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

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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 demonstrated that octreotide LAR 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 PI3K/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.
Background

Neuroendocrine tumors (NETs) are generally classified into low-to-intermediate grade versus high-grade tumors based on 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 leads to clinical symptoms such as flush 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) (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 (MEN1), von Hippel Lindau syndrome (vHL), neurofibromatosis (NF), and tuberous sclerosis (TSC) (6). Most NETs, however, are sporadic.
Pathology and staging

Apart from the TNM staging system endorsed by 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 with a uniform appearance. They produce secretory granules and often express chromogranin A (CGA) and synaptophysin. On the other hand, high-grade NETs are aggressive tumors. Cells are poorly 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. As management of high grade NETs fundamentally differs from that of low and intermediate grade NETs, uniformed reporting of grade is encouraged.

Radiological imaging

Imaging modalities frequently used for NETs include computed tomography (CT), magnetic resonance imaging (MRI), and \[^{111}\text{In-DTPA}^0\text{]octreotide scintigraphy}\ (10). Due to the vascular nature of NETs, tumors generally enhance intensely with intravenous 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 radiolabeled somatostatin analog, octreotide, can detect NETs that
express somatostatin receptor types 2 and 5, with an overall sensitivity of 80% to 90% (12, 13). While scintigraphy provides useful information about the site of disease, it does not give accurate information about the size of tumor. Fluorodeoxyglucose position emission tomography (FDG-PET) has been used in evaluating NETs. While its applicability for low grade NETs is limited because of their low metabolic activity, the usage of FDG-PETs in intermediate and high grade NETs are still being evaluated.

**Management of hormonal syndrome**

NETs are characterized by their ability to produce bioactive peptides and neuroamine, such as serotonin, histamine, prostaglandins, substance P, insulin, gastrin, glucagon, and vasoactive intestinal polypeptide (14, 15). Most patients with early -stages NETs are asymptomatic, some may present with nonspecific abdominal symptoms due to local effect of serotonin or mechanical effect of the primary tumor. Patients with advanced stages NETs can manifest with symptoms of carcinoid syndrome, 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 analogs, such as octreotide and lanreotide, block sst2 and sst5, effectively reduce the release of bioactive peptides and neuroamines (Figure 1). These agents are used for the management of carcinoid syndrome or symptoms of hormonal overproduction from NETs. Octreotide comes in two forms, the long-acting release (LAR) 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.

Interferon-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). It has delayed onset of response and more side effects compared to octreotide, so it is not usually the front-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 NETs, surgical resection of the primary tumor offers cure of localized disease; while complete metastectomy has been associated with longer survival among patients with advanced disease and should be considered where 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 Food and Drug Administration for the treatment of pancreatic NET nearly three decades ago. Analyses of 2 large case-series using Response Evaluation Criteria of Solid Tumors (RECIST) criteria have reported objective tumor response rates of 38 and 39% (21, 22).

Genetic cancer syndromes (TSC-2, NF-1, and vHL), somatic mutations identified using an exome sequencing approach, and expression profiling have consistently implicated a
dysfunction of the mammalian target of rapamycin (mTOR) pathway as a critical event in pancreatic NETs (Figure 1) (23-25). Everolimus, an oral inhibitor of mTOR, was studied in a multi-national double blind placebo controlled phase III study (Table 1) (26). The study demonstrated that everolimus significantly prolonged median progression free survival (PFS) from 4.6 to 11 months compared to placebo (Hazard Ratio [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).

NETs are vascular tumors. Hence, there is also strong rationale to study anti-angiogenic agents in NETs (Figure 1). Sunitinib, an inhibitor of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptors, was also studied in a double-blinded placebo-controlled phase III study (Table 1) (29). Treatment with sunitinib 37.5 mg daily was associated with an improvement in median PFS from 5.5 to 11.4 months (HR = 0.42, 95% CI, 0.26 - 0.66) (29). Although the study failed to achieve statistical significance due to unplanned interim analyses and early termination, its results are supported by other studies of VEGF inhibitors in pancreatic NET (30-32).

Results from these two randomized phase III studies lead to the approval of everolimus and sunitinib for the treatment of pancreatic NET and changed the treatment paradigm. However, it should be noted 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 (Figure 1, Table 1) showed that long-acting octreotide significantly improved time to progression in treatment-naïve patients with midgut carcinoids (HR = 0.34, 95% CI, 0.2 - 0.59) (34). However, the utility of somatostatin analogs such as octreotide for control of tumor growth in NETs of other primary sites remains undefined.

Anti-tumor efficacy and survival outcome with interferon in carcinoids are limited and controversial. Based on its anti-tumor activity observed in preliminary studies, interferon is currently used either alone or in combination with somatostatin analogs 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 complications rates are best employed for symptomatic NET patients with indolent disease course. Partial hepatectomy can be considered for patients when more than 90% of 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 between 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 as well as differences in expression of site dependent transcription factors, such as TTF1, 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 computed tomography using negative bowel contrast are allowing us to detect small primary tumors of the luminal gut that previously have been inaccessible to endoscopy examination. Novel positron emission tomography agents such as $[^{11}C]-5\text{-HTP}$, $^{18}F\text{-FDOPA}$, $^{68}\text{Ga-DOTA-TOC}$, and $^{68}\text{Ga-DOTA-NOC}$ 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 three randomized phase III studies has demonstrated that
rigorous evaluation of novel agents in this disease is both feasible and can lead to practice-changing outcomes.

