and origin of the primary tumor since treatment strategies differ substantially between foregut and midgut NENs. This reflects the generally accepted dogma that the former are generally more biologically aggressive and therefore require more effectual therapy. The immunohistochemical identification of CDX-2 or TTF-1 may indicate the presence of a small intestinal or bronchial/thymic primary tumor, respectively.[102] Staining of Islet-1 may indicate a primary tumor in the pancreas.[103] Molecular high resolution imaging, such as ^{68}Ga-DOTATOC positron emission tomography (PET)/computed tomography (CT) with tri-phasic CT or the use of other molecular tracers (eg, ^{18}F-DOPA, ^{11}C-HTP) may be of added value in the identification of the primary tumor. In addition, these modalities are more effective in addressing the extent of disease and thus may better inform therapeutic decision-making.[104,105] Alternatively, somatostatin receptor scintigraphy can be used, preferably as single-photon emission CT (SPECT)/CT, although this provides a lower sensitivity study as compared to PET/CT. If no primary tumor is identified by imaging modalities, or endoscopy/colonoscopy then treatment decisions are primarily guided by histological grading. Therapy may subsequently be complemented by information on growth velocity assessed by conventional imaging. Other parameters that guide therapeutic decision-making include functionality of the tumor and somatostatin receptor status. Thus patients with functioning NEN, such as the carcinoid syndrome will typically be treated with SSA and/or IFN. In nonfunctioning NENs, classified as G1 NETs, a "watch and wait" strategy may be adopted. In some centers SSAs may be used if somatostatin receptors have been identified by imaging studies. If progression is noted, PPRT may be an option although not historically available in the United States. In patients with a higher grading (NET G2 or moderately differentiated NENs) a "watch and wait" strategy may be risky, especially if the tumor burden is high. In such patients, one must have a low threshold

Table 5. Platinum-Based Chemotherapy in Well- and Moderately Differentiated NENs ("Carcinoids")

Regimen	No. of Patients	Progressive at Study Entry	Histology/Primary Tumor Sites	Objective Response PR (%)	Objective Response SD (%)	PFS/TTP (mo)	Median Overall Survival (mo)	Reference
Cisplatin	15	NI	NI	1/15 (7%)	NI	1.8	NI	Moertel et al, 1986[78]
Etoposide + cisplatin	13	NI	Overall 5 small bowel 2 lung 3 cecum/colon 1 rectum 2 CUP	0/13 (0%)	11/13 (85%)	3	10.5	Moertel et al, 1991[82]
Irinotecan + cisplatin	15*	NI	Overall 4 Small bowel 6 pancreas 3 colon 2 rectum 1 lung 2 CUP	0	11/15 (73)	4.5	11.4	Kulke et al, 2006[83]
Capecitabine + oxaliplatin	27	PD after failure of SSAs	Overall 5 Bronchial 11 EPT 7 Intestinal 4 others	8/27 (30) 3/5 (60%) 3/11 (27%) 0/7 (0%) ND	13/27 (48) 1/5 (20%) 5/11 (45%) 7/7 (100%) ND	20	40	Bajetta et al, 2007[96]
Gemcitabine + oxaliplatin	18	PD	Overall 5 Small Bowel 5 Pancreas 4 Lung 2 Thymus 4 Other	17 NI 2/5 (40%) NI 1/2 (50%) NI	12/18 (67)	7.0	23.4	Cassier et al, 2009[98]
FOLFOX-4‡	16	PD	Overall 2 bronchial, 5 pancreas, 2 stomach 2 cecum 1 each ileum, colon, rectum 2 CUP	0	10/16 (62.5)	4.5	ND	Pape et al, 2006[99]
FOLFOX-6 + bevacizumab ± octreotide‡	11	PD	Overall 6 EPT 5 CT	3/11 (27) 2/6 (33) 1/5 (20)	8/11 (72) 4/6 (67) 4/5 (80)	ND	ND	Venook et al, 2008[100]
Capecitabine+ oxaliplatin+ bevacizumab‡	40†	±PD	Overall 20 EPT 15 CUP 5 CT	7/31 (23) 6/19 (32) 1/11 (9) NI	22/31 (71)	13.7	ND	Kunz et al, 2010[73]

Abbreviations: CT, carcinoid tumor; CUP, carcinoid of unknown primary; ND, no data reported; NI, not indicated; NR, not reached; PD, progressive disease; PR, partial remission; SD, stable disease; SSAs, somatostatin analogs.

