CHAPTER 6
Managing Side Effects of mTOR Inhibitors

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Managing Side Effects of mTOR Inhibitors (Temsirolimus)

The mammalian target of rapamycin (mTOR) is a serine-threonine kinase that is active in cell division, growth, proliferation, resistance to hypoxic stress, and apoptosis. Abnormalities in the mTOR signaling pathway have been implicated in various pathologies, including renal cancer.

Temsirolimus, an ester analog of rapamycin, inhibits downstream mTOR signaling by binding to an intracellular protein, FKBP-12. The resulting complex arrests the growth of tumor cells. Temsirolimus also inhibits tumor angiogenisis by reducing synthesis of vascular endothelial growth factor.

Current and Future Uses

In 2007, the FDA approved temsirolimus for treatment of advanced renal cell carcinoma (RCC). 
- Recommended dosage is 25 mg infused over 30 to 60 minutes once a week, until disease progression or unacceptable toxicity
  - The risk of serious adverse events is increased with doses >25 mg
- To avoid potential hypersensitivity reactions (see page 6), administer prophylactic H₁ antihistamine (diphenhydramine 25–50 mg or similar antihistamine) approximately 30 minutes before each dose
- Hold temsirolimus for absolute neutrophil count (ANC) <1000 mm³, platelet count <75,000/mm³, or in the event of serious adverse events (grade 3 or higher). When toxicities are reduced to grade 2 or lower, administration of temsirolimus may be resumed with dosage reduced by 5 mg/week to a dose no lower than 15 mg/week

More than 70 clinical trials are in progress investigating the efficacy of temsirolimus in the treatment of a variety of other cancers, including colorectal cancer, multiple myeloma, lymphoma, leukemia, endometrial cancer, breast cancer, prostate cancer, brain cancer, and ovarian cancer.

Side Effects

Common side effects associated with temsirolimus include
- Rash (maculopapular)
- Asthenia/fatigue
- Mucositis/stomatitis
- Nausea
- Edema
- Anorexia
Potentially serious side effects associated with temsirolimus include¹,⁵,⁸

- Metabolic/hematologic abnormalities
- Infection
- Hypersensitivity reactions
- Pulmonary toxicities
- Gastrointestinal perforation
- Wound-healing complications
- Cerebral hemorrhage
- Renal failure

Side effects are graded on a scale of 1 to 4 according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events.

Managing Selected Side Effects

**Metabolic/Hematologic Abnormalities**

Laboratory abnormalities are to be expected with administration of temsirolimus because of the role mTOR plays in glucose and lipid metabolism.⁸,⁹ In fact, one study has suggested that such abnormalities may be indicative of successful mTOR inhibition and, thus, correlate with clinical efficacy.⁸ Temsirolimus-related laboratory abnormalities may exacerbate existing laboratory abnormalities common in patients with RCC.¹ In a phase III trial comparing temsirolimus with interferon, at least one elevated serum glucose level was recorded in 89% of patients treated with temsirolimus, and hyperglycemia was recorded as an adverse event in 26% of temsirolimus-treated patients.⁵ In the same trial, 87% of patients in the temsirolimus group had at least one elevated serum cholesterol value, and 83% had at least one elevated serum triglyceride value.⁵

Sometimes serious metabolic/hematologic abnormalities reported in temsirolimus trials include¹,⁵,⁸

- Hyperglycemia/glucose intolerance
- Hyperlipemia
- Hypertriglyceridemia
- Lymphopenia
- Leukopenia
- Anemia
- Neutropenia
- Hypophosphatemia
- Thrombocytopenia
- Elevated serum creatinine
- Elevated alkaline phosphatase/aspartate aminotransferase (AST)
To manage metabolic/hematologic abnormalities in patients treated with temsirolimus

- Monitor metabolic/hematologic levels before and during treatment. The following schedule is recommended, with increases or decreases in frequency as indicated by results and by the requirements of individual patients:
  - Weekly complete blood count with differential
  - Biweekly fasting lipid panel
  - Biweekly fasting chemistry or electrolytes
  - Biweekly coagulation test for patients taking anticoagulants

- Administer cholesterol-lowering agents (eg, statins) and/or glucose-lowering agents based on results of monitoring. Be aware of potential drug interactions. (See page 8.)

