Targeting the mTOR Pathway in Neuroendocrine Tumors

Nancy Gardner, PhD, RN, NP

Neuroendocrine tumors (NETs) are rare, generally indolent tumors that are lethal in the metastatic setting. Treatment options to control tumor growth are limited. In clinical trials, investigational oral mammalian target of rapamycin (mTOR) inhibitors have shown activity in patients with metastatic NETs. The purpose of this article is to provide oncology nurses with a background on the mechanism of action of mTOR inhibitors in the setting of NETs. Increased understanding of the role of mTOR in the pathogenesis of NETs has led to the study of mTOR inhibitor investigational agents in NETs. Treatments are evolving and currently focusing on targeted agents such as mTOR inhibitors. Understanding the mechanisms of action of targeted agents is a critical component of nursing knowledge.

Cancer therapy has changed dramatically since the late 1990s. Molecular targeted therapies are providing new treatment options with more favorable toxicity profiles, resulting in improved quality of life. With progress in drug therapy comes a new challenge for oncology nurses: to understand the mechanisms of action of targeted therapies. The purpose of this article is to help nurses better understand intracellular communication and the molecular basis behind mammalian target of rapamycin (mTOR) pathway signaling inhibition in the treatment of neuroendocrine tumors (NETs).

Neuroendocrine Tumors

NETs are rare tumors that originate from neuroendocrine cells dispersed throughout the body (Talamonti, Stuart, & Yao, 2004). Low-to intermediate-grade pancreatic islet cell and carcinoid tumors represent two types of NETs. Characteristics of these tumors are shown in Table 1. One shared characteristic is their ability to synthesize and secrete large amounts of biologically active hormones that may cause systemic hormonal syndromes. Although they are rare and usually slow growing, low-grade NETs represent a therapeutic challenge for oncologists. They often are asymptomatic and may be found incidentally during surgery for other reasons (Robertson, Geiger, & Davis, 2006). When NETs are localized, surgical excision is the mainstay of therapy (Talamonti et al.). In the metastatic setting, they can produce a variety of hormonal syndromes, are generally considered resistant to cytotoxic chemotherapy, and are incurable (Yao, 2007). The goal of metastatic therapy is to alleviate pain and symptoms of hormonal syndromes and to control progressive tumor growth (Talamonti et al.). Somatostatin analogs, which inhibit the release of pancreatic and intestinal hormones, are used for symptom control. The liver is a frequent site of metastatic disease, with more than 50% of patients with NETs developing liver metastases. Eighty percent of patients with advanced liver metastases die within five years of diagnosis (Talamonti et al.).

At a Glance

- Neuroendocrine tumors (NETs) are rare tumors characterized by the ability to synthesize and secrete peptides that can cause hormonal syndromes in the metastatic setting. Although pancreatic and carcinoid NETs are rare, data suggest that they are being diagnosed more frequently.
- Traditional cytotoxic agents are of limited efficacy in the treatment of NETs.
- To communicate effectively with their patients, oncology nurses should be knowledgeable about molecular biology and the mechanisms of action of targeted therapies such as mammalian target of rapamycin inhibitors, a relatively new class of agents.
Islet Cell Carcinomas

Islet cell carcinomas are low- to intermediate-grade NETs that arise from islets of Langerhans in the pancreas (Yao et al., 2007). They account for a minority of pancreatic neoplasms and are generally more indolent than pancreatic adenocarcinoma. They also are rare, representing about 1.3% of pancreatic neoplasms in the United States. However, because patients with pancreatic islet cell tumors survive longer than patients with other types of pancreatic cancers, these tumors represent almost 10% of pancreatic cancers by prevalence. Islet cell carcinomas are classified as functional or nonfunctional, depending on whether they produce systemic symptoms related to excess hormone production (Talamonti et al., 2004). Functional tumors, which represent up to 50% of all pancreatic islet cell tumors, secrete insulin, glucagon, gastrin, and vasoactive intestinal peptide, causing the syndromes of insulinaemia, glucagonoma, gastrinoma, and vasoactive intestinal peptideoma, respectively (Talamonti et al.; Yao et al., 2007). Patients with nonfunctional tumors may present with symptoms of pain or a local mass that causes biliary or bowel obstruction (Talamonti et al.). Pancreatic islet cell tumors usually are metastatic at diagnosis (Yao et al., 2007). As with other tumors, median survival duration declines with worsening stage of disease (124 months for patients with localized disease versus 23 months for those with metastatic disease) (Yao et al., 2007). Increased age also predicts poor outcome: At every disease stage, median survival for patients aged 60 years or older is shorter than for patients aged 59 years or younger (Yao et al., 2007).