*18 patients in total, only 15 evaluable.

†40 patients in total, only 31 evaluable.

‡Abstract presentations (ASCO).

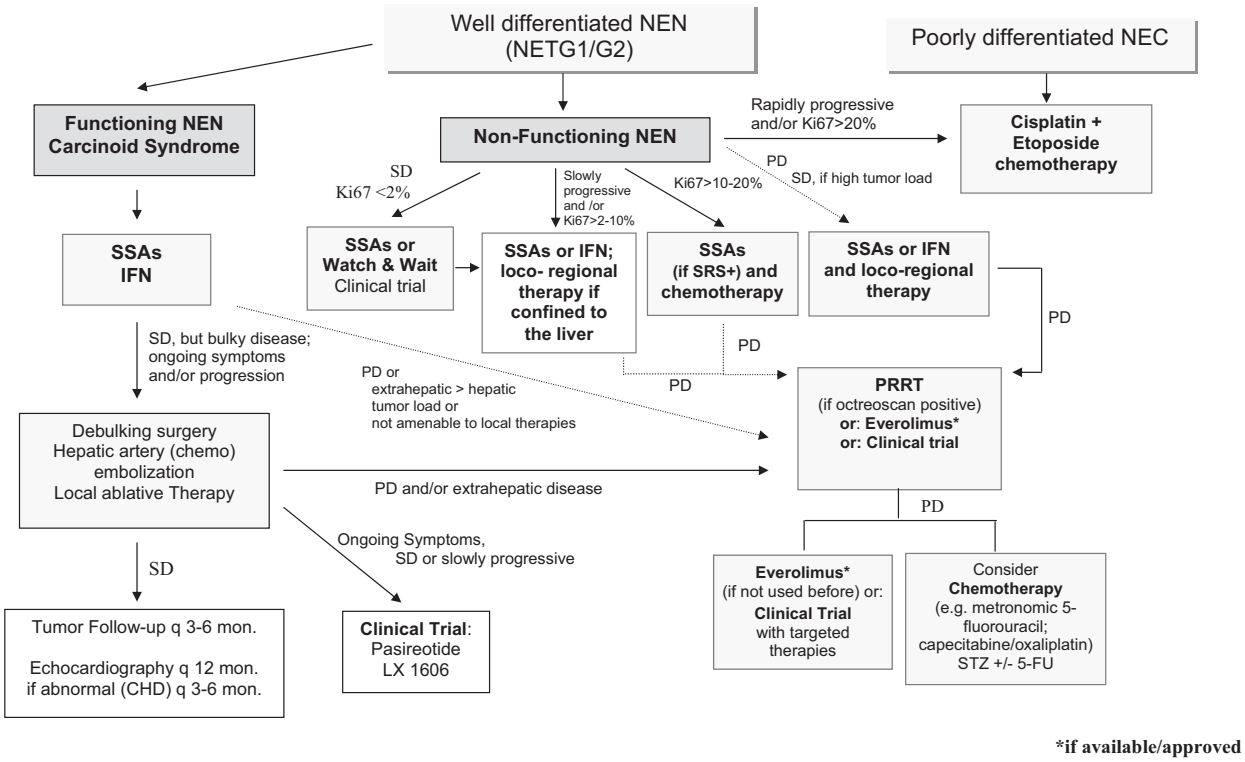

Figure 2. Potential therapeutic algorithm in metastatic non-resectable midgut NENs/"carcinoids."

for considering locoregional therapies followed by systemic treatment (eg, IFN or SSAs ± everolimus or PRRT). In patients with significant tumor growth within 3–6 months, the use of systemic chemotherapy should be considered.

