

# Metastatic Pancreatic Poorly Differentiated Neuroendocrine Carcinoma: Current Treatment Considerations

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## Background

Pancreatic poorly differentiated neuroendocrine tumors (PDNETs) are a subtype of neuroendocrine tumors (NETs) that are clinically distinguished by their very rapid growth. They are immunohistochemically diagnosed by having a higher Ki-67 cancer cell staining percentage when compared with well or intermediately differentiated NETs. These tumors are typically treated in the same manner as small cell lung cancer. Recent advances in the treatment of well or intermediately differentiated NETs have raised the question of whether such therapies may also have efficacy in PDNETs.

## Case Report

A 53-year-old patient presented in October 2012 with abdominal pain. A computed tomography (CT) scan of the chest, abdomen, and pelvis revealed a pancreatic head mass (4.9 cm × 3.1 cm) and numerous liver metastases, the largest of which was 13.6 cm × 4.9 cm. There were no chest abnormalities and the patient had no history of cigarette smoking. A liver biopsy revealed a PDNET, with a Ki-67 immunohistochemical staining of 39% and a high mitotic rate (>20/10 high-power field [HPF]). Per the World Health Organization (WHO) criteria, the tumor was classified as grade 3 neuroendocrine carcinoma. The patient received chemotherapy with carboplatin on day 1 (area under the curve [AUC], 5) and etoposide 120 mg/m<sup>2</sup> on days 1 to 3, every 3 weeks for a total of 6 cycles. During that time, a repeat CT scan showed improvement in the tumor burden. The largest liver mass decreased in

size to 12.3 cm × 9.1 cm; other masses decreased in size as well. However, shortly after completion of the last 2 cycles, a CT scan on February 27, 2013 showed that the pancreatic mass and liver masses were stable.

On March 12, 2013, a somatostatin-receptor scintigraphy study (octreotide scan) showed abnormal indium 111-pentetreotide activity in the liver lesions and pancreatic mass, consistent with a neuroendocrine carcinoma. The patient received 1 dose of octreotide acetate 20 mg and developed severe nausea and vomiting within a few days, which led to hospitalization. After recovering, the patient underwent chemoembolization of the liver with 100 mg doxorubicin-lipiodol on April 5, 2013 and again on May 7, 2013. A repeat CT on June 5, 2013 showed a “mild” interval decrease in the size of the liver masses, whereas the pancreatic mass had increased in size. Various options were discussed with the patient, including further chemoembolizations, systemic chemotherapy (eg, topotecan), resuming octreotide therapy, everolimus (Afinitor, Novartis), sunitinib (Sutent, Pfizer), or observation.

## Discussion

Pancreatic PDNETs are characterized clinically by rapid growth, initial responsiveness to platinum-based therapy, and a very poor prognosis. The National Cancer Comprehensive Network (NCCN) guidelines for well and intermediately differentiated NETs suggest treating these patients the same way in which small cell lung cancer patients are treated, as was done with our patient.<sup>1</sup> The guidelines suggest that octreotide acetate be considered as well, although no references are found in the literature to support a benefit of octreotide acetate in treating PDNETs. In searching the literature, 1 study reported a lack of inhibition of small cell lung cancer cell lines using octreotide.<sup>2</sup>

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Well and intermediately differentiated NETs are treated differently than PDNETs. These tumors are typically far more indolent. Octreotide acetate is a standard therapy, based largely on a significant prolongation in progression-free survival (PFS) of roughly 8 months when compared with a placebo.<sup>3</sup> With progression of well or intermediately differentiated NETs, everolimus and sunitinib have shown a significant PFS benefit compared with placebo. These agents have been approved by the US Food and Drug Administration for use with progression of pancreatic NETs of any grade, although the pivotal trials included only patients with metastatic, well or intermediately differentiated NETs.<sup>4,5</sup>

Per the WHO criteria, intermediate NETs are defined immunohistochemically as having Ki-67 cancer cell staining of 2% to 20%, whereas PDNETs have Ki-67 staining of more than 20%.<sup>6</sup> Greco and Hainsworth reported a series of patients with PDNETs of unknown primary site and concluded that the management of these patients should parallel treatments used for small cell lung cancer.<sup>7</sup> A recent report suggests that, like other NETs, PDNETs similarly overexpress mTOR, underscoring the possibility that patients with PDNETs should be included in trials involving targeted agent therapies for other NETs.<sup>8</sup> Per-

haps these therapies will play a role in treating PDNETs and other pancreatic NETs in the future.

