Advances in molecular biology have facilitated the identification of cellular signaling pathways, which, when altered in cancer, promote cancer cell division, survival, and angiogenesis. Researchers have used this knowledge to develop anticancer agents that target components of these pathways, such as growth factors, cell surface receptors, and intracellular proteins. Potential advantages of targeted agents include lower systemic toxicity because, unlike cytotoxic chemotherapy, these agents are selective for their targets (Chabner & Roberts, 2005) and improved patient selection and efficacy because the agents’ use can be limited to patients possessing the targeted pathway component.

Targeted agents fall into two main categories: monoclonal antibodies and protein kinase inhibitors (Kay, 2006). These types have similar mechanisms of action in that they bind the target and inhibit signal transmission along the targeted pathway. However, monoclonal antibodies are large molecules that must be administered through IV, whereas protein kinase inhibitors are small molecules that may be formulated for oral administration. Oral targeted agents are becoming more widely used (see Table 1) and many additional oral agents are being evaluated in clinical trials (see Table 2). In the United States, the pace of approval of these agents for use in cancer treatment is accelerating (Aisner, 2007).

This article uses clinical experience with an oral investigational mTOR inhibitor, RAD001, in neuroendocrine tumors (NET) as an example in addressing safety issues related to oral administration and promoting patient adherence. Oncology nurses must familiarize themselves with these issues as more oral agents become approved for use in cancer treatment.

NET arise from neuroendocrine cells dispersed throughout the body. They are rare and their clinical course often is indolent, but, in the metastatic setting, the disease is incurable. Carcinoid tumors are the most common form. Pancreatic islet cell tumors also occur (Yao, 2007). Detailed information on NET were presented in part I of this feature (Jacobs, 2009).

mTOR Inhibitors

The mTOR inhibitors are members of a new class of targeted anticancer drugs. mTOR is an intracellular protein present in every human cell and serves as a central regulator of cell growth (size), proliferation, angiogenesis, and cellular metabolism by regulating protein synthesis (Bjornsti & Houghton, 2004). Because signaling through mTOR-linked pathways is deregulated in many types of cancer, mTOR inhibitors may have broad anticancer activity. Temsirolimus, an IV-administered mTOR inhibitor, was recently approved by the U.S. Food and Drug Administration (FDA) for use in advanced renal cell carcinoma (FDA, 2007). RAD001 has demonstrated anticancer activity in a wide range of tumor types (such as non-small cell lung cancer and colon cancer) in phase I clinical trials (O’Donnell et al., 2008). Phase II and III trials are ongoing. RAD001 is currently under review by the FDA.

Nursing Experience

Nursing Responsibilities With Oral Agents

One of the primary nursing responsibilities in oncology is monitoring patients to ensure their safety. Oral administration offers some advantages compared with IV injections, including patient convenience, fewer disruptions in work and daily activities for travel to an infusion clinic, and avoidance of pain and complications (e.g., infusion-related hypersensitivity reactions); disadvantages include possible lower adherence with self-administration (Gobel, 2007; Moore, 2007). However, daily oral dosing provides continuous drug exposure, compared to intermittent IV infusions, and multiple opportunities to modify dosages to manage side effects. At the same time, accessibility and affordability issues arise because oral drugs may...
Table 1. Oral Targeted Agents Approved by the U.S. Food and Drug Administration