Table 1. Characteristics of Neuroendocrine Tumors (Pancreatic Islet Cell and Carcinoid Tumors)

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>TUMOR TYPE</th>
<th>PANCREATIC ISLET CELL</th>
<th>CARCINOID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence (per 100,000)</td>
<td>0.12, slight male preponderance</td>
<td>1–3, slight female preponderance overall, but highest incidence rates were in black males (4.48)</td>
<td></td>
</tr>
<tr>
<td>Median age at diagnosis (years)</td>
<td>59</td>
<td>61.4</td>
<td></td>
</tr>
<tr>
<td>Anatomic location</td>
<td>Pancreas*: head, 29%; body, 8%; tail, 21%</td>
<td>Gastrointestinal tract, 67.5%; trachea, bronchi, or lungs, 25.3%</td>
<td></td>
</tr>
<tr>
<td>Disease stage at presentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Localized</td>
<td>14%</td>
<td>53.3%</td>
<td></td>
</tr>
<tr>
<td>• Regional</td>
<td>23%</td>
<td>19.2%</td>
<td></td>
</tr>
<tr>
<td>• Distant</td>
<td>54%</td>
<td>12.9%</td>
<td></td>
</tr>
<tr>
<td>• Unknown or not staged</td>
<td>10%</td>
<td>14.6%</td>
<td></td>
</tr>
<tr>
<td>Median survival duration by stage (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Localized</td>
<td>124</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>• Regional</td>
<td>70</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>• Distant</td>
<td>23</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Median survival duration in patients younger than 59 years (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Localized</td>
<td>282</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>• Regional</td>
<td>114</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>• Distant</td>
<td>35</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Median survival duration in patients 60 years or older (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Localized</td>
<td>46</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>• Regional</td>
<td>38</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>• Distant</td>
<td>13</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Median five-year survival by stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Localized</td>
<td>71%</td>
<td>78.2%</td>
<td></td>
</tr>
<tr>
<td>• Regional</td>
<td>55%</td>
<td>71.7%</td>
<td></td>
</tr>
<tr>
<td>• Distant</td>
<td>23%</td>
<td>38.5%</td>
<td></td>
</tr>
<tr>
<td>• Unstaged</td>
<td>–</td>
<td>48.3%</td>
<td></td>
</tr>
<tr>
<td>Best five-year survival (all stages) by site of carcinoid tumor</td>
<td>Rectal, 88.3%; appendiceal, 71%; bronchopulmonary, 73.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor five-year survival (all stages) by site of carcinoid tumor</td>
<td>Hepatic, 18.4%; pancreatic, 37.5%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*8% overlapping, 34% unknown  
Note. Based on information from Modlin et al., 2003; Talamonti et al., 2004; Yao et al., 2007.

