

# Management of Key Adverse Events Associated With Everolimus Therapy



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## Introduction

An estimated 58,240 new cases of kidney cancer will be diagnosed in 2010 in the United States, resulting in an estimated 13,040 deaths.<sup>1</sup> Of all renal tumors, approximately 90% are renal cell carcinoma (RCC), and 85% of these are clear-cell tumors.<sup>2</sup> Approximately 25% of patients present with advanced disease, including locally invasive or metastatic RCC.<sup>3</sup> The overall 5-year survival rate for patients with kidney cancer of any stage between 1999 and 2005 was 68.4%, yet overall survival was only 10.4% among patients with metastatic disease, indicating a much poorer prognosis.<sup>4</sup>

Research during the past decade has increased our understanding of the molecular biology of RCC, and the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathways have emerged as key therapeutic targets.<sup>5</sup> These recent advances resulted in the development of new agents that either inhibit growth factors that drive angiogenesis or block their ability to stimulate cells. The availability of these novel targeted therapies has changed the standard of care for the treatment of metastatic RCC.

The multikinase inhibitor sunitinib (Sutent<sup>®</sup>, Pfizer)<sup>6</sup> inhibits the tyrosine kinase portion of the VEGF family of receptors and platelet-derived growth factor (PDGF) receptors.<sup>5</sup> Sunitinib received FDA approval for the treatment of metastatic RCC in 2006.<sup>7,8</sup> In 2 studies comparing sunitinib with interferon (IFN) as first-line therapy for metastatic RCC, sunitinib significantly prolonged progression-free survival (PFS) and overall survival (OS) by 11 vs 5 months and 26.4 vs 21.8 months, respectively.

Another multikinase inhibitor, sorafenib (Nexavar<sup>®</sup>; Bayer HealthCare Pharmaceuticals),<sup>9</sup> also inhibits the VEGF family of receptors as well as the intracellular signaling enzyme Raf kinase.<sup>5</sup> Approved in 2005, sorafenib extends PFS compared with placebo (5.5 vs 2.8 months)

in cytokine-refractory patients with advanced clear-cell RCC.<sup>10</sup>

A third multikinase inhibitor, pazopanib (Votrient<sup>®</sup>, GlaxoSmithKline), was approved in 2009 for the treatment of patients with advanced RCC.<sup>11</sup> Pazopanib inhibits the VEGF and PDGF receptor families and c-kit tyrosine kinases.<sup>12</sup> Pazopanib significantly prolongs PFS in treatment-naïve patients (11.1 vs 2.8 months) and in patients previously treated with a cytokine (7.4 vs 4.2 months) compared with placebo.<sup>13</sup>

Bevacizumab (Avastin<sup>®</sup>, Genentech)<sup>14</sup> is a humanized monoclonal antibody targeting VEGF<sup>15</sup> that was approved in 2009 for use with IFN in previously untreated patients with metastatic RCC. As a first-line therapy, bevacizumab plus IFN compared with placebo plus IFN significantly prolonged PFS (10.2 vs 5.4 months).<sup>15</sup>

Temsirolimus (Torisel<sup>®</sup>, Wyeth Pharmaceuticals), a prodrug of rapamycin formulated for intravenous administration,<sup>16</sup> is an mTOR inhibitor that has been shown to significantly prolong OS when compared with IFN alone (10.9 vs 7.3 months) in previously untreated patients with advanced RCC; it was approved in 2007.<sup>17</sup>

Despite these treatment advances, there was an unmet medical need for a therapy for patients with disease progression despite first-line therapy with a multikinase inhibitor. To address this need, everolimus (Afinitor<sup>®</sup>, Novartis Oncology) was investigated for the treatment of patients with advanced RCC after failure of treatment with sunitinib, sorafenib, or both,<sup>18</sup> and was approved for this indication in 2009. Everolimus is the first oral mTOR inhibitor for treatment of advanced RCC. The efficacy and safety profiles of everolimus are discussed in this review along with strategies to successfully manage adverse events.

