A Tale of Two Tumors: Treating Pancreatic and Extrapancreatic Neuroendocrine Tumors

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Abstract

Despite their perceived rarity, gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are rising in incidence and prevalence. The biology, natural history, and therapeutic options for GEP-NETs are heterogeneous: NETs arising in the pancreas can be distinguished from those arising elsewhere in the gastrointestinal tract, and therapy is dichotomized between these two groups. Somatostatin analogues are the mainstay of oncologic management of bowel NETs; everolimus, streptozocin, and sunitinib are approved to treat pancreatic NETs. There are significant differences in molecular genetics between pancreatic and extrapancreatic NETs, and studies are evaluating whether additional NET patients may benefit from targeted agents. We discuss the distinguishing features of these two groups of tumors, as well as the therapeutic implications of the distinction. We also examine the evolving therapeutic landscape and discuss the likelihood that treatment will be developed independently for pancreatic and extrapancreatic gastrointestinal NETs, with novel therapeutics effective for newly identified pathologically or molecularly defined subgroups.

INTRODUCTION

Epidemiology

Neuroendocrine tumors (NETs) are not common, but their incidence has increased meaningfully throughout the twentieth century, rising from 1.09/100,000 population in 1973 to 5.25/100,000 in a Surveillance, Epidemiology and End-Results (SEER) analysis (1). This rise is likely due partly to improved detection of early lesions and partly to increased focus on pathological distinctions between endocrine and exocrine tumors, given their dramatically different therapies. From the same analysis, we can conclude that the primary site has clear prognostic importance, with the median survival for patients with metastatic disease ranging from 5 months for patients with colonic primary tumors to 56 months for patients with small-bowel primary tumors. Pancreatic neuroendocrine tumors (PNETs) have an intermediate prognosis, with an estimated median survival of 27 months for patients with metastatic disease. The primary site is also associated with response to treatment, and treatment benefits vary between patients with PNET and those with other tumor subtypes.

Pathophysiology and Biological Insights

Although PNETs were originally thought to arise from pancreatic islet cells, recent work supports the notion that PNETs arise from stem-like nonislet ductal progenitor cells (2), sustaining the transition in nomenclature from islet cell carcinoma to pancreatic neuroendocrine tumor. Classical genetics and the analysis of familial syndromes provided initial insights into the biology of PNETs, demonstrating associations with the genes *MEN1*, *VHL*, *NF1*, *TSC1*, and *TSC2* (3). More recent exome sequencing of resection specimens from sporadic PNETs revealed a 44% incidence of mutations in *MEN1* and a 43% incidence of mutation in the *DAXX/ATRX* complex, as well as a 14% incidence of mutation in the mechanistic target of rapamycin (mTOR) pathway (4). Others have also suggested that menin inhibits AKT and is involved in the mTOR pathway (5). *VHL* mutations lead to increased levels of hypoxia-inducible factor-1α (HIF-1α) and secondary overexpression of vascular endothelial growth factor (VEGF), mutations in *TSC1/2* result in activation of the mTOR pathway, and *NF1* mutations result in activation of Ras GTPase, which may feed into mTOR as well. However, whole-exome sequence data suggest that other pathways, particularly those involving DNA repair, may also be important in driving the growth of pancreatic NETs. *DAXX/ATRX* mutations result in a phenotype known as alternative lengthening of telomeres (ALT) (6). In ALT, a low-fidelity DNA damage response elongates telomeres by a telomerase-independent mechanism, which is coupled with a global impairment of the DNA damage response (7). A similarly impaired DNA damage response has been reported in *MEN1*-mutated cells (8). Epigenetic data showing hypermethylation of the promoter of *RASSF1A* in more than 50% of PNETs (9)—which may similarly impact the DNA damage response through p53—further support the role of DNA repair pathways in tumor initiation or propagation.

