Role of Somatostatin Analogues in the Treatment of Neuroendocrine Tumors

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KEYWORDS

• Neuroendocrine tumors • Somatostatin analogues • Somatostatin receptors
• Carcinoid syndrome • Peptide receptor radionuclide therapy

KEY POINTS

- Functional neuroendocrine tumors (NETs) cause various clinical symptoms depending on the activity of the hormone secreted.
- Carcinoid syndrome, the classic example of a functional NET, is caused by serotonin overproduction and leads to flushing, diarrhea, edema, telangiectasia, bronchospasm, and hypotension.
- Somatostatin receptors (SSTRs) are expressed in NETs, with SSTR-2 expression being predominant in gastroenteropancreatic NETs.
- Somatostatin analogues (SSAs) control clinical symptoms arising from hormone excess in SSTR-expressing NETs.
- Recently published data from have established the antiproliferative effects of SSAs and their role in control of tumor growth.

INTRODUCTION

Neuroendocrine tumors (NETs) are epithelial neoplasms with neuroendocrine differentiation that arise in various anatomic locations throughout the body. The annual incidence of NETs in the United States is about 3.65 per 100, 000 and recent analyses have indicated a rise in the incidence of carcinoid tumors in the United States and elsewhere,[1–4] owing in part to improvements in diagnostics and increased awareness.[2,5–7]

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The clinical presentation of carcinoid tumors can be variable, depending on their anatomic site of origin. Whereas patients with indolent disease can remain asymptomatic for years, some patients may present with symptoms related to tumor bulk or from secretion of various peptides or amines from these tumors. Such secretory tumors, also called "functional tumors," cause various clinical symptoms depending on the activity of the hormone secreted. The minority of NETs are truly functional; approximately 10% of patients with small bowel NETs and 40% of patients with pancreatic NETs meet this definition. Carcinoid syndrome, caused by serotonin overproduction, is the classic example of a functional NET and is associated with symptoms such as flushing, diarrhea, edema, telangiectasia, bronchospasm, and hypotension. These symptoms occur when the secretory products from the NETs bypass metabolism in the liver and enter the systemic circulation directly. This usually occurs in the presence of liver metastases, bulky retroperitoneal disease, or primary sites of disease outside the gastrointestinal tract.[8,9] Hindgut tumors (ie, transverse, descending, and sigmoid colon; rectum; and genitourinary) are rarely functional and almost never associated with classic carcinoid syndrome. **Table 1** lists examples of various clinical syndromes arising from hormone secretion in gastroenteropancreatic (ETs).[10]

The management of NETs is multidisciplinary. For patients with unresectable and metastatic disease the intent is 2-fold: controlling tumor growth and alleviating symptoms arising from peptide hormone secretion. The treatment options for tumor control include observation (stable disease and mild tumor burden), systemic therapy with somatostatin (SST) analogues (SSAs), molecularly targeted agents and cytotoxic chemotherapies, cytoreductive surgery, and regional therapies (hepatic arterial embolization and ablative procedures). SSAs are the mainstay for control of hormone secretion. Recently, SSAs have also been recognized as antiproliferative agents in well-differentiated metastatic disease. This article reviews the application and role of SSAs in the treatment of well-differentiated NETs.

SOMATOSTATIN AND SOMATOSTATIN RECEPTOR PHYSIOLOGY

SST is a peptide hormone that was initially discovered as an inhibitor of growth hormone release in the hypothalamus of rats.[11] Subsequent studies found that SST was secreted by paracrine cells scattered throughout the gastrointestinal tract,[12] and also found in various locations in the nervous system. The physiologic effects of SST are largely inhibitory, and it has been known to reduce gastrointestinal motility and gallbladder contraction; inhibit secretion of most gastrointestinal hormones, including insulin, glucagon, and gastrin; reduce blood flow in the gastrointestinal tract; and inhibit growth hormone release from the pituitary and neurotransmission in the brain.[11,13]

SST mediates its primarily inhibitory effects by binding to at least 5 high-affinity G-protein-coupled membrane receptors (SSTR1–5).[14,15] The antiproliferative actions of SST result from cell cycle arrest and/or apoptosis downstream from tumor SSTR activation, and SSTR-induced inhibition of tumor angiogenesis and the production of factors that support tumor growth.[16–20] The SSTRs share about 40% to 60% homology, but mediate different biological actions upon activation.[12] All 5 SSTRs have been identified throughout the central nervous system, the gastrointestinal tract, and endocrine and exocrine glands, as well as on inflammatory and immune cells. Tumors arising from SST target tissues, such as the pancreas and small intestine, express a high density of SSTRs.[15,21,22] The expression of SSTR2 has been noted to be predominant in most gastroenteropancreatic NETs.[21] Well-differentiated tumors express SSTRs more often, and at higher density, than do poorly differentiated tumors.[15]

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