## Everolimus: Mechanism of Action

The significance of the mTOR pathway in RCC and other types of cancer has been reviewed by others.<sup>19-21</sup> Briefly, mTOR is a serine/threonine kinase that senses mitogen, energy levels, and nutrients in cells and has been shown to regulate cell growth in response to various environmental stimuli, acting as a gatekeeper for cell cycle progression.<sup>19,22</sup> In cancer development and metastasis, mTOR activity may be increased by multiple

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signaling pathways,<sup>20</sup> resulting in increased transcription and translation of proteins involved in regulation of cell growth, cell cycle progression, and cellular metabolism.<sup>19</sup> Through the synthesis of hypoxia-inducible factor 1 (HIF-1), mTOR regulates the production of proteins involved in angiogenesis and other responses to further increase supplies of nutrients and energy required by the growing cell.<sup>20,21</sup> Everolimus is a highly specific and potent mTOR inhibitor that forms a complex with FKBP12, inhibiting the kinase activity of mTOR<sup>20</sup> and leading to decreased synthesis of tumor-promoting proteins and inhibition of downstream signaling involved in tumor growth and progression.

**Table 1. Selected Treatment-Emergent Adverse Events<sup>23</sup>**

Adverse event, %	Everolimus 10 mg/day (N = 274)			Placebo (N = 137)		
	All grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Stomatitis	44	4	< 1	8	0	0
Infections	37	7	3	18	1	0
Asthenia	33	3	< 1	23	4	0
Fatigue	31	5	0	27	3	< 1
Diarrhea	30	1	0	7	0	0
Cough	30	< 1	0	16	0	0
Rash	29	1	0	7	0	0
Nausea	26	1	0	19	0	0
Anorexia	25	1	0	14	< 1	0
Peripheral edema	25	< 1	0	8	< 1	0
Dyspnea	24	6	1	15	3	0
Vomiting	20	2	0	12	0	0
Pyrexia	20	< 1	0	9	0	0
Mucosal inflammation	19	1	0	1	0	0
Pneumonitis	14	4	0	0	0	0

### Efficacy of Everolimus in Advanced RCC

In a phase 3 randomized, double blind, placebo-controlled clinical trial (RECORD-1), everolimus was evaluated in patients with metastatic RCC whose disease had progressed following treatment with sunitinib, sorafenib, or both sequentially.<sup>18,23</sup> Pretreated patients with clear-cell RCC from 86 centers were enrolled and stratified by the number of previous treatments and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic risk group (favorable, intermediate, or poor). Patients were randomized 2:1 to everolimus 10 mg daily plus best supportive care (BSC) or placebo plus BSC, with treatment continued until disease progression, unacceptable toxicity, or death. Results were reported originally by Motzer and colleagues in the *Lancet* in 2008, with updated results published online in *Cancer* in June 2010.<sup>18,23</sup> Everolimus (n = 277) significantly improved PFS compared with placebo (n = 139): 4.9 months vs 1.9 months, respectively (hazard ratio=0.33; 95% confidence interval 0.25-0.43; *P* < .001).<sup>23</sup> A subset analysis of relevant patient subgroups (MSKCC risk score, number of previous VEGF receptor tyrosine kinase inhibitors received, age, sex, and geographic region) demonstrated improved PFS in all subgroups.<sup>18</sup>

### Management of Everolimus Adverse Events: The Nurse's Perspective

In the RECORD-1 study, everolimus generally was well tolerated with manageable adverse effects, and most adverse events observed with everolimus were grade 1

(mild) or 2 (moderate) in severity.<sup>24</sup> The most common treatment-emergent grade 3 (severe) or 4 (life-threatening) adverse events observed more frequently with everolimus than with placebo included stomatitis/mucositis, asthenia, fatigue, rash, infections, and noninfectious pneumonitis (**Table 1**).<sup>25</sup> In addition, grade 3 or 4 hyperglycemia, hypertriglyceridemia, and hypercholesterolemia were observed in a greater proportion of patients receiving everolimus than placebo (**Table 2**).<sup>25</sup> As asthenia/fatigue are common side effects of cancer and its treatments,<sup>26</sup> this review will focus on infections, stomatitis/mucositis, noninfectious pneumonitis, laboratory abnormalities, and rash. Each of these will be discussed in detail, along with a recommended management strategy from the nursing perspective (**Table 3**).<sup>27,28</sup>

Because everolimus is administered orally, patient education to promote early recognition and prompt reporting of adverse events with everolimus is important to optimize adherence to therapy and to improve patient outcomes. A complete patient history, including adverse events observed with any prior cancer therapies, is critical. In addition, given the potential for drug-drug interactions with everolimus, a thorough review of concomitant medications is recommended.