In contrast, mutational analyses of small-intestinal carcinoid tumors have been less revealing. Exome sequencing of 48 small-intestinal NETs has recently been completed; it revealed a low mutation rate and no common mutation events, but frequent copy-number variations in several genes, most notably *SMAD4* of the transforming growth factor-β (TGF-β) cascade in 22 of the 48 tumors studied (10). Using a combination of whole-genome and whole-exome sequencing, followed by analysis of additional large data sets, other investigators identified frameshift mutations in *CDKN1B* in 14 of 180 small-intestinal NETs (11). Epigenetic studies have revealed hypermethylation of *RASSF1A* in 32% of small-intestinal NETs, exclusively in those of foregut

embryology (12). Of note, these studies found an association between *RASSF1A* methylation and overexpression of cyclin D1, perhaps highlighting an unanticipated role for cyclin overexpression in this indolent tumor. Thus, few mutations have been found in small-bowel carcinoids, and factors involved in carcinogenesis and malignant progression remain poorly understood. Future work integrating genomics and epigenetics in larger cohorts of patients is anticipated.

Stage, Grade, and Natural History

Both the European Neuroendocrine Tumor Society (13) and the American Joint Committee on Cancer have proposed staging systems for neuroendocrine tumors using the TNM (tumor, node, metastasis) system (14). Although the systems vary in their specifics, particularly with respect to defining the tumor stage by size, depth, or involvement of critical structures, both are prognostic for patients and therefore of clinical utility. However, the most critical distinction in clinical practice is between resectable and unresectable/metastatic disease, because it determines the therapy. Until adjuvant therapy becomes available, differences in earlier stages will remain prognostic rather than predictive and have limited impact on therapeutic decision-making.

Assessing the tumor grade is a diagnostic necessity for patients with gastroenteropancreatic (GEP) NETs of all primary sites. Although different classification systems are used throughout the world, all reflect the spectrum of neuroendocrine malignancies, ranging from indolent to aggressive (**Table 1**). Currently, systems primarily distinguish among high-grade (grade 3) tumors—with a mitotic count greater than 20 per 10 high-powered fields or a Ki-67 proliferation index greater than 20%—and low- or intermediate-grade (grades 1–2) tumors because their clinical behavior is largely divided along these lines (15). However, a recent large retrospective Nordic analysis revealed that a Ki-67 index of 55% has the best predictive and prognostic significance, dichotomizing the response rate to platinum-based chemotherapy between 15% for those with a Ki-67 index less than 55%, and a response rate of 42% for those patients with a Ki-67 index greater than 55% (16). Additionally, one group was able to demonstrate improved prognostication by shifting the grade 1/2 differentiation point from a Ki-67 index of 2% to 5% (17). Therefore, grading algorithms may continue to evolve and provide more predictive information, although

Table 1 Histological grading of neuroendocrine tumors (15)

Differentiation	Grade	Mitotic count	Ki-67 index	Traditional	ENETS; WHO
Well differentiated	Low grade (G1)	<2 per 10 HPFs	≤2%	Carcinoid, islet cell, pancreatic (neuro)endocrine tumor	Neuroendocrine tumor; Grade 1
	Intermediate grade (G2)	2–20 per 10 HPFs	3–20%	Carcinoid, islet cell, pancreatic (neuro)endocrine tumor	Neuroendocrine tumor; Grade 2
Poorly differentiated	High grade (G3)	>20 per 10 HPFs	>20%	Small cell carcinoma	Neuroendocrine carcinoma; Grade 3, small cell
				Large cell neuroendocrine carcinoma	Neuroendocrine carcinoma; Grade 3, large cell

Abbreviations: ENETS, European Neuroendocrine Tumor Society; HPFs, high-powered fields; WHO, World Health Organization.

only changes in the definition of grade 3 tumors will be germane to therapeutic decisions, given the current options.

Together the grade and stage determine the prognosis for any individual patient. In the SEER analysis, low-grade tumors (grades 1–2) yielded a median survival of 223 months for patients with localized disease and 33 months for patients with metastatic disease. For high-grade tumors, the analogous median survival durations were 34 months and 5 months, respectively (1). Outcomes vary by primary site for all stages of disease: patients with pancreatic primary tumors have a median survival of 136 months for localized disease and 27 months in the setting of metastases. Of note, these data were collected before the targeted therapy advances discussed under "Medical Therapy" below. Except where specifically noted, this review discusses only grades 1 and 2 NETs, because they are biologically distinct from grade 3 NETs and therapy for these tumors has seen a dramatic evolution during the past five years.

