Management of mTOR Inhibitor Side Effects

Patricia A. Creel, BSN, RN, OCN®, CCRP

Although surgery remains the primary curative treatment for renal cell carcinoma (RCC), systemic therapy also is indicated in the advanced disease setting. This article reviews the role of mammalian target of rapamycin inhibitors in the treatment of metastatic RCC. A case study is presented to illustrate side-effect management issues commonly encountered by oncology nurses in clinical practice.

Renal cell carcinoma (RCC) is responsible for 2.3% of the estimated 562,340 cancer-related deaths in the United States in 2009 (Jemal et al., 2009). Five-year survival rates vary by clinical stage; localized (89.9%), locally advanced (61.3%), and metastatic (9.9%). (Jemal et al.). About 33% of patients present with locally advanced or metastatic RCC (Bukowski & Wood, 2007). An estimated 20%–40% of patients who undergo surgical resection will eventually develop metastatic disease.

Treatment for metastatic RCC includes surgical resection, cytokine therapy, antiangiogenic therapy, and chemotherapy (National Cancer Institute [NCI], 2003). Agents that target the angiogenesis signal transduction pathway have been shown to be effective in the treatment of metastatic RCC, yet each product has characteristics that may impact the efficacy and tolerability. Consideration of a patient’s prognostic, pathologic, and comorbid factors can help clinicians identify the optimal therapeutic approach. This article will review the mechanisms of action of mTOR inhibitors, common adverse events, and side-effect management with a case study focus.

mTOR Inhibitors

Mammalian target of rapamycin (mTOR) inhibitors, which include the U.S. Food and Drug Administration (FDA)-approved agents everolimus and temsirolimus, have demonstrated efficacy in the treatment of metastatic RCC. mTOR is an intracellular protein kinase with far-reaching effects on cell proliferation, growth, and survival, making it a logical target for the treatment of tumors, particularly those such as RCC that are chemo- and radio-resistant (Cohen & McGovern, 2005). Under normal conditions, mTOR binds the intracellular protein FKBP-12, resulting in the activation of hypoxia-inducible factor. This, in turn, stimulates vascular endothelial growth factor (VEGF), which promotes angiogenesis, an important process for cell proliferation and survival. When a malfunction in these highly regulated signaling events takes place, cell proliferation may proceed uncontrolled, resulting in tumorigenesis (Cohen & McGovern) (see Figure 1). Inhibition of mTOR results in a decrease in the expression levels of the angiogenesis-promoting hypoxia-inducible factor and VEGF (Cohen & McGovern). As a result, tumor progression is slowed.

Everolimus

Everolimus is administered once daily as a 10 mg tablet with or without food (Novartis Pharmaceuticals, 2009). The dosage may be decreased to 5 mg daily if necessary for the management of severe adverse reactions. Dose-limiting toxicities include pneumonitis, dyspnea, infections, and stomatitis or mucositis.

At a Glance

- Increased angiogenesis is a prominent characteristic of renal cell carcinoma.
- Mammalian target of rapamycin (mTOR) inhibitors bind with the intracellular protein FKBP-12, resulting in decreased expression of the angiogenesis-promoting hypoxia-inducible factor and vascular endothelial growth factor.
- Common side effects of mTOR inhibitors include oral mucositis, pneumonitis, and rash. Vigilant monitoring and early intervention can minimize the severity of side effects and enhance the tolerability of treatment.

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(Novartis Pharmaceuticals). Common hematologic laboratory abnormalities include anemia, neutropenia, and thrombocytopenia. Common chemistry laboratory abnormalities include hypercholesterolemia, hypertriglyceridemia, hyperglycemia, increased creatinine, and hypophosphatemia (Novartis Pharmaceuticals; Tabernero et al., 2005) (see Table 1). Monitoring of complete blood count (CBC), creatinine, fasting glucose, and lipids is recommended prior to starting and periodically during treatment. When possible, optimal glucose and lipid control should be achieved prior to starting therapy (Novartis Pharmaceuticals).

