New Strategies for Advanced Neuroendocrine Tumors in the Era of Targeted Therapy

Mei Dong, Alexandria T. Phan, and James C. Yao

Abstract

Low- to intermediate-grade neuroendocrine tumor (NET) constitutes a group of indolent malignancies that share the capacity for secreting hormones and neuroamines. Until recently, there were few therapeutic options for oncologic control. The PROMID study showed that octreotide long-acting repeatable formulation can delay tumor growth in midgut NETs. And, recent phase III studies showed both everolimus and sunitinib improved progression-free survival in pancreatic NETs, validating the phosphoinositide 3-kinase/Akt/mTOR pathway and angiogenesis as important targets for further advances. Ongoing and planned pivotal studies targeting these pathways in other NET subtypes may widen their therapeutic application. Development of rational combinations may further improve therapeutic outcome. These successes and our improved understanding of the underlying molecular biology are likely to lead to further important advances on the horizon. Clin Cancer Res; 18(7); 1830–6. ©2012 AACR.

Background

Neuroendocrine tumors (NET) are generally classified into low- to intermediate-grade versus high-grade tumors on the basis of pathology. Low- to intermediate-grade NETs, the focus of this review, are either functional or nonfunctional, depending on whether the tumor secretes bioactive substances that lead to clinical symptoms such as flushing and diarrhea. NETs are generally further divided into carcinoid and pancreatic NETs. Carcinoids develop from neuroendocrine cells at any location in the body and are grouped according to their embryonic origin: the foregut (lungs, thymus, stomach, and duodenum); the midgut (jejunum, ileum, appendix, and proximal large bowel); and the hindgut (distal colon and rectum; ref. 1). It is estimated that 64% of all NETs originated in the gastrointestinal tract and 28% originated in the lung (2). Pancreatic NET, traditionally called islet-cell carcinoma, represents 1.3% of all malignancies arising from the pancreas (3).

Epidemiology

The incidence of NETs has increased significantly, from 1.09 to 5.25 per 100,000 individuals between 1973 and 2004 (4). A large, retrospective, case–control study identified only family history of malignancy as a significant risk factor (5). Pancreatic NETs are rare, occurring at an estimated incidence of 3 per 1,000,000 individuals (4). Infrequently, NETs arise as part of certain genetic cancer syndromes, including multiple endocrine neoplasia type 1, von Hippel-Lindau syndrome, neurofibromatosis, and tuberous sclerosis (TSC; ref. 6). Most NETs, however, are sporadic.

Pathology and Staging

Apart from the tumor–node–metastasis staging system endorsed by the American Joint Committee on Cancer in 2010, tumor grade and primary site are important prognostic determinants of cancer-related outcomes (7–9). Low-grade NETs follow a relatively indolent course. The cells are well differentiated, appearing in a sheet-like structure, and usually nonfunctional. Indices of cell proliferation include the number of mitoses per 10 high-power microscopic fields or the percentage of tumor cells with immunostaining for Ki67. Because management of high-grade NETs fundamentally differs from that of low- and intermediate-grade NETs, uniformed reporting of grade is encouraged.

Radiologic Imaging

Imaging modalities frequently used for NETs include computed tomography (CT), MRI, and $[^{111}\text{In-DTPA}]{\text{octreotide}}$ scintigraphy (10). Because of the vascular nature of NETs, tumors generally enhance intensely with i.v. contrast during the early arterial phase, with washout during the delayed venous phase. Therefore, multiphasic CT is recommended. MRI is a good modality to assess liver metastases, which are usually hypointense on T1-weighted images and hyperintense on T2-weighted images (11).
Scintigraphy using the radiolabeled somatostatin analogue, octreotide, can detect NETs that express somatostatin receptor types 2 and 5, with an overall sensitivity of 80% to 90% (12, 13). Although scintigraphy provides useful information about the site of disease, it does not give accurate information about the size of tumor. 2[18F]fluoro-2-deoxy-D-glucose position emission tomography (FDG-PET) has been used in evaluating NETs. Although its applicability for low-grade NETs is limited because of their low metabolic activity, the use of FDG-PETs in intermediate- and high-grade NETs is still being evaluated.

**Management of Hormonal Syndrome**

NETs are characterized by their ability to produce bioactive peptides and neuroamines, such as serotonin, histamine, prostaglandins, substance P, insulin, gastrin, glucagon, and vasoactive intestinal polypeptide (14, 15). Most patients with early-stage NETs are asymptomatic; some may present with nonspecific abdominal symptoms because of the local effect of serotonin or the mechanical effect of the primary tumor. Patients with advanced-stage NETs can manifest symptoms of carcinoid syndrome, which classically consists of facial flushing, diarrhea, and occasionally bronchospastic wheezing. Carcinoid syndrome can be debilitating and is usually seen in the setting of advanced or metastatic disease.