DIAGNOSIS AND SYNDROMIC PRESENTATIONS

The majority (70%) of malignant PNETs are nonfunctional, without any accompanying syndrome of hormonal hypersecretion, instead presenting with vague abdominal symptoms from mass effect. In this situation, circulating biomarkers lack sufficient diagnostic accuracy and biopsy is required. Chromogranin A (CgA), a common element in neuroendocrine dense-core granules, is cosecreted with neurohumoral products (18) and is considered the best blood biomarker. In one study assessing its diagnostic characteristics, elevated CgA had a sensitivity of 67.9% for NETs and a specificity of 85.7% (19). A 51-transcript reverse transcriptase–polymerase chain reaction (RT-PCR) test in peripheral blood has performed well in the development phase when compared with CgA (20). However, prospective validation in a spectrum of real-world situations is still needed before it can enter into clinical use.

The minority of patients with PNETs present with a syndrome of hormone hypersecretion; symptoms largely depend on the specific secreted hormone. Multiple hormones can be detected in any given tumor by immunohistochemistry, and a tumor is defined by the hormonal syndrome rather than its granule content. These syndromes are summarized in **Table 2** and described in more detail below.

Table 2 Syndromic presentations and symptomatic management of pancreatic neuroendocrine tumors including management of symptoms of hormone secretion unless or until surgical cure is achieved

Tumor	Symptoms or signs	Medical management
Insulinoma	Hypoglycemia with confusion, nausea, diaphoresis, weakness; possible loss of consciousness	Frequent small meals, dextrose, diazoxide, everolimus
Glucagonoma	Rash (necrotizing migratory erythema), cachexia, diabetes, deep venous thrombosis	Somatostatin analogues
VIPoma	Profound secretory diarrhea, electrolyte disturbances	Somatostatin analogues
Gastrinoma	Acid hypersecretion resulting in refractory peptic ulcer disease, abdominal pain, and diarrhea	Proton pump inhibitors, somatostatin analogues
Nonfunctioning	Typically diagnosed incidentally or with symptoms of mass effect	Local or systemic therapy, as clinical scenario dictates

Insulinoma

Whipple's triad of hypoglycemia, neuroglycopenic symptoms, and resolution with eating was first described in 1935 (21) and remains the classic description of an insulinoma. On suspecting the diagnosis, confirmation is generally obtained using serum assessment of insulin, proinsulin, C-peptide, and glucose (22). In the absence of easily applied clinical decision rules, an amended insulin:glucose ratio has been proposed, in which the insulin concentration at the termination of a 48-h fast (in pmol/L) is divided by 1.7 mmol/L less than the glucose concentration. A ratio greater than 32.2 (pmol/L/mmol/L) had positive and negative predictive values of 0.99 and 0.98, respectively, in an index series of 114 patients undergoing evaluation for insulinoma (23). There remains some debate about the diagnostic utility of the standard 72-h fast over the 48-h fast, with 91% of insulinoma patients having symptomatic hypoglycemia by 48 h, and an additional 6% having asymptomatic hypoglycemia by that time; 2% of patients develop hypoglycemia between 48 and 72 h, and 1% remain normoglycemic at the end of a 72-h fast (24).

Gastrinoma

Zollinger & Ellison (25) originally described a syndrome of refractory peptic ulcer disease and hypergastrinemia in association with a PNET in 1955. The diagnosis can be confirmed by elevated fasting gastrin levels; stimulation to supraphysiological levels with secretin can be used in challenging cases (26). Of note, primary hyperparathyroidism with hypercalcemia can result in secondary hypergastrinemia, obscuring the diagnosis of PNET in patients with the multiple endocrine neoplasia syndrome, type I (MEN I) (27), so careful observation is necessary after parathyroidectomy. Also, gastrinomas may present in extrapancreatic locations within the gastrinoma triangle, which generally includes the proximal duodenum. Localization can be challenging, as 30% of tumors are invisible by conventional imaging, including more than 60% of tumors smaller than 1 cm (28). In selected cases, empirical diagnostic surgery with duodenotomy may be considered (29).