### Infections

Everolimus has immunosuppressive properties and may predispose patients to the development of infections, particularly those associated with opportunistic pathogens.<sup>25</sup> In the RECORD-1 trial, infections were reported

**Table 2. Key Laboratory Abnormalities<sup>23</sup>**

Parameter, %	Everolimus 10 mg/day (N = 274)			Placebo (N = 137)		
	All grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
<b>Hematology</b>						
Decreased hemoglobin	92	12	1	79	5	< 1
Decreased lymphocytes	51	16	2	28	5	0
Decreased platelets	23	1	0	2	0	< 1
Decreased neutrophils	14	0	< 1	4	0	0
<b>Clinical Chemistry</b>						
Increased cholesterol	77	4	0	35	0	0
Increased triglycerides	73	< 1	0	34	0	0
Increased glucose	57	15	< 1	25	1	0
Pneumonitis	14	4	0	0	0	0
Elevated creatinine	50	1	0	34	0	0

in 37% of patients receiving everolimus and 18% of patients receiving placebo, with grade 3 and 4 infections occurring in 10% of patients receiving everolimus and 1% of those receiving placebo. Localized and systemic infections, including pneumonia, other bacterial infections, and invasive fungal infections (eg, aspergillosis, candidiasis) have been observed with everolimus therapy. Patients should be educated about the increased risk of infection, reminded to be vigilant for signs and symptoms of infection, and encouraged to contact their oncology healthcare provider immediately if infection is suspected. In addition, treatment of pre-existing invasive fungal infections should be completed before initiating everolimus therapy. If an invasive systemic fungal infection occurs, everolimus should be promptly discontinued and appropriate antifungal therapy should be initiated.<sup>25</sup>

**Table 3** details the management strategy recommendations for various infections.<sup>27,28</sup> If an infection is identified, appropriate treatment should be provided and everolimus treatment should be interrupted until the infection is resolved. Patients should be counseled on the importance of adhering to anti-infective therapies for the full course of treatment. For grade 4 infection, discontinue everolimus treatment and immediately institute appropriate medical intervention. Supportive care should be maintained until complete resolution of the infection and adequate bone marrow recovery has occurred. Once the patient has recovered, everolimus may be re-started at the same dose or a reduced dosage of 5 mg once daily if clinically appropriate.

Everolimus has been associated with reactivation of both hepatitis B virus (HBV) and hepatitis C virus (HCV). In a phase 1 study of everolimus in patients with ad-

vanced hepatocellular cancer, hepatitis reactivation was observed in 5 of 27 (18%) and 1 of 15 (7%) patients who were seropositive for HBV and HCV, respectively.<sup>29</sup> Patients with known or suspected past HBV infection should begin prophylactic antiviral therapy approximately 1 to 2 weeks before starting everolimus and antiviral prophylaxis should be maintained throughout everolimus treatment and for at least 4 weeks after the last dose. Patients should be monitored every 4 to 8 weeks for viral reactivation. If clinical signs and symptoms of HBV reactivation occur during everolimus treatment, patients should begin antiviral therapy or receive a sec-

ond antiviral medication if already receiving prophylactic medication. Everolimus treatment should be interrupted until alanine transaminase elevations recover to grade  $\leq 1$  or to baseline, if grade  $>1$  at baseline, and hepatitis B DNA levels are no longer above baseline. Patients with HCV should be monitored every 4 to 8 weeks for viral reactivation; if reactivation occurs, everolimus should be discontinued.