**Temsirolimus**

Temsirolimus is administered IV as a weekly 25 mg dose infused over 30–60 minutes. Treatment continues until disease progression or the toxicities associated with treatment become intolerable (Wyeth Pharmaceuticals, 2008). Patients should be premedicated with 25–50 mg diphencydramine 30 minutes before infusion to reduce the risk of hypersensitivity reactions (HSRs). HSRs occurred in 9% of patients receiving temsirolimus (Wyeth Pharmaceuticals). In the event of an HSR, the infusion should be suspended and supportive medications such as an H1 or H2 antagonist administered. When the HSR is resolved, the infusion may be resumed at a slower rate, such as 60 instead of 30 minutes (Bellmunt, Szczylik, Feingold, Strahs, & Berkenblit, 2008; Wyeth Pharmaceuticals).

As with everolimus, laboratory abnormalities associated with temsirolimus therapy include anemia, hyperglycemia, hyperlipidemia, and thrombocytopenia; however, these occur at a much higher rate. If hyperglycemia develops, it may be necessary to initiate or increase the dose of insulin or oral hypoglycemic agent. Likewise, lipid-lowering agents may be indicated for hyperlipidemia (Wyeth Pharmaceuticals, 2008).

**Side-Effect Management**

The mTOR inhibitors everolimus and temsirolimus have similar side-effect profiles (see Table 2). Careful monitoring with agents from the mTOR class. Pneumonitis is a noninfectious, nonmalignant infiltration of the lungs that typically appears with a ground-glass appearance on x-ray. Although rare (less than 2% of cases with temsirolimus and 14% with everolimus), interstitial lung disease may interfere with activities of daily living and require oxygen administration (see Table 3). Grade 1 (asymptomatic) interstitial lung disease should be monitored closely with frequent radiographic and physical assessment. Dose interruptions, corticosteroids, and antibiotics may be required with grades 2 and 3. Some patients may require a dose reduction when restarting therapy.

Temsirolimus and everolimus are metabolized through the cytochrome P450 pathway (Novartis Pharmaceuticals, 2009; Mabasa & Ensom, 2005; Neuhaus, Klupp, & Langrehr, 2001; Wyeth Pharmaceuticals, 2008), making food-drug and drug-drug interactions an important consideration because of competition for the metabolic pathway. Foods and drugs that are strong and early interventions can minimize the severity of mTOR inhibitor side effects and improve treatment tolerability. One common side effect is oral mucositis, which often presents as ulcers on the tongue, inside the lips, or within the oral cavity (see Figure 2). Management strategies for oral mucositis and ulcers include avoiding harsh agents such as hydrogen peroxide, iodine, and thyme derivatives. Antifungal agents also should be avoided unless a fungal infection is diagnosed. Oral care with a soft toothbrush and mild toothpaste in addition to saline rinses should be initiated with mTOR inhibitor therapy. Broad-spectrum oral gels applied to the lesions (e.g., aphthous ulcers or canker sores, diffuse mucositis) prior to meals may reduce discomfort during eating (Alterio et al., 2007; Eilers, 2004).

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**Table 1. Laboratory Abnormalities Associated With Everolimus and Temsirolimus Therapy**

<table>
<thead>
<tr>
<th>ABNORMALITY</th>
<th>EVEROLIMUS ANY GRADE (%)</th>
<th>TEMSIROLIMUS ANY GRADE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>92</td>
<td>94</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>77</td>
<td>87</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>57</td>
<td>89</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>73</td>
<td>83</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>37</td>
<td>49</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>50</td>
<td>57</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>23</td>
<td>40</td>
</tr>
</tbody>
</table>

*Note. Laboratory abnormalities associated with temsirolimus therapy occur at a much higher rate than with everolimus therapy, underscoring the need for a comprehensive panel before infusion and close monitoring thereafter.*

*Note. Based on information from Novartis Pharmaceuticals, 2009; Wyeth Pharmaceuticals, 2008.*
CYP3A4 pathway inhibitors (a cytochrome P450 enzyme) may increase the mTOR drug levels; strong CYP3A4 pathway inducers may decrease mTOR drug levels (see Figure 3). Patients must be educated about the dangers of these interactions, which may significantly lower the efficacy or increase the toxicity of the prescribed treatment. In addition, patients should be instructed to inform the healthcare team of all medications they are taking, both prescribed and over-the-counter. In the event that concurrent medications are unavoidable, dose modifications should be considered (Novartis Pharmaceuticals; Wyeth Pharmaceuticals).

