Update on the Management of Neuroendocrine Tumors: Focus on Somatostatin Antitumor Effects

Nancy M. Gardner-Roehnelt, PhD, NP-BC

Although neuroendocrine tumors (NETs) have been recognized as a family of complex malignancies since 1907, major progress has been made only in the past 20 years in understanding and managing the disease. The detection and reported incidence of NETs have increased fivefold since 1973, suggesting that the tumors may be more common than previously believed. NETs arise predominantly in the gastrointestinal tract but can occur in any tissue containing endocrine precursor cells and can secrete hormone peptides that exert clinical symptoms of flushing and diarrhea. With the introduction of the somatostatin analog (SSA) octreotide in 1987, symptom management of NETs improved by diminishing morbidities and mortality associated with carcinoid syndrome. Clinical results suggest that the SSA agents octreotide and lanreotide also may provide antitumor benefits in addition to their suppression of carcinoid syndrome. Oncology nurses should be aware of the expanded role of SSA agents for symptom management and tumor control in patients with NETs and communicate treatment benefits, side-effect management, and effective adherence with patients for the optimal clinical management of NETs.

Major progress has been made toward understanding neuroendocrine tumors (NETs) and improving their clinical management. An analysis from the nationwide Surveillance, Epidemiology and End Results (SEER) program revealed that NETs are more common than generally realized (Yao, Hassan, et al., 2008). The annual reported age-adjusted incidence of NETs increased almost fivefold from 1.09 per 100,000 people in 1973 to 5.25 per 100,000 people in 2007 (p < 0.001) (Yao, Hassan, et al., 2008). The increase may reflect changes in clinical practice, including refinements in disease classifications and broader use of endoscopic screening (Yao, Hassan, et al., 2008). The epidemiologic survey also showed that the prognosis for patients diagnosed with NETs depends on several factors, including tumor location, disease stage, and histology (Yao, Hassan, et al., 2008). As expected, the presence of regional or distant metastases and poorly differentiated disease were associated with poorer prognoses (Modlin, Lye, & Kidd, 2003; Yao, Hassan, et al., 2008). However, many oncology nurses and nurse practitioners may not have first-hand experience managing patients with the disease. The increasing prevalence of patients with NETs translates into the need for oncology nurses to be educated about current and optimal treatment management for this family of malignancies.

About 60% of NETs arise from cells within the intestine (Modlin et al., 2003); however, they can originate wherever endocrine precursor cells are found, including the stomach, colon, rectum, pancreas, thymus, lungs, kidneys, ovaries, prostate, breast, and skin (Arnold, 2005). One important clinical distinction among NETs is whether they are functioning or nonfunctioning with respect to hormone secretion. Functioning NETs typically are located in the pancreas and can secrete an array of hormones associated with clinical symptoms (Arnold, 2005). Carcinoid syndrome usually arises from endocrine cells within the ileum that hypersecrete serotonin, leading to flushing, diarrhea, and bronchial obstruction (Arnold, 2005). About 33%-50% of NETs are nonfunctioning and typically do not secrete symptom-causing hormones (Arnold, 2005). Whether functioning or nonfunctioning, NETs can release peptides or hormones, such as chromogranin A (CgA), that can be detected through diagnostic testing and used as biomarkers to track disease progression in patients (Arnold, 2005).
In addition to the broad array of organs and body systems that are affected by the origin of NETs, healthcare professionals are challenged by a lack of consensus in nomenclature or a universally accepted system for classifying and grading NETs (Arnold, 2005). To minimize the challenge, the World Health Organization (WHO) proposed a general approach to classifying NETs into low-grade, well-differentiated neuroendocrine tumors (NET G1); intermediate-grade, well-differentiated neuroendocrine carcinomas (NET G2); and high-grade, poorly differentiated neuroendocrine carcinoma (NET G3). Each of those classes can be characterized further for specific tumor types (Bosman, Carneiro, Hruban, & Theise, 2010).