### Stomatitis

Stomatitis is characterized by ulcerated areas in the oral cavity, on the inner surface of the lips, or on the tongue and may be associated with erythema, edema, a burning sensation, and sensitivity to spicy foods.<sup>30</sup> In RECORD-1, the overall incidence of stomatitis was 44% in patients who received everolimus; grade 3 stomatitis was observed in 4% of patients and grade 4 stomatitis in < 1% of patients.<sup>25</sup> Patients should be educated about the possibility of mouth ulcers, stomatitis, and oral mucositis and encouraged at treatment initiation to maintain good oral hygiene. A program to promote good oral hygiene should include regular oral examinations and patient education; a dental exam and cleaning should be done before the initiation of treatment if one has not been performed recently.<sup>31,32</sup> Oral assessments should be conducted during patient visits using an appropriate measurement scale such as the Oral Assessment Guide, the Oral Mucosa Rating Scale, or the Oral Mucositis Index.<sup>33</sup> In addition, the importance of regular tooth brushing, flossing, and use of oral rinses with 0.9% saline, sodium bicarbonate, or a saline and sodium bicarbonate mixture should be emphasized.<sup>31,32</sup> Patients should be advised to contact their healthcare provider at the onset of symptoms including discomfort, taste alter-

**Table 3. General Guidelines for Selected Everolimus-Related Adverse Events<sup>27</sup>**

	Grade 1			Grade 2			Grade 3			Grade 4		
	Symptoms <sup>a</sup>	Treatment	Dose Modification	Symptoms <sup>a</sup>	Treatment	Dose Modification	Symptoms <sup>a</sup>	Treatment	Dose Modification	Symptoms <sup>a</sup>	Treatment	Dose Modification
<b>Infection</b>	•Not defined	•No specific intervention	•No change	•Localized, local intervention indicated	•Standard local intervention	•Maintain dose if tolerable •if intolerable, hold dose until recovery to grade ≤1, then reintroduce at same dose •if event returns to grade 2, interrupt until recovery to grade ≤1, then reintroduce at a lower dose level •if dosing is interrupted for >21 days from intended date of next scheduled dose, discontinue treatment	•IV antibiotic, antifungal, or antiviral intervention indicated •Interventional radiology or operative intervention indicated	Standard local intervention	•Hold dose until recovery to grade ≤1, then reintroduce at lower dose level •if dosing is interrupted for > 21 days from intended date of next scheduled dose, discontinue treatment	•Life-threatening consequences <sup>d</sup>	•Standard local intervention	•Discontinue treatment
<b>Stomatitis/ Mucositis</b>	•Minimal symptoms, normal diet	•Rinse several times daily with nonalcoholic mouthwash or 0.9% salt water	•No change	•Symptomatic, but can eat and swallow modified diet	•Apply topical analgesic mouth treatments <sup>b</sup> •Topical corticosteroids <sup>c</sup>	•Maintain dose if toxicity is tolerable •if not tolerable, interrupt until toxicity grade ≤1 then reintroduce at the same dose	•Symptomatic and unable to adequately aliment or hydrate orally	•Avoid agents containing hydrogen peroxide, iodine, and thyme derivatives	•Interrupt until toxicity grade <1 then reintroduce at a lower dose	•Symptoms associated with life-threatening consequences	•Avoid anti-fungal agents unless a fungal infection is diagnosed; if fungal infection is diagnosed avoid all systemic imidazole antifungal agents <sup>e</sup> and apply topical antifungal agents	•Discontinue treatment

**Table 3. General Guidelines for Selected Everolimus-Related Adverse Events,<sup>27</sup> (continued)**

	Grade 1		Grade 2		Grade 3		Grade 4						
	Symptoms <sup>a</sup>	Treatment	Dose Modification	Symptoms <sup>a</sup>	Treatment	Dose Modification	Symptoms <sup>a</sup>	Treatment	Dose Modification				
<b>Noninfectious Pneumonitis</b>	•Asymptomatic, radiographic findings only	•No specific therapy	•No change	•Symptomatic, not interfering with ADL	•Consider corticosteroids	•Consider dose interruption/reduction •Restart at reduced dose when grade ≤ 1 then consider re-escalation •if no recovery to grade ≤ 1, discontinue treatment	•Symptomatic, interfering with ADL, O2 indicated	•Prescribe corticosteroids if infective origin is ruled out	•Hold treatment until recovery to grade ≤ 1 •May restart treatment within 2 weeks at a reduced dose (by one level) if evidence of clinical benefit	•Life-threatening; ventilatory support indicated	•Prescribe corticosteroids if infective origin is ruled out	Avoid anti-viral agents unless a viral infection is diagnosed	•Discontinue treatment

AD: Activities daily living.