- To address concerns regarding glucose levels
  - Consider treatment of grade 2 hyperglycemia (fasting glucose >160–250 mg/dL) to prevent need for dose delay or reduction
  - For hyperglycemic patients, consider initiation or increase of insulin and/or an oral hyperglycemic agent. Oral hyperglycemic agents vary according to mechanism of action, side-effect profile, and cost. Appropriate treatment depends on the patient’s renal and hepatic function, weight, comorbid conditions, and medications
  - Suspend treatment for grade 3 or 4 side effects. Once toxicities resolve to grade 2 or lower, restart therapy at a dose reduced by 5 mg/week (minimum total dose of 15 mg/week)
  - Educate patients being treated with temsirolimus regarding the increased risk of hyperglycemia and advise them to be alert for the appearance of common symptoms (eg, increased urination, increased thirst). Advise patients to alert their clinicians if symptoms appear
  - Advise patients at particular risk of hyperglycemia of dietary modifications that can help prevent or ameliorate symptoms
    - Refer patients to resources for dietary information, such as the “Making Healthy Food Choices” web page of the American Diabetes Association

- To address concerns regarding blood lipids
  - Initiate statins based on the lipid profile results
  - Cholesterol level >400 mg/dL represents grade 3 hyperlipidemia
    - Suspend treatment for grade 3 or 4 side effects. Once toxicities resolve to grade 2 or lower, restart therapy at a dose reduced by 5 mg/week (minimum total dose of 15 mg/week)
For management of myelosuppression

- In a phase III clinical trial, complete blood counts (CBC) were measured weekly. Monitoring of CBCs may need to be done more or less often at the physician’s discretion.\(^5\)
- Advise neutropenic patients of infection-prevention methods (eg, hand washing).\(^11\) (See Infection below)
- Consider transfusion or initiation of erythropoietic proteins when necessary to manage anemia.\(^1,11\)
  - One study suggests initiation of erythropoietic proteins at hemoglobin levels of 9 to 11 g/dL.\(^11\) Carefully evaluate risks and benefits of erythropoiesis stimulating agents (ESAs) in relation to severity of anemia and other comorbidities.\(^13\)
  - The same study recommends transfusion when patients are symptomatic or when hemoglobin level is <9 g/dL, with a target of 12 to 13 g/dL.\(^11\)
- Review CBC and assess risk of bleeding based on platelet count. Institute platelet precautions if platelet count <20,000/mm\(^3\).\(^14\)
- Educate patient and family concerning platelet precautions.\(^14\)
  - Advise patients at risk of thrombocytopenia to avoid aspirin, ibuprofen, or nonsteroidal anti-inflammatory medications.\(^11\) Use acetaminophen if needed
  - Advise patients of precautionary measures (eg, avoiding bruises, cuts).\(^11\)
- Institute bowel regimen when necessary to prevent constipation.\(^14\)
- Transfuse platelets as indicated.\(^14\)

**Infection**

Because temsirolimus may have an immunosuppressive effect, patients may be especially vulnerable to opportunistic infection (eg, herpes simplex, urinary tract infection, upper respiratory tract infection).\(^5,15\)

- Advise patients of the risk of increased infections, and ask them to alert clinicians if symptoms occur.\(^5\)
- Educate patients and their families regarding neutropenia precautions. Note that common infectious symptoms, such as pus or productive cough, may not be present
- Ensure that patients and their family members know whom to contact if temperature rises above predetermined parameters (>100.4°F for more than 1 hour or one-time temperature of 101°F).\(^16\)
- Monitor patients for opportunistic infections and treat as necessary.\(^5\)
  - As for all side effects, institute dose-reduction strategies noted above for grade 3 or higher events,\(^5\) when events fail to resolve with medical or supportive care.\(^1\)
- Avoid use of live vaccines (eg, intranasal influenza, measles, mumps, rubella, oral polio, bacillus Calmette-Guérin, yellow fever, varicella, TY21a typhoid) and close contact with those who have received live vaccines.\(^5\)
Hypersensitivity Reaction

In a phase III trial of temsirolimus in the treatment of advanced renal cell carcinoma, hypersensitivity/infusion reactions were observed in 9% of patients.\textsuperscript{5} Reported reactions included headache, chills, fever, flushing, wheezing, anaphylaxis, dyspnea, and chest pain.\textsuperscript{5,10}

To manage potential hypersensitivity reactions

- Follow recommendations in dosing section (page 2) regarding pre-infusion prophylactic administration of an H\textsubscript{1} antihistamine,\textsuperscript{5} and be prepared to manage such reactions should they occur
  - Infuse temsirolimus with caution when pretreatment with antihistamine is unadvisable due to allergy or other reasons\textsuperscript{10}
- Advise patients that allergic reactions have occurred with temsirolimus infusions. Ask patients to alert attending clinicians if they have difficulty breathing or observe facial swelling\textsuperscript{5}
- Take vital signs (pulse, blood pressure, body temperature) prior to infusion to establish a baseline for potential fever and hypotensive reactions\textsuperscript{10}
- If hypersensitivity reaction occurs
  - Stop temsirolimus infusion and monitor patient for 30 to 60 minutes or until reaction is resolved\textsuperscript{5}
  - Initiate appropriate intervention(s) if needed: fluids, epinephrine, corticosteroids, diphenhydramine, bronchodilators, and/or oxygen\textsuperscript{10}
  - After a mild to moderate hypersensitivity reaction, infusion may be resumed\textsuperscript{5}
    - At physician discretion
    - After administration of an H\textsubscript{1}-receptor antagonist (eg, diphenhydramine), if one was not used prior to reaction, and/or administration of an H\textsubscript{2}-receptor antagonist (eg, 1V famotidine 20 mg or 1V ranitidine 50 mg), approximately 30 minutes prior to resumed infusion
    - At a reduced rate, given over 60 minutes
  - If a severe hypersensitivity reaction occurs, stop the infusion immediately and do not resume\textsuperscript{10}