Treatment of NETs is intended to achieve the goals of tumor control (eradication or stabilization), to maximize survival, and to relieve the symptoms of functioning tumors (particularly flushing and diarrhea) while improving the patient’s overall functionality and quality of life (Anthony & Freda, 2009). For most forms of NETs, surgery is the cornerstone of first-line treatment and currently is the only curative treatment for localized disease (National Comprehensive Cancer Network [NCCN], 2011; Yao, Hassan, et al., 2008); unfortunately, about 75% of patients present late in the course of disease with inoperable tumors and metastatic disease (Lai & Chen, 2006). Before 1987, the chemotherapeutic agent streptozotocin was the only U.S. Food and Drug Administration (FDA)-approved therapy for treating patients with metastatic NETs, specifically those of pancreatic origin; however, streptozotocin has limited antitumor benefit and has been associated with a high degree of toxicity (Modlin, Kidd, Drozdov, Siddique, & Gustafsson, 2008). In comparison, the introduction of octreotide in 1987, a synthetic somatostatin analog (SSA), has improved the management of tumor-related symptoms and altered the natural history of the disease (Yao, Hassan, et al., 2008). Results of the SEER analysis demonstrated improvement in survival duration among patients with NETs diagnosed after the introduction of octreotide, which could have been the result of controlling carcinoid crisis, a major cause of morbidity and mortality (Yao, Hassan, et al., 2008).

Evidence from laboratory and clinical studies has suggested that octreotide and other SSAs might be useful antitumor agents in addition to ameliorating symptoms in the treatment of NETs. The results of the PROMID study (a prospective, randomized trial of octreotide in midgut carcinoids) and other phase III clinical studies support that hypothesis and may broaden the clinical usefulness of octreotide in patients with NETs (Rinke et al., 2009). The purpose of this article is to update oncology nurses and nurse practitioners on the clinical evidence of the antitumor effects of SSAs in patients with NETs and to review the role of SSAs in symptom management, with particular emphasis on the implications of the PROMID study with regard to optimal patient management.

**Antitumor Potential of Synthetic Somatostatin Analog**

**Pharmacology and Mechanism of Action**

Somatostatins are inhibitory peptide hormones that exert a variety of biologic effects on endocrine organs (Anthony & Freda, 2009; Susini & Buscail, 2006). Somatostatins act by binding to G protein-coupled somatostatin receptors (SSTR) (of which five subtypes exist designated SSTR1 through SSTR5) on cells in the central nervous system, hypothalamus, gastrointestinal tract, and pancreas (Anthony & Freda, 2009; Grozinsky-Glasberg, Shimon, Korbonits, & Grossman, 2008; Lesche, Lehmann, Nagel, Schmid, & Schulz, 2009). Tumors that express a high density of SSTR include pituitary adenomas, pancreatic endocrine tumors, carcinoid tumors, paragangliomas, pheochromocytomas, small cell lung cancer, medullary thyroid carcinoma, breast cancer, and malignant lymphoma (de Herder, Hofland, van der Lely, & Lamberts, 2003). Most of those tumor types express multiple subtypes of SSTR; however, SSTR2 is the predominant subtype expressed in NETs (de Herder et al., 2003). Binding of somatostatin to SSTR influences various physiologic pathways by inhibiting secretion of growth hormone or other bioactive peptides and amines secreted by NETs, or by regulating cell proliferation (Anthony & Freda, 2009; Cozzi & Attanasio, 2007; de Herder et al., 2003; Reisine & Bell, 1995); however, the clinical usefulness of human somatostatin is limited because of its short half-life of less than three minutes (Susini & Buscail, 2006).

Two synthetic SSAs (octreotide and lanreotide) with longer half-lives were developed, approved by the FDA, and became commercially available. Both agents bind preferentially to SSTR2 and SSTR5 (Anthony & Freda, 2009; Astruc et al., 2005; Hofland & Lamberts, 2003; Reubi, Horisberger, &
SSAs exert broad inhibitory effects on hormone secretion and cell proliferation; however, the precise mechanisms of action have not been fully delineated (Susini & Buscail, 2006). Direct effects mediated through interactions between somatostatin or SSA and cellular receptors include the inhibition of cell division through arrest in phases G0 to G1 and G2/M (Susini & Buscail, 2006; Tagliati et al., 2006) (see Figure 1). Indirect antitumor effects of somatostatin and SSA include suppression of growth hormone secretion, inhibition of the release of insulin-like growth factor-1 (Murray et al., 2004; Susini & Buscail, 2006), antiangiogenic effects to block formation of new blood vessels that are critical to tumor growth (Susini & Buscail, 2006), and immunomodulatory effects that recruit components of the immune system to attack tumors (Susini & Buscail, 2006).