<table>
<thead>
<tr>
<th>DRUG</th>
<th>YEAR APPROVED</th>
<th>TARGET</th>
<th>ORIGINAL INDICATION</th>
<th>ADDITIONAL INDICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BCR-ABL Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dasatinib (Sprycel®, Bristol-Myers Squibb)</td>
<td>2006</td>
<td>Multiple kinases</td>
<td>Ph+ chronic myelogenous leukemia after progression on imatinib or in patients who cannot tolerate imatinib</td>
<td></td>
</tr>
<tr>
<td>Imatinib (Gleevec®, Novartis AG)</td>
<td>2001</td>
<td>Multiple kinases</td>
<td>Ph+ chronic myelogenous leukemia</td>
<td>Ph+ acute myelogenous leukemia, gastrointestinal stromal tumor, myelodysplastic syndromes</td>
</tr>
<tr>
<td>Nilotinib (Tasigna®, Novartis AG)</td>
<td>2007</td>
<td>BCR-ABL</td>
<td>Ph+ chronic myelogenous leukemia after progression on imatinib or in patients who cannot tolerate imatinib</td>
<td></td>
</tr>
<tr>
<td><strong>EGFR (HER) Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erlotinib (Tarceva®, OSI Pharmaceuticals)</td>
<td>2004</td>
<td>Cell surface receptors (EGFR [HER])</td>
<td>Locally advanced or metastatic non-small cell lung cancer</td>
<td>Unresectable, advanced, or metastatic pancreatic cancer</td>
</tr>
<tr>
<td>Gefitinib (Iressa®, AstraZeneca)</td>
<td>2003</td>
<td>Cell surface receptors (EGFR [HER])</td>
<td>Metastatic non-small cell lung cancer</td>
<td></td>
</tr>
<tr>
<td>Lapatinib (Tykerb®, GlaxoSmithKline)</td>
<td>2007</td>
<td>Cell surface receptors (HER1/HER2)</td>
<td>Metastatic breast cancer</td>
<td></td>
</tr>
<tr>
<td><strong>Multikinase Inhibitors or Antiangiogenic Agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lenalidomide (Revlimid®, Celgene Corp.)</td>
<td>2005</td>
<td>Antiangiogenic agent</td>
<td>Myelodysplastic syndromes</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Sorafenib (Nexavar®, Bayer)</td>
<td>2005</td>
<td>Multiple receptor kinases</td>
<td>Advanced renal cell carcinoma</td>
<td></td>
</tr>
<tr>
<td>Sunitinib (Sutent®, Pfizer Inc.)</td>
<td>2006</td>
<td>Multiple receptor kinases</td>
<td>Gastrointestinal stromal tumor after progression on imatinib; advanced renal cell carcinoma</td>
<td></td>
</tr>
<tr>
<td>Thalidomide (Thalomid®, Celgene Corp.)</td>
<td>2006</td>
<td>Antiangiogenic agent</td>
<td>Multiple myeloma</td>
<td></td>
</tr>
<tr>
<td><strong>HDAC Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vorinostat (Zolinza®, Merck &amp; Co., Inc.)</td>
<td>2006</td>
<td>HDAC</td>
<td>Cutaneous T-cell lymphoma</td>
<td></td>
</tr>
</tbody>
</table>

EGFR—epidermal growth factor receptor; HDAC—histone deacetylase; Ph+—Philadelphia chromosome positive

Note. Based on information from U.S. Food and Drug Administration, 2007.

not be covered by insurance the same way IV drugs are. This could be another factor in nonadherence.

With oral agents, nurses must educate patients about proper drug administration, what foods and drugs to avoid, types of side effects that may occur and when they may occur, and when to contact the healthcare team. In addition, patients taking oral medications are monitored less frequently than patients receiving IV therapy, so the responsibility to report side effects falls on patients and family members. If nurses cannot identify side effects quickly and manage them, the potential exists for an increased risk of severe side effects requiring treatment interruption or discontinuation, particularly in stoic patients who are reluctant to report side effects because they fear that reporting them will lead to treatment interruption or discontinuation (Moore, 2007).
drug accountability) helped promote adherence for patients.

Safety

RAD001 is rapidly absorbed after oral administration, although a high-fat meal is known to delay its absorption. RAD001 is mainly metabolized in the liver by the CYP3A4 pathway (Kovarik, Beyer, & Schmouder, 2006). Patients in this trial were instructed to take the drug on an empty stomach or with a light, fat-free meal. They also were given a list of medications to avoid and were encouraged to carry this list with them in case they needed medical treatment while away from the cancer center conducting the study.

Side Effects

Molecular-targeted therapies are known to cause some dermatologic toxicities with unique characteristics depending on the agent and its target (Esper, Gale, & Muehlbauer, 2007). Skin changes have been reported as common side effects in patients taking RAD001, including skin rash (see Figure 2). Fingernail changes and mouth ulcers also have been observed (see Figures 3 and 4).

Skin rash typically presented in the face, head, scalp, and upper torso, similar to most skin rashes observed with monoclonal antibodies and tyrosine kinase inhibitors. Hand-foot skin changes also were observed during the clinical trials and occurred within the first two weeks of treatment and resolved spontaneously within four weeks without requiring a dose interruption. Changes associated with RAD001 involved skin peeling and calluses to the palmar surface of the hands and plantar surface of the feet. The changes were similar to the hand-foot skin reaction reported by Wood and Manchen (2007) but without associated redness or pain and interference with activities of daily living. Nail changes, ridging, and pitting were observed over several months.