Glucagonoma

Glucagonomas are associated with the triad of migratory necrolytic erythema (dermatitis), diabetes, and deep venous thrombosis (30), known colloquially as the 3-D syndrome. Demonstration of elevated plasma glucagon levels confirms the diagnosis of glucagonoma. These tumors are frequently large and advanced at presentation.

VIPoma

Verner & Morrison (31) described a syndrome of massive secretory diarrhea associated with hypokalemia in 1958. This syndrome was originally thought to be an early manifestation of gastrin hypersecretion, but it was eventually understood to be due to secretion of vasoactive intestinal peptide (VIP) (32), resulting in these tumors being known as VIPomas. Serum levels of VIP are measured directly when these tumors are suspected, and elevated levels confirm the diagnosis.

Other Functional Pancreatic Neuroendocrine Tumors

PNETs have also been reported to secrete somatostatin; adrenocorticotrophic hormone (ACTH), producing Cushing syndrome (33); growth hormone releasing factor (GRF), producing acromegaly (34); and various other hormones. However, these PNETs are rare and unlikely to be

encountered in clinical practice. Also, PNETs can harbor granules containing multiple different hormones (35), and their syndromic phenotype may change during the course of a patient's illness (36).

Carcinoid Tumors

The carcinoid syndrome of wheezing, flushing, and diarrhea, with eventual sequelae of right-sided cardiac valvular disease, was originally described in 1954 (37). This syndrome is related to the secretion of serotonin by the carcinoid tumor (38), canonically into the posthepatic circulation, as serotonin is deactivated into the urinary metabolite 5-hydroxyindoleacetic acid (5-HIAA) by the liver. The carcinoid syndrome is essentially associated only with small-bowel NETs, and clinicians should remain skeptical of simultaneous diagnoses of carcinoid syndrome and PNET.

SURGICAL MANAGEMENT

The primary therapy for a resectable NET is surgery (22). Small PNETs of low grade and minimal metastatic potential may be resected with simple enucleation, although larger lesions may require distal pancreatectomy or pancreaticoduodenectomy, depending on their location. Laparoscopic approaches have been attempted for insulinomas, and a meta-analysis of 452 patients demonstrated reduced length of stay but no statistically significant differences in surgical or oncologic outcomes with these approaches (39). Surgery in the context of MEN I is more nuanced because such patients typically have multiple tumors throughout the body of the pancreas, and the benefit of large operations is more difficult to demonstrate when hormonal syndromes can be controlled medically; additionally, *MEN*-associated tumors rarely develop distant metastases (40). For nonfunctional tumors less than 2 cm in diameter, the role of surgery remains somewhat controversial. A single-institution retrospective series of 133 patients with 1-cm tumors followed for a median of 45 months observed no progression in a group of patients who did not have surgery and a perioperative complication rate of 46% in the patients undergoing surgery (41). However, a SEER analysis of more than 1,300 patients, 263 of whom had tumors smaller than 2 cm, observed a 9.1% incidence of distant metastases in that subgroup (42). Another single-institution study that included 39 patients with tumors smaller than 2 cm observed 3 (7.7%) patients who eventually developed metastases (43). However, these studies included patients with mostly sporadic PNETs. The applicability of the data to *MEN1* is unclear.

For carcinoid tumors, surgery is similarly advocated in localized disease, although their tendency toward occult lymph node metastasis makes careful dissection by an experienced surgeon particularly important. No existing data support adjuvant hormonal therapy, chemotherapy, or radiation in either pancreatic or extrapancreatic NETs.

TREATMENT OF ADVANCED DISEASE

Liver Metastases

Hepatic resection. The role of liver resection for patients with hepatic metastases has been examined in retrospective reports (44, 45) and one recent meta-analysis (46). Variable 5-year survival rates are generally reported to be more than 60%. In multivariate analyses, resection with curative intent has been associated with the longest duration of survival following resection. However, given the retrospective nature of the analyses, it cannot be stated definitively whether survival is determined principally by the intervention or the underlying disease biology. In fact,

only a small fraction of patients are truly cured, with a recent systematic review reporting a 5-year progression-free survival (PFS) rate following hepatic resection with curative intent of 29% (range 6–66%) and a 10-year PFS rate of 1% (range 0–11%) (47). At the present time, we consider metastatectomy when all disease can be removed; in such scenarios, it is palliative and may provide survival benefit.