The clinical activities of octreotide and lanreotide in short- and long-acting formulations have been evaluated in a number of uncontrolled phase II clinical trials in small patient populations (Arnold, Benning, Neuhaus, Rolwage, & Trautmann, 1992; Arnold et al., 1993, 1995, 2005; di Bartolomeo et al., 1996; Ducreux et al., 2000; Faisst et al., 2003; Ricci, Antonuzzo, Galli, Ferdeghini, et al., 2000; Ricci, Antonuzzo, Galli, Orlandini, et al., 2000; Shoja- manesh et al., 2000; Yao et al., 2010; Yao, Phan, et al., 2008) (see Table 1). Pasireotide is still in early clinical development.

**Trial of octreotide LAR:** The PROMID study was the first phase III, randomized, double-blind, placebo-controlled study to evaluate tumor control with octreotide LAR (long-acting repeatable) in treatment-naive patients with well-differentiated metastatic midgut NETs (Rinke et al., 2009). Eighty-five patients were randomly assigned to octreotide LAR 30 mg intramuscularly or placebo every 28 days and were included in the intention-to-treat population. A conservative intention-to-treat analysis included only patients for whom assessments of tumor progression did not deviate from those specified in the study protocol (Rinke et al., 2009).

The impact of octreotide LAR on overall survival was inconclusive because of the low number of deaths in each treatment arm (seven in the octreotide LAR group and nine in the placebo group) (Rinke et al., 2009). However, the study was not powered to demonstrate superior overall survival because patients who progressed in the placebo group were permitted to receive octreotide LAR. Clinical response to treatment in the PROMID study was evaluated according to WHO criteria (Rinke et al., 2009). One patient in each group had a partial response during study, and no complete responses were observed. Most patients (28 of 42, 67%) treated with octreotide LAR experienced stable disease during study, whereas 53% (23 of 45) of patients treated with placebo experienced progressive disease (p = 0.0079) (Rinke et al., 2009).

Patients treated with octreotide LAR experienced greater control of flushing and diarrhea than patients who received placebo (Rinke et al., 2009). At the beginning of the study, 10 patients randomly assigned to the octreotide LAR group and 12 patients randomly assigned to the placebo group experienced one or more flushing episode per week; at month 6, 7 and 3 patients, respectively, had less than one flushing episode per week (Rinke et al., 2009). Similarly, six patients randomly assigned to octreotide LAR and seven patients randomly assigned to placebo experienced four or more episodes of diarrhea per day. After six months of treatment, two patients in the octreotide LAR and one patient in the placebo group experienced reductions in diarrhea frequency. Quality-of-life measurements were comparable between treatment groups at the six-month follow-up (Rinke et al., 2009).

Serious adverse events (AEs) occurred in 11 patients treated with octreotide LAR and 10 patients receiving placebo (Rinke et al., 2009) (see Table 2). Five patients in the octreotide LAR group and none in the placebo group discontinued treatment because of AEs. WHO AE grades 2–4, regardless of causal relationship to treatment, were more common in the octreotide LAR group than in the placebo group, and included diarrhea and flatulence. Of six reports of bile stones during the study, five occurred in the octreotide LAR group (Rinke et al., 2009).

The PROMID study demonstrated that octreotide LAR inhibited tumor growth in treatment-naive patients with metastatic, well-differentiated midgut NETs regardless of secretory symptoms or functional status (Rinke et al., 2009) (see Figure 2). Octreotide LAR also may provide a valuable treatment option after cytoreductive surgery in patients with negligible metastases (Rinke et al., 2009).

**Clinical practice guidelines and trial design:** The findings of the PROMID study have been incorporated into the updated NCCN treatment guidelines for NETs (Oberg, 2009). The update lists octreotide LAR 20–30 mg every four weeks as a management option in patients with asymptomatic unresectable carcinoid tumors (NCCN, 2011). For symptomatic disease, the NCCN continues to recommend somatostatin therapy, specifically octreotide 150–250 mcg subcutaneously twice daily or octreotide LAR 20–30 mg every four weeks, with an increase in dose frequency or short-acting octreotide as needed for symptom control (NCCN, 2011). Based on the antitumor effects of octreotide LAR in the PROMID study, octreotide is recommended in the revised 2010 Canadian and Nordic guidelines (Janson et al., 2010; Kocha et al., 2010) for the treatment of patients with NETs.
TABLE 1. Prospective Trials of Somatostatin Analogs in NETs