Carcinoid Tumors

Carcinoid tumors usually are indolent, but they exhibit a wide spectrum of biologic behavior (Modlin, Lye, & Kidd, 2005). A five-decade analysis of carcinoid tumors reported that 13% of patients had distant metastases at time of diagnosis and patients had an overall (regardless of site) five-year survival rate of 67.2%, calling into question the perception that these tumors are relatively benign (Modlin et al.). Carcinoid tumors also are rare, although their incidence appears to have increased since the late 1970s (Modlin et al.). As would be expected, they most often occur in organs with a high density of neuroendocrine cells. About 66% are found in the gastrointestinal tract, about 25% in the bronchopulmonary system, and the remainder in more obscure sites. Within the gastrointestinal tract, carcinoids are most frequently found in the small intestine (41.8%); they are found less frequently in the rectum (27.4%) and stomach (8.7%) (Modlin et al.). Overall, women are slightly more likely to develop carcinoid tumors than men. Clinical manifestations of carcinoid tumors may be vague or absent, causing delays in diagnosis (Modlin et al.; Robertson et al., 2006). However, carcinoid tumors can secrete vasoactive peptides, the most prominent of which is serotonin (Zuutena & Taal, 2005). Carcinoid syndrome, which typically does not occur until the tumor has metastasized to the lungs or liver, occurs in about 10% of patients with carcinoid tumors (Modlin et al.; Robertson et al.). Symptoms of carcinoid syndrome include flushing and diarrhea. Carcinoid heart disease is a late complication in patients with metastatic carcinoid tumors and is the cause of death in many of these patients (Zuutena & Taal).  
Most of NETs are sporadic in origin; therefore, genetic changes (mutations) associated with NETs are not inherited. The inactivation of several tumor suppressor genes is implicated in deranged cell signaling and in the development of these tumors (Arnold, Sosnowski, Schmitt-Graff, Arnold, & Blum, 2007).
Cell Signaling

Normal cellular activities are regulated by the availability of energy, nutrients, and growth factors in the cellular environment. Specific growth factors (ligands) bind specific protein receptors on the cell surface and transmit signals into the cell (Blume-Jensen & Hunter, 2001). Once within the cell, these signals are transmitted in an orderly manner through a complex network of signaling pathways. Ultimately, these signals are relayed to the genes in the nucleus that control protein production. To understand cell signaling and the relationship between abnormal signaling and cancer, knowing how genes direct the production of proteins is critical.

Relationship Between Genes and Proteins

Genes within the nucleus direct the production of proteins needed for cellular activities, including cell signaling, cell growth, and cell division (U.S. National Library of Medicine, 2008a). Protein production involves two major steps: transcription and translation, which together are known as gene expression. Transcription occurs in the cell nucleus, whereas translation occurs in the cytoplasm. During transcription, the information in an individual’s DNA is transferred to messenger RNA (mRNA), which carries the information into the cytoplasm. Once in the cytoplasm, the mRNA interacts with the ribosome, which reads the sequence. Another type of RNA, transfer RNA (tRNA), then assembles the protein from amino acids (U.S. National Library of Medicine, 2008a).

Gene Mutation

Gene mutations represent permanent changes in DNA sequence and either can be inherited from a parent (germline mutations) or can be acquired during a person’s lifetime (somatic mutations) (U.S. National Library of Medicine, 2008b). Somatic mutations occur in the DNA of individual cells and can be caused by environmental factors (e.g., sun exposure) or through errors made as DNA is copied during cell division. Because mutations change DNA sequence, they also can change the proteins encoded by the mutated gene, causing the protein to malfunction or to be lost entirely (U.S. National Library of Medicine, 2008b). Signal transmission (transduction) can be thought of as the flow of signaling through multiple interconnected pathways within the cell. The flow is regulated by proteins (enzymes) that activate (promote) or deactivate (interrupt) signaling to the next protein in the chain. Kinase enzymes transfer a phosphate group to the next protein in the chain, which generally transmits the signal to the next protein. Other proteins interrupt signaling. If the loss of a protein that interrupts signaling causes cancer, the protein is called a tumor suppressor protein. Tumor suppressor proteins often are phosphatase enzymes, which remove a phosphate group, interrupting the signal. Both types of enzymes are equally important to ensure that cells are not stimulated to grow and divide under inappropriate conditions (e.g., under conditions in which nutrient and energy levels are insufficient to support growth) (Alberts, Lewis, Raff, Roberts, & Walter, 2002). Many different genes are needed to encode the enzymes in these pathways: 520 genes have been identified for protein kinases and 130 for protein phosphatases (Blume-Jensen & Hunter, 2001).

In a normal cell, rigid controls on intracellular signaling maintain the correct balance among the rate of cell division, cell growth, and programmed cell death (apoptosis) during which cells are purposely destroyed because the cell is defective or no longer serves a useful function (Blume-Jensen & Hunter, 2001). In cancer, genetic changes disrupt this critical balance, tipping it toward the survival of cancerous cells. Mutations in some genes (proto-oncogenes and oncogenes) can cause production of critical cell signaling proteins that promote the survival and proliferation of abnormal cells. In some cases, genetic mutations permit the production of proteins in cell surface receptors that permit the receptors to transmit signals into the cell without growth factor binding (constitutive activation). Mutations in tumor suppressor genes result in the loss or underproduction of proteins that block signaling (Blume-Jensen & Hunter).