<sup>a</sup>As defined by Common Terminology Criteria for Adverse Events (CTCAE v3.0).<sup>28</sup>

<sup>b</sup>Benzoic acid, butyl aminobenzoate, tetracaine hydrochloride menthol, or phenol.

<sup>c</sup>Triamcinolone oral paste 0.1% Kenalog® in Orabase®.

<sup>d</sup>Septic shock, hypotension, acidosis, or necrosis.

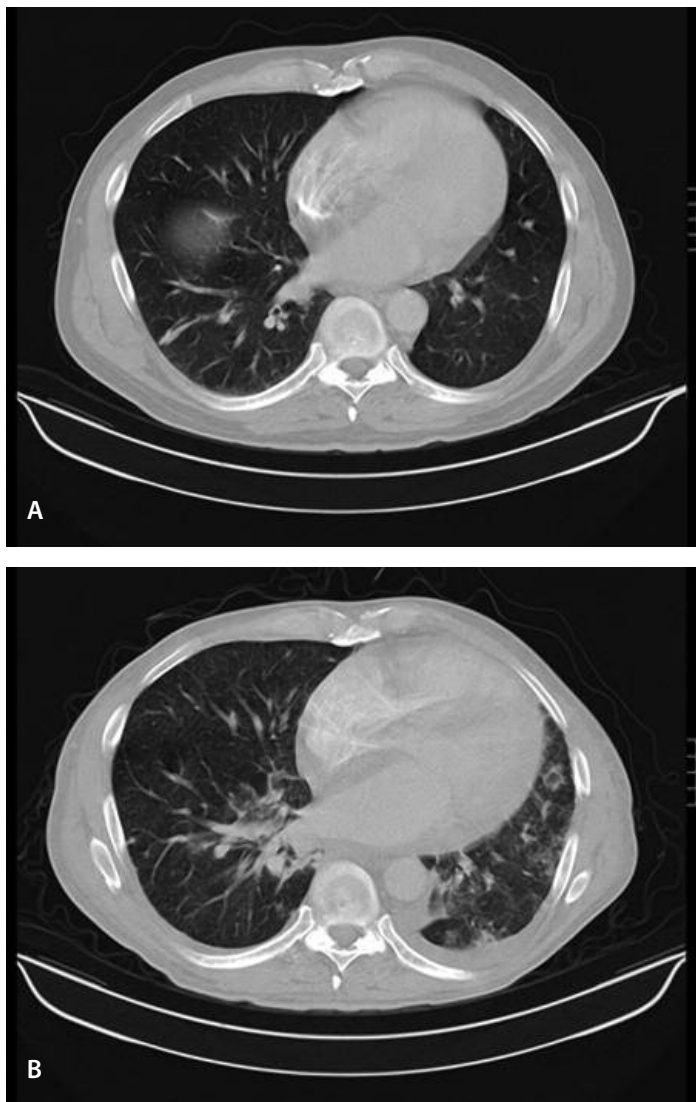
<sup>e</sup>Ketoconazole, fluconazole, itraconazole, etc.

ations, or the appearance of lesions. **Table 3** details the management strategy recommendations for stomatitis.<sup>27,28</sup> Adequate treatment with topical agents, such as analgesics, should be provided if grade 1 or 2 stomatitis is identified, and the use of alcohol or peroxide-containing mouthwashes should be avoided. If everolimus treatment is interrupted due to intolerable stomatitis symptoms, consider re-starting treatment with a reduced dose, if appropriate.