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# Commentary

## Evolving Understanding and Management of Poorly Differentiated Neuroendocrine Tumors

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**Editor's Note: A correction was made to this commentary on March 7, 2014.**

Poorly differentiated neuroendocrine tumors (PDNETs) are known to arise from a wide variety of sites. These sites include the lung, pancreas, gastrointestinal tract, urinary bladder, prostate, cervix, uterus, and parotid gland, although primary sites other than the lung are rare.

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PDNETs are often grouped together as “extrapulmonary small cell carcinomas” because in addition to their histologic similarity, this group of tumors shares biologic and clinical characteristics. All are rapidly growing neoplasms with the potential for early metastasis; the majority have distant metastases at the time of diagnosis. Secretion of bioactive peptides, frequent in various low-grade neuroendocrine carcinomas (eg, carcinoids, islet cell tumors), is uncommonly associated with PDNETs, and somatostatin receptor scintigraphy (octreotide scan) is usually negative.

PDNETs are also distinct from low-grade neuroendocrine tumors in their initial sensitivity to traditional cytotoxic chemotherapy. The high response rate to platinum-based therapy was first described in anaplastic carcinoid tumors arising in the gastrointestinal tract. In contrast, platinum-based regimens were inactive against typical carcinoids and pancreatic neuroendocrine tumors.<sup>1</sup> Subsequently, responses to platinum-based therapy have been reported in PDNETs arising in a variety of sites, and in PDNETs of unknown primary site.<sup>2-4</sup>

Neuroendocrine tumors have traditionally been assumed to have a common origin, with a spectrum of biology ranging from carcinoid-type tumors (indolent) to PDNETs (aggressive). However, the molecular biology of neuroendocrine tumors is just beginning to be elucidated, and evidence currently suggests that

PDNETs represent a completely different tumor type. Small cell lung cancer, the best studied high-grade neuroendocrine tumor, is characterized by multiple molecular abnormalities; deletions of chromosome 3p are the most common, but deletions of several other chromosomes (eg, 5q, 10q, and 17p) are also frequently seen.<sup>5,6</sup> A similar spectrum of chromosomal abnormalities has been described in PDNETs arising from other sites,<sup>6</sup> suggesting similarities in molecular biology among these tumors in addition to their clinical similarities. In contrast, well differentiated carcinoids share none of the molecular abnormalities that are common in PDNETs, suggesting a different carcinogenesis.<sup>7</sup>

The patient described by Sorscher<sup>8</sup> had a PDNET arising in the pancreas; he had a typical clinical course, as evidenced by the presence of advanced metastatic disease at diagnosis, initial sensitivity to platinum-based chemotherapy, and subsequent progression of treatment-resistant disease. As pointed out by Sorscher, newer targeted therapies, including agents with activity against low-grade neuroendocrine tumors, have had limited evaluation in PDNETs. Octreotide, a standard part of therapy for low-grade neuroendocrine tumors, has not been systematically studied in PDNETs, although a recent case report described a patient with a pancreatic PDNET and a positive octreotide scan who had benefit with single-agent octreotide.<sup>9</sup> Concurrent use of octreotide with chemotherapy is listed as a treatment option in the National Comprehensive Cancer Network guidelines for such tumors, with only anecdotal supporting evidence. However, since the large majority of PDNETs have negative octreotide scans, this treatment has limited applicability.

Clinical evaluation of other targeted agents has been limited to small cell lung cancer, owing to the rarity of other PDNETs. In small cell lung cancer (as in other PDNETs), multiple pathways that are potential targets of currently available therapeutic agents are overexpressed, including the PI3K/mTOR pathway. However, current evidence indicates that most of these abnormalities are “bystander” abnormalities, rather than key drivers of the malignant process. In a single phase 2 trial, everolimus (Afinitor, Novartis)—an mTOR inhibitor with activity

against low grade neuroendocrine tumors—had limited activity against small cell lung cancer.<sup>10</sup> Inhibition of the c-Kit pathway, which is frequently overexpressed in small cell lung cancer, has also been ineffective.<sup>11</sup> Given the marked differences in molecular biology between PDNETs and low-grade neuroendocrine tumors, the failure to identify therapies effective in both types is not surprising.

No substantial improvements in the therapy of small cell lung cancer or other PDNETs have occurred in over 20 years. To improve the therapy of these neoplasms, critical “driver” molecular abnormalities must be identified and exploited. A number of candidates are currently in early clinical testing. Owing to the similar spectrum of molecular abnormalities, it is likely that new targeted drugs that are highly effective against small cell lung cancer will also have activity in the treatment of other PDNETs.

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