INTEGRATION OF THERAPIES

For all targeted therapies investigated in NENs thus far, tumor remissions are a notably rare event (<10%). Although it has been widely reported that there is a high rate of disease stabilization ranging between 67%–84%, the methodologies for assessing this parameter are insensitive and limited. PFS has, overall, been reported to range between 13.6 months and 16.4 months for different therapies with the caveat that direct comparisons are not applicable. In the case of sunitinib and streptozotocin-based chemotherapy, the PFS was lower (10 months and 5 months, respectively) (Tables 3 and 4). These modest responses may reflect the tumor biology, which is associated with slow tumor growth and long survival times exceeding 60% and reaching up to 90% at 5 years.[9,106]

Systemic chemotherapy may be an option in selected patients who have tumors with a relatively high proliferative rate at diagnosis or in the course of the disease if the tumor converts to a more malignant phenotype. It is not recommended for early use in the management of NENs.

As long as evidence of superiority of a specific treatment compared to another is lacking, therapeutic strategy is frequently based on individualized decision-making. While this may occur in an interdisciplinary setting that assesses the different components of an individual patients' disease, strategy is often determined by treatment availability and the philosophy of the clinicians. A major consideration is the avoidance of toxicity and the need to maintain the relatively good quality of life evident in patients. Based on the available information that has been evaluated in this review, a treatment algorithm is proposed for the optimization of the therapeutic management of these tumors (Figure 2).

CONCLUSION

There are very limited data suggesting "targeted" therapy is effective in NENs. The most relevant predictable agents, however, are the SSAs, although data from only one small placebo controlled trial are available to support an antiproliferative effect.[34] When SSAs fail, IFN is considered in some countries despite the substantial adverse events associated with such therapy. The former (especially octreotide) are recommended as first line therapeutic option in midgut NENs based on the PROMID study and the marginal evidence that SSAs may have efficacy in low proliferating (<2% Ki-67) tumors.[34] It has been suggested by inference that a similar strategy should be considered in other NENs, such as rectal or bronchial, although no rigorous data exist to support this. While there is some evidence that SSAs are effective in type I gastric "carcinoids," it is dubious as to whether treatment with a

disease regarded as approximately 98% benign warrants therapeutic intercession. IFN is mostly used after failure of SSA monotherapy or in the rare event that SSAs are not tolerated as a first-line intervention. With respect to tumor growth control after SSA failure, IFN may represent an option especially in the case when locoregional therapies have already been used or are not useful, eg, in disseminated extrahepatic disease.

Despite these observations, it should be specifically noted that none of the currently available agents provides a cure for neuroendocrine tumor disease. In addition, any assessment of therapeutic outcome for individual subtypes of NENs with respect to specific therapies is limited not only by the paucity of patient numbers but also by the marked differences in tumor biology. This is reflected by different survival times for different tumor primary sites irrespective of the disease stage at diagnosis.[8,9] These two issues as well as the fact that none of the drugs is approved for antiproliferative therapy, notwithstanding the difficulty in developing and identifying targeted therapies, has led to a focus on the development of trials that accept the failure of curative therapy. Current studies thus focus on combination therapies with the aims of improving response rates or prolonging response duration. The main combination partners include, but are not restricted to SSA, mTOR inhibitors, and angiogenesis inhibitors, a strategy that appears to be more market-oriented rather than scientifically or biologically focused. This observation reflects the fact that there exists a paucity of rigorous preclinical data that provide any scientific rationale for these combination therapies. Although mTOR and VEGF-targeted agents are being explored in clinical trials,[35,75] their explicit role in the antiproliferative management of carcinoids still requires considerable elucidation. Future selection of targeted therapies for carcinoids requires careful consideration especially in respect of recently reported significant toxicity and potentially increased mortality associated with the use of novel targeted drugs in cancer therapy.[107] Other studies examining SSAs with a broader receptor agonist profile (pasireotide) and an oral serotonin synthesis inhibitor, LX1606, are under clinical investigation in the expectation of optimizing carcinoid symptom control.

The key limitation in the utility of currently available agents remains the inability to preemptively identify targets in a particular tumor. Current technology is relatively insensitive and unable to identify subtle responses to therapy. Hence, a vital mandate in improving outcome is the identification of appropriate biomarkers that can be used as parameters of therapeutic efficacy and thereby guide therapy. The need to define cross-talk between the pathways involved in growth promoting signals and the integration of tumor microenvironment signaling is a critical requirement to developing more effective therapeutic agents.

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