### Noninfectious Pneumonitis

Noninfectious pneumonitis, a class effect of rapamycin derivatives including everolimus, is a nonmalignant infiltration of the lungs that is evident radiologically and is usually nonsymptomatic (grade 1 or 2) and limited in extent. Most cases have been reversible upon drug discontinuation.<sup>18,34</sup> In RECORD-1, the incidence of noninfectious pneumonitis was 13.5% among patients receiving everolimus.<sup>34</sup> Most cases—9.9%—were grade 1 or 2, asymptomatic, or symptomatic but did not interfere with the activities of daily living). Grade 3 noninfectious pneumonitis occurred in 3.6% of patients causing interference with daily living or requiring oxygen therapy, and there were no reports of grade 4 cases. Noninfectious pneumonitis was resolved for 61% and 60% of patients with grade 2 and 3 events, respectively, upon everolimus dose reduction or interruption, or corticosteroid therapy.

Pneumonitis should be considered in patients presenting with cough or dyspnea with hypoxia or pleural effusion when other causes have been excluded. Radiographic changes indicative of grade 1 pneumonitis reported as “ground glass opacities,” “patchy opacities,” or “infiltrates,” may be observed on computed tomography scans in asymptomatic patients, as well as in symptomatic patients with grade 2, 3,



**Figure 1.** Pneumonitis computed tomography (CT) images. Courtesy of the Cleveland Clinic Taussig Cancer Institute, used with permission. **A:** Baseline CT scan demonstrates normal vasculature and lymph nodes with several small bilateral lung nodules. **B:** CT scan done following completion of the fourth cycle of everolimus demonstrates bilateral infiltrates consistent with pneumonitis.

or 4 pneumonitis (**Figure 1**). Patients with a history of pulmonary conditions should be carefully monitored and advised to promptly report any new or worsening respiratory symptoms.

**Table 3** details the management strategy recommendations for noninfectious pneumonitis.<sup>27,28</sup> Everolimus should be withheld in patients with evidence of moderate noninfectious pneumonitis until recovery to grade  $\leq 1$  and begin corticosteroid therapy if infectious causes have been excluded. Everolimus may be restarted within 2 weeks at a reduced dose if there is evidence of clinical benefit. If there is no recovery to grade  $\leq 1$  pneumonitis within 3 weeks, everolimus should be discontinued. Treatment discontinuation is recommended for cases of grade 4 noninfectious pneumonitis.<sup>25</sup>



**Figure 2.** An example of grade 3 skin rash associated with everolimus treatment. Courtesy of the City of Hope, used with permission.

### Rash

In RECORD-1, treatment-related rash was observed in 29% of patients receiving everolimus and was mostly grade 1 or 2 in severity.<sup>25</sup> An example of a grade 3 skin rash associated with everolimus treatment is shown in **Figure 2**. The patient had been receiving everolimus therapy for 12 weeks when he developed a skin rash covering approximately 50% of his body. He was evaluated

by a dermatologist, who treated the rash and pruritus with systemic corticosteroids. Discontinuation of everolimus was ordered by the medical oncologist. Additional supportive measures included tepid (not hot) baths with an oatmeal-based product added to the water, liberal application of moisturizers to the affected areas 3 to 4 times each day, and careful drying of the skin after bathing. The patient was able to resume everolimus treatment with a 50% dose reduction. Patients should be advised that skin rash is a possible adverse event associated with everolimus therapy and should be encouraged to report these symptoms promptly. Adequate treatment should be provided if grade 1 or 2 rash is identified; however, treatment with a systemic corticosteroid is not routinely recommended for management of everolimus-induced rash. If everolimus treatment is interrupted due to intolerable rash, resuming treatment at a reduced dose may be considered.

### Laboratory Abnormalities

**Table 2** details the key laboratory abnormalities that were reported at a higher rate in the everolimus arm than in the placebo arm of the RECORD-1 trial.<sup>25</sup> Decreased hemoglobin, lymphocytes, platelets, and neutrophils have been reported with everolimus therapy, therefore, complete blood count monitoring is recommended at baseline and periodically after treatment begins.<sup>25</sup> Thrombocytopenia should be treated with supportive care and everolimus dose reduction or interruption may be considered. Patients should be counseled to avoid aspirin, ibuprofen, or non-steroidal anti-inflammatory drugs with the exception of acetaminophen).<sup>35</sup>