Orthotopic liver transplantation. Orthotopic liver transplantation has been explored as an option for patients whose disease is not amenable to limited hepatic resection. Two systems have been devised for patient selection: the Milan criteria (48) and the European Neuroendocrine Tumor Society consensus criteria (49), both of which emphasize selecting patients with indolent biology, previously resected primary tumors, and no evidence of extrahepatic disease. Similar to hepatic resection, the 5-year disease-free survival in the two largest series was approximately 30% (50, 51). A recent systematic review highlights the heterogeneity of results and illustrates the need for prospective data (52). Given the risks involved, we consider transplantation to be an investigational approach in the management of NETs, and a prospective clinical trial would be the ideal method to determine its true benefit in a defined population of patients.

Hepatic artery embolization. Hepatic artery embolization is often considered in patients with liver metastases that cannot be resected. Based on the observation that hepatic metastases are preferentially perfused via the hepatic artery (53), embolization was originally performed with a catheter-infused foam into the hepatic artery (bland embolization), leading to excellent symptomatic control (54). However, embolization can also be performed with chemotherapy (e.g., doxorubicin, cisplatin, or streptozocin) delivered on drug-eluting beads (55). Finally, radioactive isotopes [frequently yttrium-90 (^{90}Y)] attached to glass or resin microspheres can be selectively delivered to the tumor via the hepatic artery; this is known as selective internal radiation therapy (SIRT) (56). Although no prospective data are available, all three techniques (bland embolization, chemoembolization, and SIRT) are equally reasonable palliative approaches for symptomatic patients with NETs (57, 58). Two recent retrospective reviews have suggested that the three techniques have similar response rates and times to progression, although each review had fewer than 50 patients, which limits meaningful conclusions (59, 60). Additional local techniques, such as radiofrequency ablation (61), are also used for palliation, but comparative data from prospective clinical trials are lacking.

Medical Therapy

Somatostatin and somatostatin analogues. Many neuroendocrine tumors express somatostatin receptors, and their hormone secretion can be inhibited by somatostatin. However, not until the synthesis of octreotide, a biologically stable somatostatin analogue (62), were investigators able to use the compound to suppress hormonal symptoms in patients with PNETs (63, 64) and carcinoid tumors (65, 66) alike. The PROMID (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) study subsequently demonstrated a benefit in time to progression for patients with advanced midgut NETs treated with octreotide (67). The recently completed CLARINET (Controlled study of Lanreotide Antiproliferative Response In NeuroEndocrine Tumors) trial demonstrated a similar benefit in PFS for patients with pancreatic or extrapancreatic NETs treated with the somatostatin analogue lanreotide (68). Therefore, somatostatin analogues can be considered for control of both hormonal symptoms and tumor growth in patients with all GEP-NETs.

Streptozocin. Streptozocin, an alkylating agent preferentially brought into cells by the largely islet cell–specific glucose transporter-2 (GLUT2) (69), has long demonstrated activity in PNETs but not in carcinoid tumors. This difference has been observed since its initial testing in many malignancies at the US National Cancer Institute (70). A subsequent series verified the activity of streptozocin in PNETs (71), although cross-sectional imaging was not available at the time, and investigators used hormonal secretion and physical examination as the primary means of assessing disease burden, which limited accurate assessment of response rates in modern terms. Subsequent randomized studies by Moertel and colleagues (72, 73) demonstrated improved activity with the addition of 5-fluorouracil or doxorubicin, although these studies were similarly limited. Single-center data suggest that combining 5-fluorouracil, doxorubicin, and streptozocin is both tolerable and capable of producing a 39% response rate using modern radiographic assessment (74), which is notably different from the 6% radiographic response rate observed with a streptozocin-based doublet in two separate single-center studies (75, 76). Streptozocin-based chemotherapy has been approved by the US Food and Drug Administration (FDA) for treating PNETs, although the specific regimen is determined by a patient's comorbidities and the provider's preferences.