Pulmonary Toxicities

Rare but potentially fatal instances of interstitial lung disease (ILD)/pneumonitis have been associated with administration of temsirolimus.\textsuperscript{1,5} Symptoms may include dyspnea, cough, hypoxia, and fever; however, some patients diagnosed with ILD were asymptomatic.\textsuperscript{5} To manage potential lung toxicities

- Advise patients of the risk of ILD, and ask them to report new or worsening respiratory symptoms to their clinicians\textsuperscript{5,10}
- Monitor for symptoms of ILD. When symptoms are detected, follow up with computed tomography scan or chest x-ray
Pneumonitis is often described as having a “ground-glass” opacity on chest x-ray\textsuperscript{1,10}. Patients with ILD are likely to display a decrease in diffusing capacity of the lung to carbon monoxide measurement on pulmonary function tests\textsuperscript{1}.

Consider treating symptomatic lung toxicities with corticosteroids or antibiotics.\textsuperscript{1,5,17} Interruption of temsirolimus treatment and/or dose reductions may also be required.\textsuperscript{1,5}

- Asymptomatic patients who demonstrate radiologic changes may continue temsirolimus treatment without intervention at physician discretion\textsuperscript{1}.

**Gastrointestinal Perforation**

Incidents of bowel or intestinal perforation have occurred with administration of temsirolimus.\textsuperscript{5,17} Symptoms may include fever, metabolic acidosis, bloody stools, diarrhea, and/or acute abdominal pain.\textsuperscript{5,17}

To manage potential cases of gastrointestinal perforation\textsuperscript{5}:

- Monitor patients for symptoms, and intervene when present.
- Ask patients to promptly report abdominal symptoms, such as abdominal pain, nausea/vomiting, constipation, or bloody stools, to their clinicians. GI perforations are managed surgically, so immediate notification when symptoms arise is imperative.
- If emergent surgical intervention is needed, notify the surgical team of the potential for wound-healing complications.

**Wound-Healing Complications**

Wound-healing complications have been reported in patients being treated with temsirolimus.\textsuperscript{5}

To manage potential wound-healing complications:

- Discontinue treatment 2 to 4 weeks before surgery and for 1 to 2 weeks after surgery\textsuperscript{11}.
- Monitor patients after surgery for signs of delayed healing or infection.
- Assess the patient’s nutritional status. Treatment-related side effects, such as anorexia, mucositis, nausea, and fatigue, can compromise the patient’s nutritional status further, delaying the wound-healing process.
Renal Failure
Rapidly progressing acute renal failure, sometimes resulting in death, has been reported in patients taking temsirolimus. Some of these cases did not respond to dialysis. For example, in one study among 416 patients treated with temsirolimus for RCC, five patients experienced acute kidney failure, with one fatality. Clinicians should monitor creatinine when biweekly chemistries are drawn.

Drug Interactions
Temsirolimus is metabolized primarily by the CYP3A4 enzyme. Therefore co-administration with strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole, grapefruit juice) may increase plasma concentrations and toxicities of temsirolimus and should be avoided. If co-administration with strong CYP3A4 inhibitors is necessary, consider reduction of temsirolimus dosage to 12.5 mg/week.

Similarly, co-administration with strong CYP34A inducers (eg, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifampicin, phenobarbital) may decrease plasma concentrations of temsirolimus and should be avoided. If co-administration is unavoidable, consider doubling the recommended weekly dosage of temsirolimus from 25 mg to 50 mg. (For more on inducers and inhibitors of CYP450 enzymes, please see the Appendix.)

In an early clinical trial, co-administration with sunitinib resulted in dose-limiting toxicities (eg, grade 3 or 4 erythematous maculopapular rash, gout/cellulitis requiring hospitalization).

Special Populations
Temsirolimus may harm fetal development and should not be used during pregnancy. Animal studies have also demonstrated deleterious impact on male fertility. Use of contraception is advised during treatment. The risk of temsirolimus for nursing infants is unknown, but the drug’s active metabolite, sirolimus, has demonstrated tumorigenicity. Research has not established the safety of temsirolimus administration in pediatric patients. Response characteristics of geriatric patients to temsirolimus relative to those of younger patients are also unknown.
References


