Neuroendocrine Tumors
A Rare Finding: Part I

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Neuroendocrine tumors (NET) are very rare and many oncology nurses have never cared for a patient with the disease. NET arise from neuroendocrine cells dispersed throughout the body and are characterized by their ability to synthesize and secrete hormones and amines (Yao, 2007). NET can be subdivided into carcinoid and pancreatic islet cell tumors, which are difficult to distinguish by histology. Carcinoid tumors are derived from embryonic gut cells (Modlin, Lye, & Kidd, 2003) (see Figure 1). Although they can develop in any location, about 60% occur in the intestine and about 25% occur in the bronchopulmonary system. Islet cell tumors originate in the pancreas (Yao).

According to the Surveillance, Epidemiology, and End Results (SEER) 9 database, the incidence of carcinoid tumors, the most common form of NET, is about 3 cases per 100,000 per year and has increased in the last 30 years (Modlin et al., 2003; Talamonti, Stuart, & Yao, 2004). For carcinoid tumors, the average age at diagnosis is 61.4 years (Modlin et al.). Incidence varies with gender, age, and race. Slightly more women (55.1%) are diagnosed with carcinoid tumors; however, age-adjusted incidence rates are highest in African American men. Pancreatic islet cell tumors are much less common than carcinoids, and epidemiologic data are sparse. A population-based study by Yao et al. (2007) of the SEER 9, 13, and 17 databases indicated that the median age at diagnosis is 59 years. In the latest SEER database (SEER 17), the incidence of islet cell carcinomas is 0.12 per 100,000 and represents 1.3% of cancers arising in the pancreas, which is relatively rare as well.

Diagnosis

Although NET are characterized by the ability to secrete hormones and amines, hormonal syndromes resulting from this secretion usually occur only after the tumor has metastasized (Yao, 2007). At presentation, the signs and symptoms of NET are varied, making diagnosis difficult. Patients with carcinoid tumors may present with asymptomatic hepatico-megaly or bowel obstruction or their tumors may be found incidentally at surgery for unrelated reasons (Talamonti et al., 2004). Patients also may present with symptoms such as flushing, diarrhea, and asthma (Talamonti et al.; Yao). Pancreatic islet cell tumors are similarly difficult to diagnose. They are classified as functioning (up to 50% of tumors) if they secrete peptides that cause systemic clinical symptoms; nonfunctioning if they do not. Patients with nonfunctioning tumors may present with pain or a mass causing biliary or bowel obstruction (Talamonti et al.).

Clinical Course

The clinical course of NET often is indolent, but the tumors also can be aggressive and resistant to therapy (Yao, 2007). NET usually are classified as low grade or high grade based on histologic differentiation, tumor size, angiogenesis, infiltrative growth, and presence of metastasis. Clinical diagnosis is based on hormonal symptoms (if present); urinary 5-hydroxyindoleacetic acid (the breakdown product of serotonin); serum chromogranin A (a glycoprotein secreted by NET); and radiologic imaging, including OctreoScan® (Mallinckrodt Inc.) or positron-emission tomography scan (Robertson, Geiger, & Davis, 2006; Talamonti et al., 2004).

For localized primary tumors, surgical excision is the mainstay of therapy; NET are incurable in the metastatic setting (Talamonti et al., 2004). The liver is a frequent metastatic site. An estimated 50%–90% of patients with NET will develop liver metastases, and 80% of patients with advanced liver disease will die within five years of diagnosis. Liver-directed therapies, such as chemoembolization and radiofrequency ablation, are used to treat liver metastases (Talamonti et al.).

Hormonal Symptoms and Management

In the metastatic setting, carcinoids can secrete serotonin and other bioactive amines, causing diarrhea, carcinoid syndrome (diarrhea, flushing, and, less frequently, wheezing), carcinoid crisis (severe flushing and diarrhea leading to dehydration, hypotension, and arrhythmias), and carcinoid heart disease (a late complication) (Yao, 2007). Functional
pancreatic islet cell tumors can produce insulin, glucagons, gastrin, somatostatin, and vasoactive intestinal polypeptide, causing insulinoma, glucagonoma, gastrinoma, and vasoactive intestinal polypeptideoma. The release of these amines cause the different symptoms patients experience. Some examples include the watery diarrhea experienced by patients whose tumors secrete vasoactive intestinal polypeptide and the severe hypoglycemia experienced by patients with insulinomas. Pancreatic islet cell tumors also produce pancreatic polypeptide, which is not associated with a distinct clinical syndrome (Yao).