Somatostatin (SST) analogues, such as octreotide and lanreotide, block sst2 and sst5, effectively reducing the release of bioactive peptides and neuroamines (Fig. 1). These agents are used for the management of carcinoid syndrome or symptoms of hormonal overproduction from NETs. Octreotide comes in 2 forms, the long-acting repeatable form and the short-acting rescue form. It is generally well tolerated. Side effects, including cholelithiasis, hypothyroidism, bradycardia, and hyperglycemia, are generally manageable, infrequently affecting the patients’ quality of life.
IFN-α binds to receptors on NET cells and can lead to degradation of secretory peptide and tumor growth suppression. It has been used to control carcinoid syndrome with or without octreotide (16–18). Because it has delayed onset of response and more side effects compared with octreotide, so it is not usually the first-line agent for symptomatic patients with NETs.

### Oncologic Management of NETs

High-grade or poorly differentiated NETs are treated with platinum-based chemotherapy. For low- to intermediate-grade NETs, surgical resection of the primary tumor offers cure of localized disease; however, complete metastectomy has been associated with longer survival among patients with advanced disease and should be considered when possible (19, 20). Systemic therapy options for tumor control remain limited for NETs.

#### Systemic therapy for pancreatic NETs

Streptozocin-based chemotherapy was approved by the U.S. Food and Drug Administration for the treatment of pancreatic NET nearly 3 decades ago. Analyses of 2 large case series using Response Evaluation Criteria of Solid Tumors criteria have reported objective tumor response rates of 39% and 38%, respectively (21, 22).

In genetic cancer syndromes (TSC-2, neurofibromatosis-1, and von Hippel-Lindau syndrome), somatic mutations identified using an exome-sequencing approach, and expression profiling have consistently implicated a dysfunction of the mTOR pathway as a critical event in pancreatic NETs (Fig. 1; refs. 23–25). Everolimus, an oral inhibitor of mTOR, was studied in a multinational double-blind placebo-controlled phase III study (Table 1; ref. 26). The study showed that everolimus significantly prolonged median progression-free survival (PFS) from 4.6 to 11 months [HR = 0.35; 95% confidence interval (CI), 0.27–0.45; P < 0.0001]. Everolimus also significantly reduced insulin, glucagon, and gastrin secretions among patients with functional pancreatic NETs (27, 28).

#### Table 1. Recent and ongoing phase III studies in advanced NETs

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>Median PFS and/or TTP (months)</th>
<th>P-value</th>
<th>Study status and reference</th>
</tr>
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<tbody>
<tr>
<td><strong>Pancreatic NETs</strong></td>
<td></td>
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<tr>
<td>Sunitinib</td>
<td>171</td>
<td>11.4 PFS</td>
<td>0.0001^a</td>
<td>Study completed</td>
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<tr>
<td>Placebo</td>
<td></td>
<td>5.5 PFS</td>
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<td>Raymond et al., 2011 (29)</td>
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<tr>
<td>Everolimus</td>
<td>410</td>
<td>11.0 PFS</td>
<td>&lt;0.0001</td>
<td>Study completed</td>
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<tr>
<td>Placebo</td>
<td></td>
<td>4.6 PFS</td>
<td></td>
<td>Yao et al., 2011 (26)</td>
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<td><strong>Carcinoid tumors</strong></td>
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<tr>
<td>Octreotide LAR</td>
<td>90</td>
<td>14.3 TTP</td>
<td>&lt;0.0001</td>
<td>Study completed</td>
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<tr>
<td>Placebo</td>
<td></td>
<td>6.0 TTP</td>
<td></td>
<td>Rinke et al., 2009 (34)</td>
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<tr>
<td>Everolimus + octreotide LAR</td>
<td>429</td>
<td>16.4 PFS</td>
<td>0.026^b</td>
<td>Study completed</td>
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<tr>
<td>Placebo + octreotide LAR</td>
<td></td>
<td>11.3 PFS</td>
<td></td>
<td>Pavel et al., 2011 (56)</td>
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<tr>
<td>Lanreotide</td>
<td>200</td>
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<td>Accrual completed</td>
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<tr>
<td>Placebo</td>
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<tr>
<td>Bevacizumab + octreotide LAR</td>
<td>400</td>
<td></td>
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<td>Recruiting</td>
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<tr>
<td>IFN-α + octreotide LAR</td>
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<tr>
<td><strong>Carcinoid syndrome</strong></td>
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<tr>
<td>Octreotide LAR</td>
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<td></td>
<td></td>
<td>Recruiting</td>
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<td>Pasireotide LAR</td>
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<tr>
<td>Lanreotide</td>
<td>100</td>
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<td>Recruiting</td>
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<tr>
<td>Placebo</td>
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**Abbreviations:** LAR, long-acting repeatable; PFS, progression-free survival; TTP, time to progression.