The PI3K-Akt Cell Survival Pathway

The phosphoinositide 3-kinase (PI3K)-Akt intracellular pathway is important in the control of cell growth and proliferation; in cancer, signaling proteins in this pathway often are abnormal (Vivanco & Sawyers, 2002). Mutations in genes

**Figure 1. Targets of Selected Anticancer Agents**

Bevacizumab  
Cetuximab  
Panitumumab  
Trastuzumab  
Lapatinib  
Gefitinib  
Erlotinib  
Sorafenib  
Sunitinib  
PDGR  
VEGFR  
IGF-1R  
EGFR  
HER2  
P13K  
PTEN  
TSC1  
TSC2  
mTOR  
mTOR inhibitor  
Nucleus  
Cytoplasm  
EGFR—epidermal growth factor receptor; IGF-1R—insulin-like growth factor-1 receptor; mTOR—mammalian target of rapamycin; PDGFR—platelet-derived growth factor receptor; PI3K—phosphoinositide 3-kinase; PTEN—phosphate and tensin homolog; TSC—tuberous sclerosis complex; VEGFR—vascular endothelial growth factor receptor  
Note: Multiple receptors (EGFR, PDGFR, VEGFR, and IGF-1R), which may be expressed on different cell types, are shown on the same cell. Intracellular proteins that promote signaling are shown in green, and tumor suppressor proteins, representing signal interruption or blockade, are shown in red. The multikinase inhibitors sorafenib and sunitinib are shown targeting VEGFR and PDGFR, although they also target additional receptors.
that encode critical kinase and phosphatase enzymes in this pathway cause excessive signaling, resulting in unregulated cell growth and division. For example, mutations in genes that encode kinase enzymes, such as the receptor protein Erb2 (HER2), and cytoplasmic enzymes, such as PI3K and Akt, cause excessive signaling through the PI3K-Akt pathway. Mutations in tumor suppressor genes can cause underproduction or loss of critical proteins that block signaling. Phosphate and tensin homolog (PTEN) enzyme suppresses signaling through the PI3K-Akt pathway, perhaps the second most commonly mutated tumor suppressor in humans (Shaw & Cantley, 2006).

With the increased understanding of molecular biology, researchers have identified many potential targets for cancer therapy (Sebolt-Leopold & English, 2006). Among the targets are growth factors, such as vascular endothelial growth factor (VEGF), and kinase enzymes in cell surface receptors and in components of intracellular signaling pathways. Figure 1 illustrates the targets of selected anticancer agents.

The mTOR Pathway

mTOR is a kinase protein in the PI3K-Akt pathway that receives signals from Akt. In response to signaling through Akt and adequate intracellular concentrations of energy and nutrients, mTOR activation promotes the translation of proteins, including those required for cell growth and those required for progression through the cell cycle (Bjornst & Houghton, 2004; Faivre, Kroemer, & Raymond, 2006). mTOR is an essential protein that appears to be genetically stable. To date, no mutation in the gene encoding mTOR has been identified, and disruption of mTOR appears to confer embryonic lethality (Bjornst & Houghton). Therefore, increased mTOR activity appears to result from mutations in genes encoding other proteins in the PI3K-Akt-mTOR pathway rather than from mutations in the gene encoding mTOR (Huang, Bjornsti, & Houghton, 2003).

Increased signaling to mTOR can result from mutations in tumor suppressor genes in the PI3K-Akt-mTOR pathway, causing the loss or underproduction of tumor suppressor proteins. Proteins that may be lost include PTEN, tuberous sclerosis complex (TSC1, TSC2), neurofibromin 1 (NF1), and serine/threonine kinase 11 (LKB1) (Shaw & Cantley, 2006). Mutations in the gene encoding PTEN are observed in many different tumor types, as well as in individuals with cancer predisposition syndromes such as Cowden disease (Cully, You, Levine, & Mak, 2006). Loss of these tumor suppressor proteins is also associated with familial cancer syndromes characterized by phakomatoses, suggesting that cancer cells use these changes to promote their survival (Shaw & Cantley).