Temozolomide. Retrospective studies have suggested that temozolomide-based regimens may be similar in efficacy to streptozocin-based regimens in treating PNETs (77–79), although reported response rates have varied significantly, ranging from 8% (77) when used as a single agent to 70% (80) when used in combination with capecitabine. In the largest retrospective series, 18/53 (34%) patients with PNETs experienced a partial or complete response to temozolomide-based therapy (79). In prospective studies, temozolomide has been evaluated in combination with thalidomide, bevacizumab, or everolimus, with response rates ranging from 34% to 45% (81–83). Taken together, these data suggest that in advanced PNETs temozolomide may have efficacy similar to that of streptozocin-based therapy.

Everolimus. Everolimus, a small-molecule inhibitor of mTOR, received FDA approval for the treatment of advanced PNETs in 2011 on the basis of the pivotal RADIANT-3 (RAD001 in Advanced Neuroendocrine Tumors–3) study. It demonstrated an improvement in median PFS from 4.6 months to 11 months in patients whose disease had progressed prior to enrollment in the study; the hazard ratio for PFS was 0.35 (84). It has also benefited patients with refractory hormonal symptoms, even in the setting of progressive disease (85). In the phase II study of everolimus that led to that pivotal study, the objective response rate (ORR) was 27% in PNETs and 17% in carcinoid tumors, suggesting activity in both groups (86). However, in the RADIANT-2 study, everolimus for functional carcinoid tumors was not significantly better than control arm. Although the median PFS was 5.1 months longer for treated patients, the hazard ratio was 0.77, and the p value ($p = 0.026$) did not cross the prespecified significance boundary of $p = 0.0246$ (87). The RADIANT-4 study, seeking to determine whether everolimus will benefit patients with nonfunctional carcinoid tumors, has recently completed accrual.

Sunitinib. Sunitinib, an inhibitor of the VEGF pathway, has also been used for treating advanced PNETs. In phase II testing this agent demonstrated a 16.7% ORR in PNETs and a 2.4% ORR in carcinoid tumors (88), leading to a pivotal study of its use in PNETs. The pivotal study was stopped after accruing 171 of a planned 340 patients when an unplanned interim analysis observed a PFS of 11.4 months in the sunitinib group compared with 5.5 months in the placebo group (89). Because the interim analysis was unplanned, statistical evaluation of the primary endpoint is challenging, but the agent is almost certainly active in PNETs, and therefore it received FDA approval.

A MODERN APPROACH TO DISEASE MANAGEMENT

Based on the state of the evidence and our own experience, we propose a practical approach to the initial management of advanced pancreatic and extrapancreatic NETs (**Figure 1**). In this approach, treatment is driven by the volume of disease and pace of progression, with specific options determined by the primary site. In all situations, resection with curative intent should be attempted if feasible. For low-volume systemic disease that is indolent in its pace, somatostatin analogues are reasonable regardless of the primary site. For extrapancreatic NETs, liver-directed therapies can be considered for high-volume indolent liver metastases. For those carcinoid tumors demonstrating progressive disease despite somatostatin analogue therapy, clinical trials are the most appropriate option. In PNETs, we prefer targeted therapies for lower-volume progressive disease and cytotoxic chemotherapy for higher-volume disease that needs more rapid reduction in tumor mass, although there are no randomized data to support this specific practice.