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Sample</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Octreotide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arnold et al., 1992</td>
<td>Phase II, multicenter, noncomparative study to evaluate antitumor effect of octreotide 200 mcg every 8 hours subcutaneously for at least 12 months</td>
<td>115 adult patients with NETs and extensive metastases</td>
<td>40% mortality rate among 85 patients who completed study. Among 68 patients who completed at least three months of treatment, PR was observed in 4% and SD in 50%.</td>
</tr>
<tr>
<td>Arnold et al., 1993</td>
<td>Phase II, multicenter, noncomparative study to evaluate the antitumor effect of octreotide 200 mcg every 8 hours subcutaneously for at least 12 months</td>
<td>21 adult patients with NETs and extensive metastases and known tumor growth behavior before study treatment</td>
<td>Five patients had a response to treatment, seven had a questionable response, and nine had clear treatment failure. Observations of favorable responses were independent of expression of somatostatin receptors.</td>
</tr>
<tr>
<td>Arnold et al., 1996</td>
<td>Phase II noncomparative study at a tertiary cancer center to evaluate the effect of octreotide 150–250 mcg three times per day subcutaneously on survival and tumor growth</td>
<td>34 adult patients with advanced inoperable NETs (primarily pancreatic or midgut tumors)</td>
<td>Median 29-month follow-up (range = 1–47 months); median survival had not been reached. 19 of 20 patients receiving octreotide as first antineoplastic therapy survived one year, and median survival had not been reached through median follow-up of 29 months (range = 12–41 months). 17 of 34 (50%) patients experienced disease stabilization for at least two months (median = 5 months, range = 0–27 months); no patient experienced major objective response.</td>
</tr>
<tr>
<td>Arnold et al., 2005</td>
<td>Randomized trial to compare time to treatment failure and survival time with octreotide 200 mcg three times per day versus octreotide 200 mcg three times per day plus IFN-α 4.5 × 10⁶ IU three times per week</td>
<td>105 adult patients with metastatic or locally advanced NETs (primarily pancreatic or midgut tumors)</td>
<td>No statistically significant differences were noted between groups on response to treatment or survival at 3, 6, and 12 months.</td>
</tr>
<tr>
<td>di Bartolomeo et al., 1996</td>
<td>Phase II multicenter study to evaluate tumor control with octreotide 500 mcg three times per day versus octreotide 1,000 mcg three times per day subcutaneously</td>
<td>58 adult patients with NETs and evidence of disease progression before study treatment</td>
<td>After treatment of five months (median), two (3%) patients with carcinoids had OR. 27 (47%) patients had SD for at least six months and continued for at least 12 months in 13 (22%) patients. Duration of survival was 22 months (median = 22 months, range = 1–32 months).</td>
</tr>
<tr>
<td><strong>Octreotide LAR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pavel et al., 2011</td>
<td>Phase III, randomized, double-blind, placebo-controlled study to evaluate efficacy of octreotide LAR depot plus everolimus 10 mg per day versus octreotide LAR alone</td>
<td>429 patients with advanced carcinoid tumors and documented disease progression</td>
<td>Median PFS of 16.4 months compared to 11.3 months with placebo plus octreotide LAR in the placebo plus octreotide LAR group.</td>
</tr>
</tbody>
</table>
| Ricci, Antonuzzo, Galli, Ferdeghini, et al., 2000 | Phase II noncomparative study to evaluate the efficacy of octreotide LAR 20 mg every four weeks after failure on prior depot lanreotide intramuscularly | 15 adult patients with progressive metastatic NETs who had response or disease stabilization on lanreotide depot but subsequently failed | • Objective responses: – PR: one patient (7%); SD: six patients (40%).
• Duration of disease stabilization: – X = 7.5 months (range = 6–12 months) |

(Continued on the next page)

a Response defined as standstill or decrease in tumor growth after progression prior to study treatment or decrease in tumor growth after standstill prior to study treatment (Arnold et al., 1993).

b Questionable response assumed if growth before study was unknown but, during study treatment, standstill occurred and was followed by progression or slow progression was followed by faster progression (Arnold et al., 1993).