Rationale for Targeting mTOR in Neuroendocrine Tumors

Evidence suggests that abnormal mTOR activation, caused by defects in tumor suppressor genes and increased signaling through the PI3K-Akt pathway, is involved in the pathogenesis of NETs (see Figure 2). Defects in TSC2 are associated with islet cell tumors, and the loss of NF1 is associated with carcinoid tumors (Tan, Hall, Semeraro, Irons, & Freeman, 1996; Verhoef et al., 1999). In addition, carcinoid cells express insulin-like growth factor 1 (IGF-1) receptors and secrete growth factors (e.g., IGF-1) that stimulate the PI3K-Akt-mTOR pathway (von Wichert et al., 2000). mTOR inhibition also suppressed the growth of carcinoid cells in preclinical studies (von Wichert et al.).

mTOR is involved in angiogenesis because it acts as a key regulator of cellular response to oxygen deprivation (hypoxia) (Kaper, Dornhoefer, & Giaccia, 2006). Hypoxia is a characteristic feature of many solid tumors and has been associated with malignant progression (Vaupel, 2004; Vaupel & Harrison, 2004).

mTOR regulates the production of hypoxia-inducible factors, which in turn stimulate the production of more than 30 proteins including angiogenic proteins, such as VEGF (Vaupel & Harrison, 2004). If the PI3K-Akt-mTOR pathway is intact, hypoxia decreases mTOR activity (and therefore the production of hypoxia-inducible factors and angiogenic proteins) (Brugarolas & Kaelin, 2004). However, if the PTEN or TSC2 tumor suppressor proteins are lost, mTOR retains its activity despite hypoxia, potentially promoting the growth and survival of hypoxic...
tumor cells (Brugarolas et al., 2004). Evidence indicates that angiogenesis is involved in the pathogenesis of NETs: VEGF expression was detected on human NET cells, and strong VEGF expression correlated with poorer prognosis than weak or no VEGF expression (Zhang et al., 2007). Figure 3 illustrates how increased signaling to mTOR caused by excess signaling through IGF-1 receptor and inactivating mutations in tumor suppressor genes could potentially be blocked by mTOR inhibition. Based on these observations, clinical trials with mTOR inhibitors were initiated in NETs, and encouraging results have been reported with an investigational oral mTOR inhibitor, RAD001 (Yao et al., 2008). Everolimus currently is under review by the U.S. Food and Drug Administration (FDA) for approval use with NETs.

Implications for Nursing Practice

mTOR inhibitors represent a relatively new class of antineoplastic agents that presents unique challenges and opportunities for oncology nursing practice. Everolimus is currently approved by the FDA for use in the treatment of renal cell carcinoma after failure of treatment with sunitinib or sorafenib. Nurses must be knowledgeable about the mechanism of action of mTOR inhibitors and the rationale for their use in treatment of NETs to provide optimal nursing care. Nurses are responsible for knowledge about targeted agents and should communicate this knowledge to their patients. Patients armed with information about drugs' mechanisms of action and rationale for use demonstrate higher probability of adherence and lower probability of treatment-limiting toxicity (Cameron, 1996; Moore, 2007). Issues of particular concern in patients with NETs include adherence, because of the oral administration of this agent, retention of information in an older patient population, and symptom management during long-term therapy (see Figure 4). Deaths from acute respiratory failure (0.7%), infection (0.7%), and acute renal failure (0.4%) were observed in patients treated with everolimus (Novartis Pharmaceuticals, 2008).

Concepts about targeted therapies are challenging to communicate, and patients may not have the educational background to comprehend complex medical language. Patients may benefit from multimedia reinforcement by integrating audio CDs, pictures, and videos into the teaching process. Pictures are particularly useful when hearing, language, comprehension, or literacy may be of concern. As mTOR inhibitor therapy becomes part of the treatment protocol for NETs after clinical testing and FDA approval, oncology nurses will play an integral role in improving patient quality of life, ensuring adherence to oral therapy regimens, and alleviating side effects through informative patient education, effective assessment, and appropriate intervention.

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References


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