Mouth ulcers observed in patients taking RAD001 differ from those reported by patients receiving cytotoxic chemotherapy, making it difficult to characterize the ulcers as oral mucositis. They present as aphthous ulcers (canker sores), appearing in an isolated, sporadic fashion on the tip or sides of the tongue, inside the lips, or on the oral mucosa, requiring no treatment or changes in food habits. In addition, metabolic dyscrasias were observed, most of which are not typical of cytotoxic agents: hypophosphatemia, hyperglycemia, and hypertriglyceridemia (Yao, 2007). All patients were encouraged to call their nurse at the first sign of a side effect (i.e., skin rash or oral ulcers). The importance of early intervention to avoid treatment interruption or dose reduction was the main factor that contributed to patients promptly reporting side effects. Patients also kept daily records of any side effects in the diary that was given to them, which was reviewed by nurses at each clinic visit to determine a possible link between a missed dose and a side effect. Patients also were encouraged to call the nurses on a weekly basis, regardless of whether they experienced a side effect. In other words, they were encouraged to check in with the nursing staff.

Nursing Implications

Oncology nurses must be knowledgeable about antineoplastic agents used to treat their patients. Although most oncology nurses are familiar with IV-administered cytotoxic agents and the associated side effects, side effects associated with new oral targeted therapies may be different. Nurses should educate patients being treated with novel oral agents on how the agents work, what side effects to anticipate, and how to manage the side effects. Explaining to patients that, with early intervention, most side effects can be managed with minimal treatment interruption.

Table 2. Selected Investigational Oral Targeted Agents

<table>
<thead>
<tr>
<th>AGENT</th>
<th>TARGET</th>
<th>TUMOR</th>
<th>DEVELOPMENT STAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multikinase Inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Axitinib (Pfizer Inc.)</td>
<td>Cell surface receptors (VEGFR, PDGFR)</td>
<td>Multiple cancers; phase III in thyroid and pancreatic cancers</td>
<td>Phase II–III</td>
</tr>
<tr>
<td>Cediranib [AZD2171] (AstraZeneca)</td>
<td>Cell surface receptors (multiple VEGFR)</td>
<td>Glioblastoma multiforme, non-small cell lung cancer, colorectal cancer</td>
<td>Phase II–III</td>
</tr>
<tr>
<td>Pazopanib (GlaxoSmithKline)</td>
<td>Cell surface receptors (VEGFR, PDGFR, KIT)</td>
<td>Multiple tumor types: renal cell carcinoma, ovarian cancer, soft tissue sarcoma</td>
<td>Phase II–III</td>
</tr>
<tr>
<td>SU-14813 (Pfizer Inc.)</td>
<td>Cell surface receptors (VEGFR, PDGFR, KIT, FLT-3)</td>
<td>Breast cancer</td>
<td>Phase II</td>
</tr>
<tr>
<td>Vandetanib (Zactima™, AstraZeneca)</td>
<td>Cell surface receptors (VEGFR, EGFR)</td>
<td>Non-small cell lung cancer</td>
<td>Phase III</td>
</tr>
<tr>
<td>Intracellular Kinase Inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZD0530 (AstraZeneca)</td>
<td>Intracellular kinase (SRC)</td>
<td>Solid tumors and hematologic malignancies</td>
<td>Phase II</td>
</tr>
<tr>
<td>RAD001 (Novartis AG)</td>
<td>Intracellular kinase (mTOR)</td>
<td>Renal cell carcinoma, neuroendocrine tumors</td>
<td>Phase III</td>
</tr>
<tr>
<td>Deacetylase Inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBH589 (Novartis AG)</td>
<td>Multiple deacetylases</td>
<td>Hematologic malignancies</td>
<td>Phase I–II</td>
</tr>
<tr>
<td>MGCD0103 (Pharmion)</td>
<td>Deacetylase</td>
<td>Myelodysplastic syndrome, acute myelogenous leukemia, solid tumors, hematologic malignancies</td>
<td>Phase I–II</td>
</tr>
</tbody>
</table>