CR—complete response; IFN—interferon; LAR—long-acting repeatable; MR—minor response; NETs—neuroendocrine tumors; OR—objective response; PD—progressive disease; PFS—progression-free survival; PR—partial response; SD—stable disease; SR—slow release; TTP—time to progression
TABLE 1. Prospective Trials of Somatostatin Analogs in NETs (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Sample</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Octreotide LAR (Continued)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Shojamanesh et al., 2002 | National Institutes of Health study to evaluate tumor response and survival with octreotide LAR 30 mg once per month intramuscularly | 15 adult patients with progressive malignant gastrinoma | • Mean duration of response: 25 months (range = 5.5–54.1 months)  
• 8 of 13 (53%) patients had a tumor response after three months of treatment.  
  – 7 (47%) had tumor stabilization.  
  – 1 (6%) had a decrease in tumor size.  
  – No patients had a CR. |
| Yao, Phan, et al., 2008 | Phase II open-label study to evaluate the activity of octreotide LAR 30 mg every 28 days in combination with everolimus 5 mg per day or 10 mg per day for a planned 12 courses of treatment | 60 adult patients with metastatic, unresectable, low-to-intermediate grade NETs | Completed Combinations of octreotide LAR and everolimus showed promising antitumor activity. |
| Yao et al., 2010 | Phase II, open-label, multinational, noncomparative study to evaluate antitumor activity with everolimus 10 mg per day orally alone (stratum 1) or added to ongoing therapy with octreotide LAR at prestudy doses of 30 mg or less intramuscularly every 28 days (stratum 2) | 160 adult patients with advanced pancreatic NETs who were experiencing disease progression during or after cytotoxic chemotherapy; patients treated with combination therapy had documented disease progression on prior therapy with octreotide LAR alone | • Completed  
• Stratum 1 (n = 115)  
  – OR: 11 patients (10%)  
  – SD: 78 patients (68%)  
  – PD: 16 patients (14%)  
• Stratum 2 (n = 45)  
  – OR: 2 patients (4%)  
  – SD: 36 patients (80%)  
  – PD: No patients  
• Confirmed Yao, Phan, et al. (2008) findings |

**Lanreotide**

| Faiss et al., 2003 | Randomized, multicenter study to compare the antitumor effect of lanreotide 1 mg three times per day alone, IFN-α 5 x 10^6 IU three times weekly, or the combination of lanreotide plus IFN-α | 80 adult patients with progressive NETs who had surgical removal of the primary tumor but had no other antitumor or tumor reduction treatment | • No statistically significant differences among the three treatment groups on tumor response at one year:  
  – PR: 1 or 2 patients per group  
  – SD: 5 or 7 patients per group  
  – PD: 14 or 15 patients per group  
  – CR: No patients  
• TTP was similar across treatment groups. |

**Lanreotide SR**

| Ducreux et al., 2000 | Phase II noncomparative study to evaluate the antitumor effect in patients with symptomatic NETs treated with lanreotide PR 30 mg intramuscularly every 14 days for six months and in patients with asymptomatic NETs treated with lanreotide PR 30 mg intramuscularly every 10 days for a planned duration of at least 12 months | 39 adult patients with symptomatic or asymptomatic inoperable NETs with evidence of progression before study treatment | • Response to treatment:  
  – OR: 2 patients (5%)  
  – MR: 2 patients (5%)  
  – 19 patients (49%) had no significant increase in their tumor size for a mean of 9.5 months.  
  – PD: 16 patients (41%) |
| Ricci, Antonuzzo, Galli, Orlandini, et al., 2000 | Phase II noncomparative study to evaluate the efficacy of depot lanreotide 30 mg intramuscularly every two weeks | 25 adult patients with advanced NETs (pancreatic or carcinoid); all had measurable disease and had undergone primary surgery | • Response to treatment:  
  – PR: 2 patients (8%)  
  – SD: 10 patients (40%)  
  – PD: 13 patients (52%)  
• Response duration:  
  – 21 months or longer in patients with PR  
  – A median of 8.5 months for patients with SD |

