Systemic Therapies for Advanced Pancreatic Neuroendocrine Tumors

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KEYWORDS

• Neuroendocrine tumors • Pancreatic neuroendocrine tumors • Carcinoid tumors
• Octreotide • Lanreotide • Sunitinib • Everolimus

KEY POINTS

- Pancreatic neuroendocrine tumors (NETs) are genetically and clinically different than extrapancreatic NETs (ie, carcinoid tumors) and often respond to cytotoxic and targeted treatments.
- Asymptomatic patients with low-volume advanced pancreatic NETs often have indolent disease, and some can be followed expectantly. Careful evaluation of each individual patient with an initial interval of observation and assessment can help define who needs treatment sooner.
- Somatostatin analogues (octreotide and lanreotide) can decrease hormone production in functional tumors and can control neuroendocrine tumor growth; given their favorable toxicity profile, they are generally used as first-line treatment in unresectable patients.
- Sunitinib and everolimus are 2 targeted therapies approved for progressive pancreatic NETs and are generally reserved for use in tumors that have progressed on somatostatin analogue therapy.
- Pancreatic NETs can respond to cytotoxic chemotherapy; the most commonly used agents include alkylating, fluorouracil, and platinum drugs.

INTRODUCTION

Well-differentiated neuroendocrine tumors (NETs) are an uncommon and heterogeneous group of neoplasms that arise throughout the body, most commonly in the lung and gastrointestinal tract.[1] These tumors are subdivided into carcinoid tumors and pancreatic NETs (panNETs). Carcinoid tumors develop from the neuroendocrine

Disclosure Statement: Dr D. Reidy-Lagunes is on the advisory board for Novartis, Pfizer, and Ipsen. In addition, Dr D. Reidy-Lagunes does both research and consulting for Novartis. Dr N. Raj has nothing to disclose.
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Hematol Oncol Clin N Am 30 (2016) 119–133
http://dx.doi.org/10.1016/j.hoc.2015.09.005 **hemonc.theclinics.com**
0889-8588/16/$ – see front matter

tissues of the aerodigestive tract, and panNETs develop from the endocrine tissues of the pancreas (ie, islets of Langerhans). This group of well-differentiated NETs is both morphologically and clinically distinct from high-grade neuroendocrine carcinomas, tumors that are characterized by an extremely aggressive behavior and are treated along small cell lung cancer paradigms with platinum-based chemotherapy.[2] Epidemiologic data from the last 30 years have demonstrated that the incidence of NETs continues to increase, although there have been no significant changes in survival from this disease.[3,4]

panNETs are the second most common tumor of the pancreas and represent 1% to 2% of all pancreatic neoplasms.[5,6] Although most panNETs are slow growing, after the development of metastatic disease (most commonly in the liver), median survival ranges from 2 to 5 years; most patients with liver metastases will die of the disease.[7] About one-third of panNETs are functional tumors and produce clinical syndromes due to excessive hormone secretion; these functional panNETs are classified by the hormones they hypersecrete and include insulinoma (secrete insulin and cause hypoglycemia), gastrinoma (secrete gastrin and cause Zollinger-Ellison syndrome, which is characterized by severe peptic ulcer disease), glucagonoma (secrete glucagon and cause hyperglycemia), and vasoactive intestinal polypeptide (VIP) (VIPoma, secrete VIP and cause severe secretory diarrhea).[6,8–10] Nonfunctional panNETs are tumors that do not secrete hormones or the products they secrete do not cause a clinical syndrome, such as pancreatic polypeptide, chromogranin A, ghrelin, neurotensin, subunits of chorionic gonadotropin, and neuron-specific enolase.[10] Metastatic disease is a common presentation for most patients with panNETs, especially those with nonfunctioning tumors given the absence of clinical symptoms that would warrant earlier clinical evaluation.[7]

Asymptomatic patients diagnosed with advanced, metastatic panNETs are often monitored initially; however, with time, often their disease will progress and require treatment. The typical indications for therapy are pain and symptoms due to tumor bulk, symptoms from hormone secretion for functional tumors, high tumor burden, or progression of disease under observation.[8] Given the heterogeneous clinical presentations and complex spectrum of aggressiveness of panNETs, their treatment is challenging and requires multimodality management with surgeons, interventional radiologists, medical oncologists, endocrinologists, and gastroenterologists. This article focuses on the data and rationale supporting the use of systemic treatments for advanced, metastatic, well-differentiated panNETs.

PATHOLOGY

Since 2010, the classification of panNETs has been based on the revised criteria from the World Health Organization, which is defined by the cytologic grade and the proliferative index (as assessed by the Ki-67 and/or mitotic count).[11] In these revised criteria, tumors are broken down by differentiation status (well and poorly differentiated) and grade (grade 1, low; grade 2, intermediate; and grade 3, high). Although the family of well-differentiated tumors are classically of the grade 1 or grade 2 type and generally have a more indolent, less aggressive course, grade 3 or high-grade neuroendocrine carcinomas are typically poorly differentiated and classified as large or small cell carcinomas; these grade 3 neuroendocrine carcinomas are highly aggressive, akin to small cell lung cancers, and are associated with a poor prognosis.

To support this belief, many studies have looked at the relationship between tumor grade and survival; not surprisingly, tumor grade seems to be correlated with survival; in one retrospective analysis of 425 patients with panNETs, the 5-year survival rates