FUTURE DIRECTIONS

Peptide Receptor Radionuclide Therapy

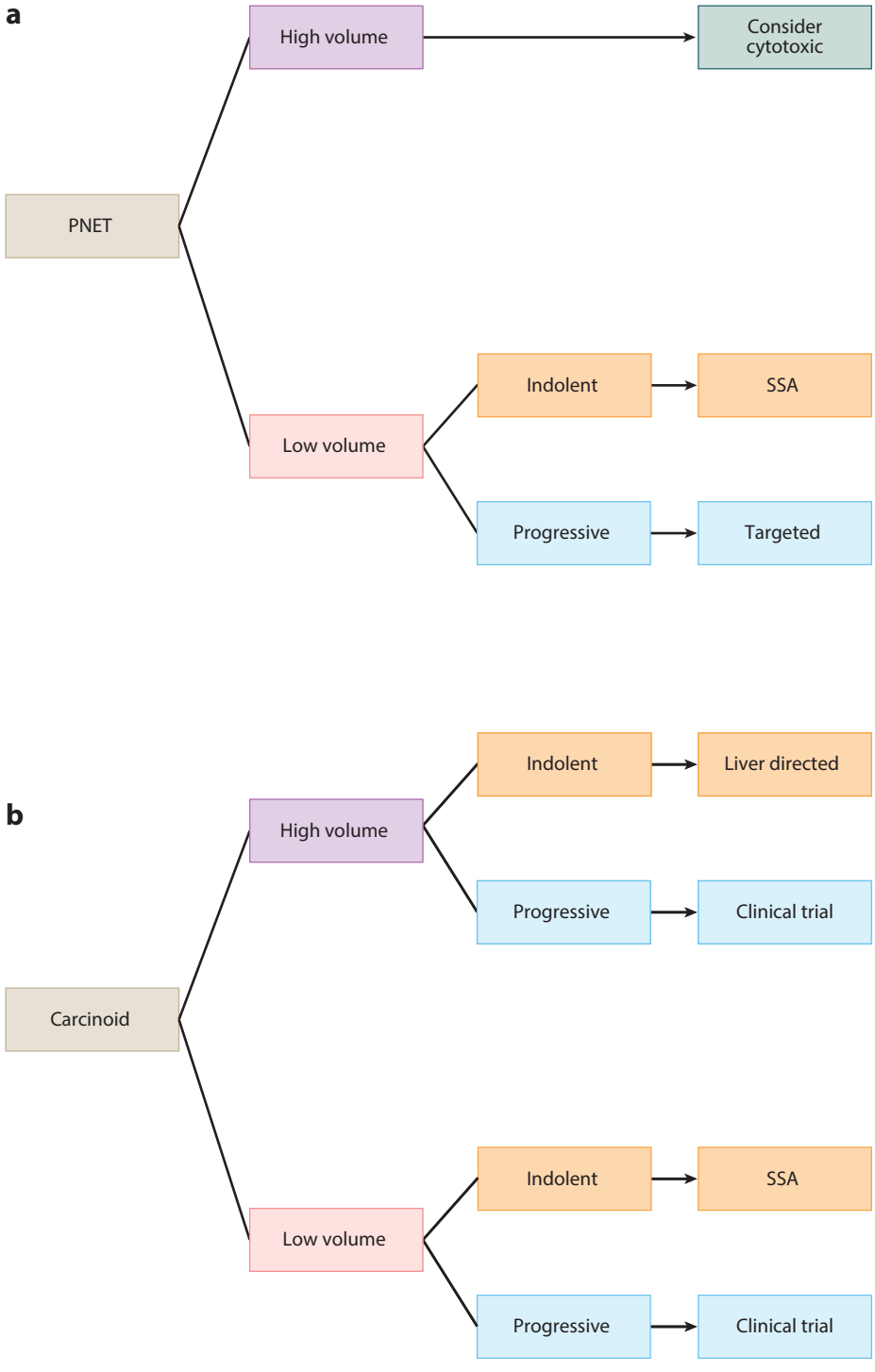
The frequent expression of somatostatin receptors on neuroendocrine tumors provides a rationale for using somatostatin as a targeting agent for radionuclide therapy in patients with advanced disease. In a prospective phase II study of 90 patients with metastatic functional carcinoid tumors refractory to octreotide who were treated with ^{90}Y-DOTA-Tyr^3-octreotide (^{90}Y-edotreotide), more than 50% of patients showed symptomatic improvement. Modest responses were also noted, including in 4% of patients who had a partial radiological response (90). In a study of 504 patients treated with ^{177}Lu-DOTA-Tyr^3-octreotate, efficacy results for 310 patients suggested an ORR as high as 30%; however, the lack of an intention-to-treat analysis and missing data for 194 patients make the interpretation of the results difficult (91). NETTER-1 [a study comparing treatment with 177Lu-DOTA0-Tyr^3-octreotate to octreotide long-acting repeatable (LAR) in patients with inoperable, progressive, somatostatin receptor positive midgut carcinoid tumors], an ongoing phase III study, is comparing ^{177}Lu-DOTA-Tyr^3-octreotate with high-dose (60 mg intramuscularly every 28 days) octreotide LAR in patients with advanced small-bowel carcinoid tumors.