*Response defined as standstill or decrease in tumor growth after progression prior to study treatment or decrease in tumor growth after standstill prior to study treatment (Arnold et al., 1993).*  
*Questionable response assumed if growth before study was unknown but, during study treatment, standstill occurred and was followed by progression or slow progression was followed by faster progression (Arnold et al., 1993).*  
CR—complete response; IFN—interferon; LAR—long-acting repeatable; MR—minor response; NETs—neuroendocrine tumors; OR—objective response; PD—progressive disease; PFS—progression-free survival; PR—partial response; SD—stable disease; SR—slow release; TTP—time to progression.
Revised guidelines from the North American Neuroendocrine Tumor Society recommend octreotide therapy for all patients with advanced, unresectable, moderate- to well-differentiated, and low to intermediate midgut NETs in the management of locoregional disease, carcinoid syndrome, advanced disease after cytoreductive resection (alone or in combination with interferon therapy) (Boudreaux et al., 2010; Phan et al., 2010). Given the strengthened position of octreotide LAR as an accepted treatment for its symptomatic benefit and for its antitumor potential, it most likely will become a commonly used control arm in NET clinical trials in the future.

Management of Patients Treated With Somatostatin Analog

Octreotide is available as an immediate-release subcutaneous formulation (Novartis Pharmaceuticals, 2010a) and as a sustained release intramuscular formulation administered every four weeks (Novartis Pharmaceuticals, 2010b) (see Table 3). Octreotide has been registered in most countries for control of hormonal symptoms associated with gastrointestinal and pancreatic NETs and acromegaly. Patients are initially treated with immediate-release octreotide by subcutaneous injection for at least two weeks before receiving sustained release octreotide. The subcutaneous injection formulation helps determine dosing and tolerability; the dose should be titrated to control hormonal symptoms. The nurse should provide disease education and information about octreotide and its administration to the patients at the time of the first subcutaneous injection. Patient counseling should include the effectiveness of alternating injection sites in a systematic manner to avoid multiple injections at the same site in a short period of time, instruction on self-administration of the injection, instruction on proper storage and disposal, and education about AEs that could occur when receiving octreotide. Common AEs are nausea, abdominal cramps, loose stools, mild steatorrhea, and flatulence, which usually start within hours of the first injection. If tolerability of these AEs is an issue, they can be controlled by lowering the dose. The patient should be advised that common gastrointestinal AEs generally subside within the first few weeks of treatment. A risk of developing gallstones also exists when receiving octreotide therapy—the risk may be dose dependent—and many patients will experience pain and erythema at the injection site. Patients may be more adherent to octreotide therapy if they are aware of the AEs.

If the patient tolerates octreotide injection, he or she can be switched to sustained release octreotide. When switching the patient, continue the subcutaneous injections for the first two weeks to help prevent breakthrough symptoms. If breakthrough symptoms occur when the patient is receiving maintenance sustained release octreotide, he or she may be given supplemental octreotide subcutaneous injections for a few days until the symptoms are controlled. If breakthrough symptoms occur, discuss dietary triggers of symptoms with the patient. Although dietary triggers vary by patient, common triggers include alcohol, caffeine, tomato-based dishes, pineapple, nuts, high-fiber cereal, bread, vegetables, high-sugar food and drinks, and coffee. Patients should be instructed to limit the intake of these foods and to consume them in smaller amounts.

TABLE 2. PROMID Study: Incidence of Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Octreotide LAR (N = 42)</th>
<th>Placebo (N = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever or fatigue</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Hematopoietic system</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Treatment discontinuation from adverse events</td>
<td>5</td>
<td>–</td>
</tr>
</tbody>
</table>

LAR—long-acting repeatable

Note. Based on information from Rinke et al., 2009.

FIGURE 2. PROMID Primary Study End Point: Time to Tumor Progression in the Conservative Intention to Treat

dairy food, and spicy or high-fat food. Patients may benefit from tracking food intake and symptoms in a diary to help identify potential triggers.

The nurse practitioner and patient relationship plays an important role in adherence. The nurse practitioner should discuss the importance of adherence at every scheduled visit for patients receiving long-term treatment with octreotide, and he or she should educate patients about the importance of treatment adherence in the control of carcinoid syndrome. The patient should understand that octreotide works at metastatic sites to control deregulated activity of cells and reduces hormone production, which subsequently control symptoms (i.e., diarrhea and flushing). Open-ended communication about emotional and practical issues is key to identifying reasons for nonadherence. Educational, behavioral, psychosocial, or affective interventions may improve patient adherence.