For patients with hormonal symptoms, symptom management is an important therapeutic goal (Talamonti et al., 2004). NET express increased numbers of somatostatin receptors; somatostatin analogs bind these receptors, inhibiting hormone release. The availability of somatostatin analogs, particularly long-acting formulations (e.g., octreotide), has improved patient quality of life by alleviating hormonal symptoms. However, these agents seldom cause tumor shrinkage (Talamonti et al.).

### Management of Unresectable Disease

For unresectable disease, treatment is based on the grade and location of the primary tumor. Although somatostatin analogs provide symptomatic relief, chemotherapy and immunotherapy appear to have limited ability to control tumor growth (Yao, 2007). No agent currently is approved for tumor growth control in the United States; however, in Europe, interferon alpha in combination with somatostatin analogs is approved for use in patients with metastatic carcinoid tumors with carcinoid syndrome. Islet cell tumors may respond to streptozocin-based chemotherapy, but additional treatment options are limited (Yao).

### mTOR Inhibitors

The mTOR inhibitors are a new class of targeted anticancer drugs that act specifically on a protein binding site in cells which may impact regulation of cell growth, proliferation, angiogenesis, and cellular metabolism by regulating protein synthesis (Bjornsti & Houghton, 2004). In many cancer cells, mTOR-linked signaling pathways are deregulated, causing abnormal mTOR activity and promoting cancer cell growth, proliferation, and angiogenesis.

NET express insulin-like growth factor-1 (IGF-1) and its receptor, IGF-1R, which ultimately activate mTOR (von Wichert et al., 2000). Preclinical research supports the evaluation of RAD001 in NET. Studies in carcinoid cell lines showed that IGF-1 stimulates proliferation, whereas treatment with an mTOR inhibitor inhibited IGF-1-stimulated cell proliferation and colony formation (von Wichert et al.).

In human pancreatic NET cell lines, RAD001 potently inhibited cell growth in a dose-dependent manner (Zitzmann et al., 2007). In addition, a study by Zhang et al. (2007) showed that NET expressed angiogenic growth factors and that elevated expression of vascular endothelial growth factor correlated with increased angiogenesis and shorter progression-free survival in patients with NET (Zhang et al.). mTOR inhibitors have antiangiogenic activity; they decrease production of hypoxia-inducible factor, ultimately decreasing production of proangiogenic proteins by tumor cells (Brugarolas, 2007).

### Nursing Implications

Nurses dealing with patients who have NET will be challenged by symptom management. Patients often have diarrhea and flushing, which can greatly impact their quality of life. Teaching patients when to report symptoms to the healthcare team becomes imperative because patients may experience dehydration related to the diarrhea. Diarrhea management may include agents such as loperamide, lomotil, atropine, and Octreotide injections. Hydration management should include adequate fluid intake, making it imperative that patients understand how much fluid and what types to take over a 24-hour period. Dietary teaching should occur to help patients with hypoglycemia along with glucose level monitoring.

Because many patients present with metastatic disease and treatment options are limited, nurses will be instrumental in addressing palliative care needs. Education about treatment options, such as surgical care along with postoperative care for any radiologic procedures, will need to occur. Oral drugs, such as mTOR inhibitors, will require patient education about side effects, safety management, and adherence (the Oncology Nursing 101 feature in the April 2009 issue will review mTOR inhibitors, specifically RAD001). End-of-life care may become what the oncology nurses help patients and their families move through, because metastatic NET almost always are fatal.

### Conclusion

Because NET are indolent in nature, and present with such vague symptoms, the community oncology nurse, as well as the gastroenterology nurse, should becomes familiar with this type of cancer. Currently, no therapy has been approved by the U.S. Food and Drug Administration to treat this type of cancer. The palliative treatment aim for patients with metastatic NET is to control the symptoms of the disease.
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