Bevacizumab

Based on the observation that increased VEGF correlated with increased tumor vascularity and poorer prognosis in GEP-NET patients (92), inhibition of the VEGF pathway has been under investigation for the treatment of NETs for the past several years. Initial therapy with a combination of bevacizumab and 2-methoxyestradiol did not yield objective responses using the Response Evaluation Criteria in Solid Tumors (RECIST) (93), but a subsequent combination of bevacizumab and temozolomide yielded a 33% ORR in PNETs (94); and a study of bevacizumab with capecitabine and octreotide revealed an ORR of 26.3% in PNET patients. When combined with everolimus in a mixed cohort of 39 GEP-NET patients, bevacizumab yielded an ORR of 26% (95). Similarly, the combination of bevacizumab and temsirolimus yielded an ORR of 37% in a cohort of 50 PNET patients who had progressive disease prior to enrollment (96). Overall, these results have led to widespread interest in bevacizumab as a novel therapy for GEP-NETs, and randomized studies are evaluating its role in both patients with PNETs and patients with midgut carcinoid tumors.

Figure 1

(*a*) Approach to initial therapy for advanced pancreatic neuroendocrine tumors. Consideration of concurrent administration of a somatostatin analogue is also reasonable. (*b*) Approach to initial therapy for advanced extrapancreatic neuroendocrine tumors. Consideration of concurrent administration of a somatostatin analogue is also reasonable. Abbreviations: PNET, pancreatic neuroendocrine tumor; SSA, somatostatin analogue.



Pazopanib

Given the importance of the VEGF pathway in the progression of NETs and the activity of sunitinib in the management of PNETs, there has been increasing interest in evaluating other VEGF receptor–targeted tyrosine kinase inhibitors in NETs. Pazopanib was evaluated in a phase II study that included parallel cohorts of patients with carcinoid or pancreatic NETs; in a preliminary report, the study found an ORR of 17% in the PNET cohort and 0% in the carcinoid cohort (97). Similarly, a 6% ORR was observed in a mixed cohort of 33 patients in the PAZONET study (a phase II trial of pazopanib in patients with metastatic neuroendocrine tumors who may have previously received antiangiogenic or mTOR treatment) (98). A randomized placebo-controlled phase II study evaluating pazopanib in patients with advanced carcinoid tumors is ongoing.

Immunotherapy

Recent years have seen an explosion in the use of immunotherapeutic agents for several tumor types. Given that streptozocin is known to induce a T cell–dependent autoimmune insulitis in mice (99), it is plausible that these novel immune checkpoint inhibitors may have a role in NETs as well.

DNA Damage Response

The emerging importance of mutations in *DAXX* and *ATRX*, which are involved in chromatin remodeling and beget an ALT phenotype that is dependent on a faulty DNA damage response, presents opportunities for novel therapeutic approaches. The impaired double-strand break repair mechanism inherent in the ALT phenotype (7) may be an appealing target for poly(ADP-ribose) polymerase (PARP) inhibition in an effort to confer synthetic lethality, potentially in combination with the alkylating agents already in use for PNETs.

CONCLUSION

In this review, we present PNETs as distinct molecular and biological entities from extrapancreatic NETs. Surgery and local ablation techniques are similarly effective in both groups, but systemic agents show important differences in antitumor activity. Somatostatin analogues are known to be effective in relieving hormonal symptoms and prolonging time to progression in all GEP-NETs, providing a rational basis for the formal evaluation of radiopeptide therapy using somatostatin analogues to target tumor cells in the same patient population. Alkylating agents, such as streptozocin and temozolomide, as a class have shown the clearest efficacy for treating PNETs. Similarly, the targeted agents everolimus and sunitinib have shown clear evidence of benefit in PNETs, although studies continue to explore the role of these agents in treating bowel NETs. In the future, trials will likely continue to address pancreatic and extrapancreatic NETs separately. As we gain deeper biological insight into the heterogeneity of these tumors, we may be able to identify additional pathways to target and new subgroups that benefit from specific interventions. In the meantime it remains simultaneously the best of times and the worst of times.

DISCLOSURE STATEMENT

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