Somatostatin Analogues in Neuroendocrine Tumors

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Patients with advanced neuroendocrine tumors may experience symptoms related to tumoral secretion of hormones and vasoactive amines as well as symptoms related to tumor bulk. The carcinoid syndrome, manifested by episodic flushing, diarrhea, and the development of cardiac valvular fibrosis is one of the more common secretory symptoms experienced by these patients and is associated with secretion of serotonin. Somatostatin analogues, which bind to somatostatin receptors expressed on neuroendocrine tumor cells, have been successfully used to decrease hormone secretion and improve associated symptoms. More recent studies have shown that somatostatin analogues can also have an antiproliferative effect and slow tumor growth. Two somatostatin analogues, octreotide and lanreotide, which target primarily somatostatin receptor subtypes 2 and 5, are currently available for use in patients with advanced neuroendocrine tumors. The placement of these 2 analogues within the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Neuroendocrine Tumors has been a key focus of recent panel discussions.¹

Octreotide was the first somatostatin analogue commercially available for patients with advanced neuroendocrine tumors. In an initial single-arm study enrolling 25 patients with carcinoid syndrome, treatment with repeated subcutaneous octreotide injections was associated with a marked decrease in symptoms of flushing and diarrhea and with decreases in urinary levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA).² A long-acting depot formulation of octreotide—octreotide LAR—is administered via an intramuscular injection every 28 days. This treatment was compared with subcutaneous octreotide in a randomized trial enrolling 93 patients.³ This study showed that octreotide LAR has comparable activity to subcutaneous octreotide with regard to symptom control. Based in large part on these studies, both subcutaneous octreotide and octreotide LAR have been recommended in the NCCN Guidelines for control of symptoms of hormone hypersecretion in patients with neuroendocrine tumors.¹

More recent data have supported the inclusion of octreotide in the guidelines as an agent to control neuroendocrine tumor growth. Although several early studies suggested that octreotide may have an antiproliferative effect, a randomized study demonstrating this effect was not published until 2009. This study (the PROMID study) randomized 90 patients with metastatic midgut neuroendocrine tumors to receive either intramuscular octreotide LAR at 30 mg monthly or placebo.⁴ Enrollment was discontinued before planned study completion, due to both slow recruitment and an observed positive effect of octreotide. At data analysis, time to tumor progression was 14.3 months in the treatment arm and only 6 months in the placebo arm (hazard ratio [HR], 0.34; P = .000072). Although octreotide LAR never received FDA approval for this indication, the PROMID data led to the inclusion of octreotide in the NCCN Guidelines in 2010 as a recommended agent for tumor control in carcinoid tumors.

Lanreotide is similar, although not identical, to octreotide in both its molecular structure and its somatostatin receptor–binding profile. A long-acting formulation of lanreotide depot, somatuline depot, is administered every 28 days but differs from octreotide LAR in its mode of administration (it is administered as a deep subcutaneous injection rather than an intramuscular injection) and, to some extent, in its pharmacokinetic profile. Like octreotide LAR, however, treatment with lanreotide LAR has been shown to improve symptoms associated with carcinoid syndrome. A European open-

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label, multicenter study performed with lanreotide and published in 2004 enrolled 71 patients with carcinoid syndrome and showed that treatment with lanreotide was associated with decreases in flushing, diarrhea, and urinary 5-HIAA levels. A more recent randomized study, the ELECT study, in which patients with carcinoid syndrome received treatment with lanreotide or placebo, provided further evidence supporting the use of lanreotide in patients with carcinoid syndrome.

The efficacy of lanreotide in controlling neuroendocrine tumor growth was evaluated in the CLARINET study, a randomized trial in which 204 patients with both pancreatic and nonpancreatic gastrointestinal neuroendocrine tumors were randomized to receive either lanreotide, administered every 28 days, or placebo. This study showed that treatment with lanreotide was associated with a clear improvement in progression-free survival: median progression-free survival was not reached in the treatment group and was 18 months in the placebo group (HR, 0.47; P<.001). Lanreotide was subsequently approved in both Europe and the United States for this indication in late 2014.

The NCCN Neuroendocrine Tumors Panel considered the potential roles of octreotide and lanreotide for controlling symptoms of hormone hypersecretion and for controlling growth in both pancreatic and nonpancreatic neuroendocrine tumors. FDA approvals for these agents are relatively narrowly focused: octreotide is approved for the treatment of carcinoid syndrome, and lanreotide is approved for control of tumor growth in gastroenteropancreatic neuroendocrine tumors.

One option considered by the NCCN panel was a conservative approach, in which guidelines would strictly follow FDA indications, based on data from registration studies. The approach would, however, ignore the substantial body of clinical evidence showing that both drugs control symptoms associated with hormone hypersecretion and that both drugs have the ability to slow tumor growth. The similar clinical profiles of the 2 drugs are consistent with the fact that both drugs share a highly similar mechanism of action. The panel therefore elected to adopt a broader approach, recommending either octreotide or lanreotide as a reasonable option for symptom control and as a reasonable option for control of tumor growth in patients with advanced neuroendocrine tumors.

References