Lanreotide sustained release intramuscular formulation, administered every two weeks, is licensed in Europe for control of hormonal symptoms associated with NETs and acromegaly (Ipsen Pharma Biotech, 2011). Patients who do not respond to treatment with octreotide may benefit from treatment with lanreotide. The most common AEs associated with lanreotide use are gastrointestinal disorders, biliary disorders, and injection site pain. A long-acting formulation has been developed as a deep subcutaneous injection and has been introduced in several European countries; however, published data on its use are not available.

**New Molecular Targets in the Treatment of Neuroendocrine Tumors**

Future clinical studies will inhibit multiple physiologic pathways active in NETs using combination therapy with SSA and targeted agents such as mammalian target of rapamycin (mTOR) and vascular endothelial growth factor receptor (VEGFR). Dysregulation of mTOR and VEGFR signaling pathways has been shown to contribute to tumor cell proliferation in NETs. Inhibitors to both pathway targets have demonstrated antitumor activity in patients with metastatic NETs (Konno et al., 1998; Raymond et al., 2011; Yao et al., 2010, 2011; Yao, Phan, et al., 2008).

**Implications for Nurse Practitioners**

SSAs have traditionally been used for symptomatic management and hormonal control in patients with advanced NETs. With the reporting of new clinical data, patients may not have the educational background to fully understand the new clinical use of SSAs in not only controlling their disease symptoms, but also in stabilizing tumor growth and prolonging survival. Use of SSAs for antitumor effects in patients presents new educational opportunities and management issues in patients with asymptomatic unresectable NETs. Management of unique biliary, gastrointestinal, and glucose intolerance side effects should include surveillance for cholecystitis and for increases in risk of constipation and flatulence. Bowel management strategies should be used for constipation, and alterations in glucose control should be managed for patients with diabetes. Education regarding expanded use of SSAs is critical because patients often are in communication with other patients and may already be familiar with SSAs as a treatment for diarrhea and flushing. However, patients may not understand the rationale for SSA use as an active antitumor agent. Nurse practitioners must be educated on the mechanism of action, on the potential drug risks of SSAs, and on patient management to allay the concerns of their patients and make them aware of the potential survival benefits of adherence to SSA therapy for treatment of NETs. The knowledge and competence in nurse practitioners communicating the relevance and impact

<table>
<thead>
<tr>
<th>TABLE 3. Management of Patients Treated With Somatostatin Analogs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatostatin Analog</td>
</tr>
<tr>
<td>--------------------</td>
</tr>
<tr>
<td>Lanreotide SR</td>
</tr>
<tr>
<td>Octreotide</td>
</tr>
<tr>
<td>Octreotide LAR</td>
</tr>
</tbody>
</table>

LAR—long-acting repeatable; NETs—neuroendocrine tumors; SR—sustained release

Note. Based on information from Ipsen Pharma Biotech, 2011; Novartis Pharmaceuticals, 2010a, 2010b.
Implications for Practice

- The use of somatostatin analog as an antiproliferative biologic agent provides patients with a therapeutic option since interferon.
- The favorable toxicity profile allows for the use of somatostatin analog in almost all patients.
- Hypersensitivity reactions are rare, but can occur. The most common is gastric atony. A test dose of the short-acting formulation is necessary to identify patients who have a hypersensitive reaction before administering long-acting formulation.

of the PROMID study data will provide patients with increased awareness and confidence in the initiation of therapy.

Conclusions

SSAs target SSTRs on NETs and are useful in the management of symptomatic disease in patients with those tumors. Early evidence from phase II studies in which small percentages (usually less than 10%) of patients experienced partial tumor responses and much larger percentages (about 40%–50%) of patients achieved stable disease with SSA therapy, despite having had metastatic progressive disease before starting therapy, supports the broader use of the agents for their antitumor effects beyond symptomatic control in NETs. The antitumor activity of octreotide LAR has been confirmed in the prospective, phase III, placebo-controlled PROMID study (Rinke et al., 2009). The results of the study support what clinicians have long suspected based on anecdotal evidence: Patients treated with an SSA benefit from delayed progressive disease and increased survival as well as attenuation of hormone-induced symptoms for improved quality of life. Results of clinical trials will provide additional data regarding the antitumor effects of SSA in combination with everolimus in patients with advanced NETs.

References