^aNot statistically significant due to unplanned analyses and early termination.

^bNot statistically significant. Prespecified boundary is P ≤ 0.0246.
Results from these 2 randomized phase III studies led to the approval of everolimus and sunitinib for the treatment of pancreatic NET and changed the treatment paradigm. However, it should be noted that the combination of daily everolimus and sunitinib is poorly tolerated and should not be combined in routine clinical use (33).

Systemic therapy for carcinoid

Cytotoxic chemotherapy has minimal benefit for advanced carcinoids. With no new agent approved over the past 3 decades, treatment options for these indolent tumors are very limited. The PROMID study (Fig. 1; Table 1) showed that long-acting repeatable octreotide significantly improved time to progression in treatment-naïve patients with midgut carcinoids (HR = 0.34; 95% CI, 0.2–0.59; ref. 34). However, the utility of somatostatin analogues such as octreotide for control of tumor growth in NETs of other primary sites remains undefined.

Antitumor efficacy and survival outcome with IFN in carcinoids are limited and controversial. On the basis of its antitumor activity observed in preliminary studies, IFN currently used either alone or in combination with somatostatin analogues for patients with symptomatic carcinoids (35).

Liver-directed therapy approaches

Taking advantage of the liver’s regenerative capacity and its dual blood supply from both the hepatic artery and portal vein, liver-directed therapies have long been used in the management of NETs. These approaches associated with moderately higher complication rates are best employed for symptomatic NET patients with indolent disease course. Partial hepatectomy can be considered for patients when more than 90% of the tumor can be removed safely (36). Hepatic arterial embolization and chemoembolization can be considered as palliative measures in place of surgery (37). Newer radio-embolization techniques may have reduced acute toxicity but have not been prospectively compared with other established liver-directed modalities.

On the Horizon

Improved diagnostics

With increasing recognition of the differences in biology and clinical behavior among pancreatic, thoracic, and gastrointestinal NETs, advanced imaging and molecular diagnostics will play progressively important roles in the classification and optimal management of NETs.

Much of the proof of concept for novel molecular diagnostics has already been done. For example, studies using comparative genomic hybridization and single-nucleotide polymorphism have shown distinct patterns of allelic alternation for pancreatic and ileal NETs (38, 39). These patterns of tissue-specific transcription factors, such as TTF1 and CDX2, could be leveraged to identify occult primary tumors.

Advances in cross-sectional and nuclear imaging are allowing us to peer into the human body with unprecedented spatial resolution and characterize abnormalities with increasing precision. Advanced techniques in CT using negative bowel contrast are permitting us to detect small primary tumors of the luminal gut that previously have been inaccessible to endoscopy examination. Novel PET agents, such as $[^{11}C]$/5-HTP, $[^{18}F]$/FDOPA, $[^{68}Ga]$/DOTA-TOC, and $[^{68}Ga]$/DOTA-NOC, are offering significantly improved spatial resolution for functional imaging (40, 41).

Novel systemic therapy approaches

Major advances in the systemic therapy of NETs have been seen in the past several years. The recent completion of 3 randomized phase III studies has shown that rigorous evaluation of novel agents in this disease is feasible and can lead to practice-changing outcomes.

Therapy targeting phosphoinositide 3-kinase/Akt/mTOR pathway in pancreatic NET

The substantial efficacy of everolimus and the link of multiple germline and somatic mutations in the phosphoinositide 3-kinase (PI3K)/Akt/mTOR pathway genes to pancreatic NETs show the importance of this pathway in tumorigenesis (Fig. 1; refs. 24, 26). Nonetheless, therapeutic resistance frequently emerges over time. A number of strategies having potential to overcome such resistance are under development. Inhibition of TORC1 by everolimus may lead to upregulation of Akt through an insulin-like growth factor (IGF)/PI3K–dependent pathway. Strategies to downregulate IGF with somatostatin analogues such as octreotide and pasireotide, or inhibit IGF1 signaling with a monoclonal antibody, such as cixutumumab, are being developed in combination therapy with everolimus. The PI3K/Akt/mTOR pathway can also be blocked at multiple points by using serine–threonine kinase inhibitors that simultaneously inhibit PI3K and mTOR, such as BEZ235 or agents that inhibit both TORC1 and TORC2, such as INC128.

Therapy targeting angiogenesis in pancreatic NET

Pancreatic NETs are also among the few malignancies in which the VEGF inhibitor sunitinib has shown benefit in a pivotal trial (29). Nonetheless, much of the initial promise of antiangiogenic therapy remains unfulfilled. Resistance to antiangiogenic therapy eventually develops. Preclinical studies suggest resistance mechanisms may involve upregulation of transcription factors that control the expression of multiple proangiogenic molecules (42–44). Further development strategies are taking advantage of a single agent or a combination of agents that target multiple proangiogenic pathways. Strategies targeting VEGF, along with fibroblast growth factor or MET, are already in development for other malignancies. Alternatively, targeting VEGF along with transcription factors, such as hypoxia-inducible factor or Sp1, can be another strategy against eventual therapeutic resistance.

