Systemic Therapies for Advanced Gastrointestinal Carcinoid Tumors

Claire K. Mulvey, MD[a], Emily K. Bergsland, MD[b,*]

KEYWORDS

- Gastrointestinal neuroendocrine tumors • Somatostatin analogues
- Carcinoid syndrome • Carcinoid tumor
- Mammalian target of rapamycin (mTOR) pathway

KEY POINTS

- Low- and intermediate-grade neuroendocrine tumors are an indolent group of malignancies that can cause symptoms from hormone hypersecretion and/or tumor mass.
- Somatostatin analogues are the mainstay of therapy for the control of symptoms associated with carcinoid syndrome.
- Systemic treatment of advanced disease remains a challenge; only somatostatin analogues have proven antitumor activity in advanced gastrointestinal neuroendocrine tumors.
- Gastrointestinal neuroendocrine tumors represent an active area of research. Clinical trials with peptide receptor radionuclide therapy, inhibitors of the mammalian target of rapamycin and vascular endothelial growth factor signaling pathways, immunotherapy, and other therapeutic approaches are ongoing.
- Improved understanding of the underlying molecular biology may lead to additional treatment advances.

INTRODUCTION

Neuroendocrine tumors (NETs) are a relatively rare, heterogeneous group of neoplasms arising nearly anywhere in the body with an annual incidence of 5 cases per 100,000 people in the United States.[1] The updated World Health Organization

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[a] Department of Medicine, University of California, San Francisco, 505 Parnassus Avenue, Box 0119, San Francisco, CA 94143, USA; [b] Division of Hematology/Oncology, Department of Medicine, University of California, San Francisco, 1600 Divisadero Street, A727, San Francisco, CA 94115, USA
* Corresponding author.
E-mail address: emily.bergsland@ucsf.edu

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classification system of gastroenteropancreatic NETs emphasizes the tumor site of origin, clinical syndrome, and degree of differentiation when categorizing these malignancies. Well-differentiated NETs (formerly known as carcinoid tumors) arising from the tubular gastrointestinal tract tend to be indolent and slow growing, in contrast to poorly differentiated neuroendocrine carcinomas (NECs), which are more aggressive and associated with a poor prognosis. The treatment of well-differentiated NETs depends on the presence of symptoms and the tumor site of origin. Pancreatic NETs are distinguished from nonpancreatic gastrointestinal NETs (GINETs) given evidence suggesting a differential response to therapy and differences in the molecular underpinnings of each disease.

Somatostatin analogues (SSAs) continue to play a key role in controlling hormone-mediated symptoms. In addition, clinical trials completed in the last decade have definitively demonstrated the antitumor properties of these agents in patients with advanced disease. Based on an improved understanding of the mechanisms underlying NET tumor progression, several novel therapeutic targets have been identified, including the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) signaling pathways. Therapeutic clinical trials of novel agents are ongoing, but none has been definitively validated in GINETs. As a result, the systemic treatment of unresectable disease remains a challenge, and there is a significant unmet medical need for additional systemic treatments.

SYSTEMIC THERAPY FOR THE CONTROL OF SYMPTOMS FROM HORMONE HYPERSECRETION

Somatostatin Analogues

GINETs can be classified as functional or nonfunctional. Nonfunctional tumors do not secrete hormones and present with symptoms from tumor mass and growth, such as obstruction, abdominal pain, and bleeding. Functional tumors can secrete several biologically active hormones and peptides, including serotonin, histamine, amines, and prostaglandins. Carcinoid syndrome is an uncommon, but potentially dramatic manifestation of functional GINETs, affecting approximately 20% of patients with advanced well-differentiated tumors of the jejunum or ileum.[2] The symptoms are intermittent, attributable to hormonal hypersecretion, and may include flushing, diarrhea, rhinorrhea, wheezing, and ultimately can result in right-sided valvular heart disease. Most GINETs are associated with carcinoid syndrome only after they have metastasized to the liver, as hormones produced by tumor cells (most commonly serotonin) can be released directly into the systemic circulation, thus bypassing hepatic metabolism.[3]

For patients with hormone-mediated symptoms from a GINET, therapy with a somatostatin analogue (SSA) is appropriate. Somatostatin is a small, 14-amino acid peptide that inhibits the secretion and synthesis of many gastrointestinal (GI) hormones. Effects of native somatostatin include inhibition of endocrine and exocrine secretion, gastric and intestinal motility, gallbladder contraction, angiogenesis, and cell proliferation. Somatostatin's effects are mediated through 5 high-affinity G-protein coupled receptors. Most GINETs express a receptor for somatostatin, and somatostatin analogues have been shown to be highly effective at controlling the debilitating symptoms of NETs.[4] The 2 synthetic SSAs that are used clinically, octreotide and lanreotide, have significantly longer half-lives than native somatastatin, which has a half-life of approximately 1 to 2 minutes. These analogues have high affinity for somatostatin receptor 2 and 5, in particular. The antisecretory effect of somatostatin has made SSA essential for managing GINETs.