In RECORD-1, increases in serum cholesterol and triglyceride levels were more frequent seen in the everolimus group than in the placebo group (77% vs 35% and 73% vs 34%, respectively); however, grade 3 and 4 increases were observed in 4% and < 1% of everolimus-treated patients, respectively.<sup>25</sup> In RECORD-1, grade 3 increases in serum glucose were observed in approximately 15% of patients receiving everolimus therapy versus 1% of those receiving placebo, and grade 4 events were observed in < 1% and 0%, respectively.<sup>25</sup> Therefore, serum glucose and lipid levels should be monitored at baseline and periodically after initiation of everolimus therapy. Hyperglycemia and hyperlipidemia should be treated using standard treatment guidelines.<sup>36,37</sup> Optimal glycemic and lipid control should be achieved before a patient starts receiving everolimus.<sup>25</sup>

Increased serum creatinine concentrations, usually mild, have been reported in patients treated with everolimus and assessing renal function with blood urea nitrogen or serum creatinine measurements before beginning therapy and periodically thereafter is recommended.<sup>25</sup>

Nurses should pay careful attention to patients with pre-existing diabetes or a history of elevated lipids during the course of everolimus therapy and play an important role in communicating any symptom changes such

as increased thirst or more frequent urination that could indicate an elevated glucose level to the physician. In addition, physicians should be notified of increases in lipid levels, and dosages of lipid-lowering agents should be modified accordingly.

### Drug Interactions, Vaccines, and Special Populations

Patients should be advised to inform their health care providers of all prescription drugs, nonprescription drugs, and dietary supplements they are taking before beginning everolimus therapy and to inform all health-care providers that they are receiving everolimus therapy. Everolimus is a substrate of cytochrome P450 (CYP) 3A4 and P-glycoprotein (PgP) and is a mixed inhibitor of CYP2D6.<sup>25</sup> **Table 4** provides a list of clinically relevant agents that may alter everolimus concentrations during coadministration.<sup>25</sup> Due to significant increases in everolimus serum concentrations, coadministration with strong or moderate inhibitors of CYP3A4 or PgP should be avoided. In addition, while taking everolimus, patients should be advised to avoid grapefruit and grapefruit juice, as well as star fruit and star fruit juice<sup>38</sup>, which are CYP3A4 inhibitors that can lead to increased serum concentrations of everolimus. For patients who require co-administration of a strong CYP3A4 inducer, consider increasing the everolimus dose from 10 mg daily to 20 mg daily, using 5-mg increments. If the inducer is discontinued, everolimus dose should be returned to the dose used before initiation of the inducer.

Patients should be advised to avoid receiving live vaccines and close contact with those who have recently received live vaccines during everolimus therapy.<sup>25</sup>

There are no adequate and well-controlled studies of everolimus use in pregnant women (Pregnancy Category D). However, because of its mechanism of action, everolimus may cause fetal harm when administered to a pregnant woman.<sup>25</sup> If everolimus is used during pregnancy or if pregnancy occurs during treatment, the patient should be advised of the potential hazard to the fetus. An effective method of contraception is recommended while receiving everolimus and for up to 8 weeks after ending treatment in women of childbearing potential.

For patients with moderate hepatic impairment (Child-Pugh class B), the starting dose for everolimus should be 5 mg daily. Use of everolimus by patients with severe hepatic impairment (Child-Pugh class C) has not been assessed and is not recommended.<sup>25</sup>

### Adherence to Oral Cancer Therapies

The availability of more oral agents for the treatment of cancer is creating a new paradigm, with the need for new patient management strategies to optimize the efficacy and safety of these therapies. It is estimated that treatment adherence averages only 50% in patients with chronic illnesses.<sup>39</sup> Because patients perceive cancer as a life-threatening and serious disease, higher rates of adherence are expected. Potential consequences of nonad-

