

# Management of mTOR Inhibitor Side Effects

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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.

**R**enal 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

### 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.

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

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