Dermatologic reactions ranging from mild rash to severe pruritic dermatitis may occur as a result of mTOR inhibitor therapy and are graded on a scale of 1–4 (see Figure 4 and Table 4). Monitoring and early intervention with topical moisturizers and powders may be effective for low-grade rashes. Patients also should be instructed to avoid hot water and harsh soaps that may dry the skin. Antihistamines may provide benefit for pruritic rashes. Dose interruptions may be required for severe (grade 3 or higher) rash until the rash improves (Hutson, Figlin, Kuhn, & Motzer, 2008).

Case Study

Mrs. P was a 62-year-old woman who was diagnosed with metastatic RCC. Her medical history included a primary right radical nephrectomy for a 10 cm clear cell tumor and venous tumor thrombus invading the inferior vena cava, a complication that affects 5%–10% of patients with RCC (National Comprehensive Cancer Network [NCCN], 2008). A radical nephrectomy was performed because of the size and location of the tumor. Pathology revealed spread to the ipsilateral adrenal gland and a poor nuclear histologic grade (Fuhrman grade 3).

Two months following the nephrectomy, a computed tomography (CT) scan of the chest, abdomen, and pelvis revealed signs of advanced disease: lesions in lymph nodes and lungs, as well as potential lesions (sub-centimeter) in the liver. In addition, Mrs. P had multiple poor prognostic risk factors, including a poor Karnofsky performance status (70%). She reported weight loss, fatigue, and shortness of breath during exertion. She also had a history of atrial fibrillation which was controlled, and a current left ventricular ejection fraction (assessed via echocardiogram) of 40% (normal is 50% or higher). A comprehensive laboratory workup revealed anemia (Hgb = 10 g/dl), lactate dehydrogenase (320 U/L), and creatinine levels (1.8 mg/dl). Baseline cholesterol, triglycerides, and phosphorus also were assessed and were within normal limits.

Multiple treatment options were considered and discussed with Mrs. P. High-dose interleukin-1 and sunitinib were ruled out because of her history of cardiac dysfunction (NCCN, 2008). Given her multiple poor prognostic risk factors and potential for improved overall survival, the oncologist chose to begin treatment with temsirolimus. Everolimus also was considered but not selected because the agent is indicated after failure of treatment with sunitinib or sorafenib (Motzer et al., 2008; NCCN; Novartis Pharmaceuticals, 2009).

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### Table 2. Adverse Events Associated With Everolimus and Temsirolimus Therapy

<table>
<thead>
<tr>
<th>ADVERSE EVENT</th>
<th>EVEROLIMUS ANY GRADE (%)</th>
<th>TEMSIROLIMUS ANY GRADE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia</td>
<td>25</td>
<td>32</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>24</td>
<td>28</td>
</tr>
<tr>
<td>Fatigue</td>
<td>31</td>
<td>-</td>
</tr>
<tr>
<td>Mucositis</td>
<td>19</td>
<td>41*</td>
</tr>
<tr>
<td>Nausea</td>
<td>26</td>
<td>37</td>
</tr>
<tr>
<td>Pneumonitis or pneumonia</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Rash</td>
<td>29</td>
<td>47</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>44</td>
<td>41*</td>
</tr>
</tbody>
</table>

* Includes aphthous stomatitis, glossitis, mouth ulceration, mucositis, and stomatitis

**Note.** The mammalian target of rapamycin inhibitors everolimus and temsirolimus have similar side-effect profiles.

**Note.** Based on information from Novartis Pharmaceuticals, 2009; Wyeth Pharmaceuticals, 2008.

### Table 3. Management of Interstitial Lung Disease

<table>
<thead>
<tr>
<th>GRADE</th>
<th>DESCRIPTION AND ACTION TAKEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Asymptomatic Monitor closely with frequent radiographic and physical assessment.</td>
</tr>
<tr>
<td>2–3</td>
<td>Symptomatic not interfering with activities of daily living (ADL) (grade 2) or interfering with ADL (grade 3) Dose interruption may be required. Corticosteroids and antibiotics may be indicated. Oxygen may be indicated. Dose reduction may be required at resumption of therapy.</td>
</tr>
</tbody>
</table>

**Note.** The response to interstitial lung disease depends on the disease grade. In the most severe cases, therapy should be withheld until resolution.