**Therapy targeting PI3K-Akt-mTOR pathway in pancreatic NET**

The substantial efficacy of everolimus and the link of multiple germline and somatic mutations in the PI3K-Akt-mTOR pathway genes to pancreatic NETs demonstrate the importance of this pathway in tumorigenesis (Figure 1) (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 up-regulation of Akt through an IGF-PI3K dependent pathway. Strategies to down-regulate IGF with somatostatin analogs such as octreotide and pasireotide or inhibit IGF1 signaling with monoclonal antibody such 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 is also among the few malignancies where a VEGF inhibitor, sunitinib, has demonstrated benefit in a pivotal trial (29). Nonetheless, much of the initial promise of anti-angiogenic therapy remains unfulfilled. Resistance to anti-angiogenic therapy eventually develops. Pre-clinical studies suggest resistance mechanisms may involve up-regulation of transcription factors that control the expression of multiple pro-angiogenic molecules (42-44). Further development strategies are taking advantage of agent or
combination of agents that target multiple pro-angiogenic pathways. Strategies targeting VEGF along with FGF or MET are already in development for other malignancies. Alternatively, targeting VEGF along with transcription factors such as HIF or Sp1 can be another strategy against eventual therapeutic resistance.

**Cytotoxic chemotherapy in pancreatic NET**

In contrast to carcinoid tumors, recent prospective and retrospective studies have suggested that oral cytotoxic alkylating agent temozolomide is active in pancreatic NETs (45-47). In one retrospective series, for example, temozolomide-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 temozolomide.(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 carcinoid**

Several single arm phase II studies have demonstrated activity for angiogenesis inhibitors in advanced carcinoids. While most studies using VEGF TKI have reported a lower response rate in carcinoids compared pancreatic NETs, potential for delay of tumor growth remains (Figure 1) (30-32). In a small-randomized run-in study, patients with advanced carcinoid tumors were randomly assigned to treatment with bevacizumab or pegylated interferon-alpha 2b (49). Clinical activity of bevacizumab was evidenced by a response rate of 18% and an improved PFS rate at week 18 (95% versus 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 bevacizumab in addition to octreotide. Results of this study will likely define the role of VEGF inhibitors in carcinoids.

**Therapy targeting mTOR pathway in Carcinoid**

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

**Future development of immunotherapy in carcinoid**

Immunotherapy is another promising area for advance. Past studies have demonstrated relevant clinical activity for interferon and subcutaneous 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 CTLA-4 and PD-1 provide opportunities for future advances.

**Personalizing therapy in NETs**

NETs are heterogeneous in their biologic behavior and aggressiveness. This along with the recent emergence of multiple active therapies has led to considerable 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 OS. Further, early CGA or NSE response was linked favorable therapeutic benefit (21, 53). If these findings are validated in subsequent studies, biomarkers can be used select patients for therapy versus active surveillance among newly diagnosed patients with significant tumor burden, and guide frequency of monitoring among patients on active therapy.

Emerging data also suggests that high methylguanine-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 linked to outcome (25). Taken together, these suggest 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.
Table 1. Recent and ongoing phase III studies in advanced NETs

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>Median PFS/TTP (months)</th>
<th>P</th>
<th>Status and reference</th>
</tr>
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<tr>
<td><strong>Pancreatic NETs</strong></td>
<td></td>
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<tr>
<td>Sunitinib</td>
<td>171</td>
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<td>.0001*</td>
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<tr>
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<tr>
<td>Everolimus</td>
<td>410</td>
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<td>&lt; .0001</td>
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<tr>
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<td>4.6</td>
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<tr>
<td><strong>Carcinoid tumors</strong></td>
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<tr>
<td>Octreotide LAR</td>
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<td></td>
<td>6.0</td>
<td></td>
<td>Rinke et al, 2009</td>
</tr>
<tr>
<td>Everolimus+octreotide LAR</td>
<td>429</td>
<td>16.4</td>
<td>.026**</td>
<td>Study completed</td>
</tr>
<tr>
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<td></td>
<td>11.3</td>
<td></td>
<td>Pavel et al, 2011</td>
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<tr>
<td>Lanreotide</td>
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<tr>
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<td>Recruiting</td>
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<tr>
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<td><strong>Carcinoid Syndrome</strong></td>
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<tr>
<td>Placebo</td>
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</table>

* Not statistically significant due to unplanned analyses and early termination
** Not statistically significant. Pre-specified boundary is P ≤ .0246.
**Figure 1.** Targeting critical signaling pathways in neuroendocrine tumors. Recent data from pivotal phase III studies have demonstrated the importance of somatostatin, mTOR, and angiogenic pathways in neuroendocrine tumors.
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