**Table 4. Clinically Relevant Drug Interactions That May Occur During Co-Administration With Everolimus<sup>25</sup>**

<b>Inhibitors That May Increase Everolimus Blood Concentrations<sup>a</sup></b>	
Antibiotics	Erythromycin Clarithromycin Telithromycin
Antidepressant	Nefazodone
Antiemetic	Aprepitant
Antifungals	Fluconazole Itraconazole Ketoconazole Voriconazole
Calcium channel blockers	Diltiazem Verapamil
HIV protease inhibitors	Amprenavir Atazanavir Fosamprenavir Indinavir Nelfinavir Ritonavir Saquinavir
Reverse transcriptase inhibitor	Delavirdine
Miscellaneous	Grapefruit juice
<b>Inducers That May Decrease Everolimus Blood Concentrations<sup>b</sup></b>	
Antibiotics	Rifabutin Rifampin
Anticonvulsants	Carbamazepine Phenobarbital Phenytoin
Steroid hormone	Dexamethasone

<sup>a</sup>Due to significant increases in exposure of everolimus, co-administration with strong or moderate inhibitors of CYP3A4 or Pgp should be avoided.  
<sup>b</sup>If patients require co-administration of a strong CYP3A4 inducer, consider increasing the everolimus dose from 10 mg daily to 20 mg daily, using 5-mg increments. If the strong inducer is discontinued, the everolimus dose should be returned to the dose used before initiation of the strong CYP3A4 inducer.

herence to cancer therapy are treatment resistance, progressive disease, and death.<sup>40</sup>

It is critical that healthcare providers regularly reinforce the importance of treatment adherence. Patients should be advised that even if their condition is improving and symptoms are no longer a reminder of the disease, the disease still lingers.<sup>40</sup> For some patients, keeping track of the frequency, cycle, and dose of an oral agent may be especially difficult. In addition, patients may underestimate the risks associated with oral chemotherapy and risk over-adherence that may lead to toxicity or skipped doses causing inferior outcomes. A patient diary or reminder sheet is an effective tool to promote adherence and safe administration of oral chemotherapy.

Adherence to oral cancer therapies is difficult to monitor, particularly when long-term treatment is required and the patient may not have frequent, routine clinic visits. Healthcare providers should ensure proper patient education and contact patients periodically by telephone to assess adherence to oral therapy and monitor for potential adverse events.<sup>41</sup> Oncology nurses are in an ideal position to provide individualized patient support during oral chemotherapy.<sup>42</sup> Treatment adherence is directly influenced by the amount and quality of patient education and the quality of the patient's support system.<sup>42</sup> It is critical to discuss the expected adverse events associated with the therapy, particularly those with the potential to cause the greatest harm. Oncology nurses can help distinguish symptoms that can be self-managed from those that require medical attention and advise patients and their family members or caregivers accordingly. Enhancing communication between the healthcare provider and the patient is an effective strategy in improving adherence.<sup>39</sup>

### **Patient Involvement in Everolimus Therapy**

Because everolimus is orally administered, patient management strategies differ from those for intravenously administered anticancer agents. Intravenously administered anticancer agents require a visit to a health care provider for drug administration, which allows for regular communication between the health care provider and the patient regarding physical status and observed adverse events.<sup>41</sup> With oral everolimus, patients should be educated on how to recognize potential adverse events and are encouraged to report adverse effects to the health care provider as soon as possible. Patients should be educated on the importance of attending all follow-up visits and providing a calendar that lists follow-up visits is one potential tool to encourage adherence.

Patients should be encouraged to fill all prescriptions at the same pharmacy and to inform all healthcare providers of concurrent medications and dietary supplements. In addition, patients should be advised to inform all healthcare providers that they are receiving everolimus before beginning any new medication or receiving a new vaccine.

### **Summary**

Keeping current with new therapies for cancer treatment is an ongoing task for oncology nurses today. Everolimus represents a new mTOR therapy for the treatment of advanced kidney cancer. The administration of an oral cancer treatment can present new challenges for patients and their families. Oncology nurses are continually at the forefront of evaluating new ways to assist patients in controlling treatment side effects. Often, the time spent educating patients about what to expect with these new medications is inadequate, making the transition to oral therapies more difficult and frightening than it has to be. Knowledge of drug class and mechanism of

action are critical for appropriate and effective patient education and for nursing assessment and management of treatment-related side effects.

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