**Note.** Based on information from National Cancer Institute, 2003; Wyeth Pharmaceuticals, 2008.
CYP3A4 Inducers
- Dexamethasone (Decadron®)
- Omepazole (Prilosec®)
- Phenobarbital (Solfoton®)
- Phenytoin (Dilantin®)
- Rifampicin or rifampin (Rifadin®, Rimactane®)

Common CYP3A4 Inhibitors
- Atazanavir (Reyataz®)
- Ciprofloxacin (Cipro®, Ciflox®, Ciplox®)
- Clarithromycin (Biaxin®)
- Erythromycin (Erythromycin®, Ibstone®, E-Base®, E-Mycin®, E.E.S®, Ery-Tab®, ERYC®, EryPed®)
- Fluoxetine (Prozac®)
- Grapefruit or grapefruit juice
- Indinavir (Crixivan®)
- Itraconazole (Sporanox®)
- Ketoconazole (Nizoral®)
- Nefavodone (Serzone®)
- Nelfinavir (Viracept®)
- Norfloxacin (Noroxin®, Noroxicin®)
- Telithromycin (Ketek®)
- Troleandomycin (TAO®)
- Ritonavir (Norvir®)
- Saquinavir (Fortovase®, Invirase®)
- Verapamil (Calan®, Covera HS®, Isoptin®, Verelan®)
- Voriconazole (Vfend®)

Note. Mammalian target of rapamycin inhibitors are metabolized through the cytochrome P450 pathway. Patient education is, therefore, an integral component of the treatment plan so that patients are informed of potentially hazardous drug-drug and food-drug interactions.

Figure 3. CYP3A4 Food and Drug Interactions
Note. Based on information from Cupp & Tracy, 1998; Novartis Pharmaceuticals, 2009; Trubetskoy et al., 2005; Wyeth Pharmaceuticals, 2008.

Given the potential side effects associated with temsirolimus, parameters were evaluated in her preinfusion assessment: baseline pulmonary function because of the risk of interstitial lung disease (Wyeth Pharmaceuticals, 2008), CBC and chemistry analysis, baseline skin assessment including dermatologic history, and a review of all of the medications she was taking, including over-the-counter medications. In addition, a monitoring plan was devised: weekly CBC with differential, biweekly fasting cholesterol and triglyceride, and biweekly fasting chemistry panel (from the risk of hyperglycemia) and phosphorus if not included in panel. Coagulation panels also were ordered (Malizzia & Hsu, 2008).

During her second treatment, when she was 10 minutes into her weekly temsirolimus infusion, Mrs. P complained of flushing, chest tightness, and shortness of breath, which all are classic signs of HSRs. The infusion was immediately stopped; and, in accordance with institutional protocol, an H2 blocker was administered. On resolution of the HSR, the temsirolimus infusion was resumed but at a slower rate of over 60 minutes (Wyeth Pharmaceuticals, 2008). Mrs. P was able to complete her course of therapy because of the quick and decisive action of her oncology nurse at the earliest signs of distress. During cycle 5 of temsirolimus therapy, Mrs. P presented to the clinic with a grade 2 pruritic rash. Mrs. P had been avoiding hot water and using non-fragranced moisturizer. Her nurse practitioner prescribed a topical steroid cream and encouraged her to use a topical powder with menthol and zinc oxide. Mrs. P responded well to the intervention and was able to continue with therapy.

Conclusion
Agents that target the angiogenesis signal transduction pathway have been shown to be effective in the treatment of
metastatic RCC. The introduction of mTOR inhibitors has led to improved overall survival rates in this setting. However, as with any novel oncology therapy, nurses must have a working knowledge of appropriate side-effect management strategies to ensure that therapeutic goals are achieved.

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References