EGFR—epidermal growth factor receptor; FLT-3—fms-like tyrosine kinase 3; mTOR—mammalian target of rapamycin; PDGFR—platelet-derived growth factor receptor; SRC—nonreceptor protein tyrosine; VEGFR—vascular epidermal growth factor receptor.
CYP3A Inducers
Carbamazepine
Dexamethasone
E ethosuximide
Glucocorticoids
Griseofulvin
Nafcillin
Nelfinavir
Nevirapine
Oxcarbazepine
Phenobarbital
Phenytoin

CYP3A Inhibitors
Amiodarone
Anastrozole
Azithromycin
Cannabinoids
Cimetidine
Clarithromycin
Clobazam
Cyclosporine
Danazol
Delavirdine
Dexamethasone
Diethylidithiocarbamate
Diltiazem
Dirithromycin
Disulfiram
Entacapone (high dose)
Erythromycin
Ethinyl estradiol
Fluconazole (weak)
Fluoxetine
Fluvoxamine
Gelostodene
Grapefruit juice
Indinavir
Isoniazid
Itraconazole
Ketoconazole

Phenobarbital
Phenytoin
Primidone
Progesterone
Rifabutin
Rilpamip
Rофоксёб (мild)
St. John’s wort
Sulfadimidine
Sulfispyrazole
Troglitazone

Figure 1. Medications to Avoid With RAD001 Use

will lessen their anxiety regarding possible dose modification (Moore, 2007).

Nurses should provide patients with clear, written directions for administration of oral agents because the agents are self-administered in the home setting. Oral agents may have food-drug or drug-drug interactions; therefore, a thorough medication review should be carried out before therapy begins. Drugs with potential interactions should be identified and safer drugs substituted, if possible. Consultation with an oncology pharmacist to assist in identifying potential drug-drug interactions may be useful. To prevent any potential interactions, the nurse must provide clear instructions about which foods and drugs to avoid. Patients also should be instructed to contact the oncology nurse before beginning any new medications prescribed by another healthcare provider.

Because oral agents are self-administered, patients may need reminders to take their medications. In some institutions, multidisciplinary teams of nurses, pharmacists, and physicians are collaborating to develop new processes and procedures to support adherence (Birner, Bedell, Avery, & Ernstoff, 2006). Some existing devices used to promote adherence (e.g., pill containers) are not appropriate for RAD001 and other moisture- and light-sensitive drugs that must be kept in the original package until time of dosing. Nurses must check storage requirements of novel agents before suggesting alternate medication storage containers.

Conclusion

NET are of a relatively indolent nature. Nonetheless, therapeutic options for advanced NET are very limited. Abnormalities in the mTOR pathway have been described in a variety of tumors, including NET, which may cause resistance to apoptosis, increased proliferation, and altered metabolism. Results of therapy targeting mTOR and vascular epidermal growth factor receptor suggesting antiangiogenic activity have led to the development of large-scale studies which are currently being conducted.

In this article, RAD001 was described as an example of one of the newer oral agents being used in oncology. Oral anti cancer agents are becoming more widely available. Patients treated with approved oral agents are followed less closely than patients taking investigational agents in a clinical trial. Healthcare providers in the community must be educated about these agents and the importance of patients’ adherence to treatment. This depends on patients’ motivation to be an active participant in treatment as well as their education about their disease and treatment, how to manage side effects attributed to the treatment, and when to call the nurse for assistance. The potential for patients missing doses or not taking medications as prescribed is a major concern in adherence to oral agents and efficacy of treatment (Moore, 2007).

The healthcare provider prescribing these agents must recognize the need for patient education. Hospitals and clinics will be challenged to find who will be responsible for this patient teaching and how it may be reimbursed. Whose role will this become? Will it fall to the chemotherapy nurse or a clinic nurse, the prescriber, or the pharmacist? A system will have to be implemented to ensure that patients are given instructions on the safe administration of the oral agents, side effects to report, and when to call the healthcare team before they are discharged.

In general, patients with cancer may feel they have no control over their cancer treatment and situation. In this phase II study, many patients felt that they had some control after nurses encouraged them to participate in the reporting of side effects as well as self-administration of an oral drug. This control helped enhance patient adherence to prescribed oral therapy, thereby possibly improving efficacy.
The author gratefully acknowledges Beverly Bach, BA, and Susan Moore, RN, MSN, ANP, AOCN®, for their editorial assistance with this manuscript.

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