Cytotoxic chemotherapy in pancreatic NET

In contrast with carcinoid tumors, recent prospective and retrospective studies have suggested that oral cytotoxic
allylating agent temozolomide is active in pancreatic NETs (45–47). In one retrospective series, for example, temozolo-
mide-based therapy was associated with an overall response rate of 34% in patients with pancreatic NETs (45). In smaller case series, higher response rates have been reported for the combination of capecitabine and temozolo-
mide (48). However, an adequate prospective controlled study to define the role of temozolomide or temozolomide-
based combination in pancreatic NET is lacking, and promising activity of this cytotoxic agent awaits confirmation.

Therapy targeting angiogenesis in carcinoïd

Several single-arm phase II studies have shown activity for angiogenesis inhibitors in advanced carcinoïds. Although most studies using VEGF tyrosine kinase inhibitors have reported a lower response rate in carcinoïds compared with pancreatic NETs, potential for delay of tumor growth remains (Fig. 1; refs. 30–32). In a small randomized run-
in study, patients with advanced carcinoïd tumors were randomly assigned to treatment with bevacizumab or pegyl-
ated IFN-α-2b (49). Clinical activity of bevacizumab was evidenced by a response rate of 18% and an improved PFS rate at week 18 (95% vs. 68%). These encouraging results led to the development of a pivotal phase III study led by the Southwest Oncology Group (Table 1), in which patients are randomized to receive either interferon-α-2b or bevacizu-
mb in addition to octreotide. Results of this study will likely define the role of VEGF inhibitors in carcinoïds.

Therapy targeting mTOR pathway in carcinoïd

Parallel to its development in pancreatic NETs, everoli-
mus was also evaluated in a phase III study among patients with progressive, well-differentiated NETs and carcinoïd syndrome (Table 1). Patients received long-acting repeat-
able octreotide plus everolimus or placebo (50). The study showed a clinically important 5.1 months (from 11.3 to 16.4 months) improvement in PFS (HR = 0.77; 95% CI, 0.59–1.00; ref. 50). The observed P-value of 0.026, however, missed the prespecified boundary of 0.0246. The efficacy of everolimus in NETs of nonpancreatic origin will need to be confirmed in a future study.

Future development of immunotherapy in carcinoïd

Immunotherapy is another promising area for advance. Past studies have shown relevant clinical activity for IFN and s.c. interleukin-2 (51, 52). The expression of multiple cancer-testis antigens provides additional rationale. Although there has been little systematic and rigorous development of immunotherapy in NETs, the recent advances in targeting of cytotoxic T-lymphocyte antigen 4 and PD-1 provide opportunities for future advances.

Personalizing therapy in NETs

NETs are heterogeneous in their biologic behavior and aggressiveness. This characteristic, along with the recent emergence of multiple active therapies, has led to consider-

able interest in predictive and prognostic biomarkers that may allow us to tailor therapy. In addition to the known prognostic value of tumor grade, recent studies have also confirmed the prognostic value of plasma levels of CGA and neuron-specific enolase (NSE). In a multi-
national study with central radiology review, patients with baseline elevated CGA or NSE had significantly shorter PFS and overall survival (53). Further, early CGA or NSE response was linked to favorable therapeutic benefit (21, 53). If these findings are validated in subsequent studies, biomarkers could be used to select patients for therapy versus active surveillance among newly diag-
nosed patients with significant tumor burden and to guide frequency of monitoring among patients on active therapy.

Emerging data also suggest that high methylguanin-DNA methyltransferase (MGMT) expression is associated with therapeutic resistance to temozolomide (45, 54). If confirmed in future prospective studies, low MGMT expression could help select patients for treatment.

Predictive biomarkers of therapeutic benefits for mTOR and VEGF inhibitors remain elusive. Multiple somatic mutations in the mTOR pathway, however, have been identified (24). Expression levels of PTEN and TSC2 have also recently been linked to outcome (25). Taken together, these findings suggest that future studies evaluating the function of the mTOR pathway may reveal predictive markers of benefit. For VEGF inhibitors, recent studies suggest that functional imaging holds promise for identifying patients likely to respond to treatment (55). Confirmation of these findings in a prospective study will open the way for a personalized approach to treatment.

Disclosure of Potential Conflicts of Interest

J.C. Yao, commercial research grant, Novartis; consultant, Novartis, Pfizer, Ipsen. No potential conflicts of interest were disclosed by the other authors.

Received November 15, 2011; revised January 6, 2012; accepted January 16, 2012; published OnlineFirst February 15, 2012.

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