Managing Stomatitis in Patients Treated With Mammalian Target of Rapamycin Inhibitors

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Mammalian target of rapamycin (mTOR) inhibitors are a class of targeted cancer therapeutic agents with clinical benefit for multiple tumor types. Oral ulcerations are a common side effect of mTOR inhibitors; however, the clinical findings resemble aphthous stomatitis rather than the mucositis seen with chemotherapy. Consequently, the appearance of aphthous-like oral ulcerations has been referred to as mTOR inhibitor-associated stomatitis (mIAS). The severity of mIAS can be minimized by following common preventive steps and initiating treatment at the first sign of mouth discomfort, thereby reducing the likelihood of treatment discontinuation. mIAS can be managed through prophylactic measures, such as patient education in oral hygiene and avoidance of triggers. Patients who develop mIAS may be treated topically using rinses or other local therapies, including corticosteroids. In severe cases, dose modifications may be required. Oncology nurses have an important role in the management of patients with cancer and are well positioned to offer strategies for minimizing the occurrence and impact of mIAS.

At a Glance

- Stomatitis commonly occurs during treatment with mammalian target of rapamycin (mTOR) inhibitors; the ulcers resemble canker sores rather than chemotherapy-induced mucositis.

- Steps that may be taken to minimize mTOR inhibitor-associated stomatitis (mIAS) include good oral hygiene; avoiding spicy, acidic, hard, and hot foods and beverages; using mildly flavored toothpaste; and cleansing with baking soda rinses.

- Treatment of mIAS may include specific medications, palliative interventions, and dose modifications.
chemotherapy regimens and is a well-recognized DLT. Mucositis associated with standard cytoreductive agents presents clinically as nonspecific ulceration for which localized palliative treatments and systemic analgesics are the standard of care. Oral ulcers that develop secondary to mTOR inhibitors, although technically referred to as mucositis according to the National Cancer Institute Common Terminology Criteria for Adverse Events, more often have a distinct presentation that clinically mimics aphthous stomatitis (commonly called canker sores) (Sonis, Treister, Chawla, Demetri, & Haluska, 2010) (see Figure 1). As a result, those terms have been used interchangeably to describe mTOR inhibitor-associated mouth ulcers in patients with cancer (Raymond et al., 2004; Sonis et al., 2010). The lack of a clear definition of mTOR inhibitor-associated oral lesions has created confusion as to the optimal course of their prevention and treatment.

Recent observations have shown that inflammation of the oral mucosa associated with mTOR inhibitor use in patients with cancer is distinct from conventional mucositis and seems to have a different underlying pathoetiology (Sonis et al., 2010). These oral ulcerations are referred to more accurately as mTOR inhibitor-associated stomatitis (mIAS) for their closer similarity to canker sores or recurrent aphthous stomatitis (Scully, 2006; Sonis et al., 2010). mIAS ulcers are distinguished from lesions of viral etiology based on their localization to the nonkeratinized moveable oral and oropharynx mucosa, as opposed to the mucosa of the palate, gingival, or dorsal tongue surface (Sonis et al., 2010). In the solid organ transplantation literature, mTOR inhibitor treatment has been associated with aphthous-like oral lesions (Mahé et al., 2005). Experience with mTOR inhibitors, derived from organ transplantation studies, has helped guide management approaches for mIAS in patients with cancer, but the benefit of these measures has not been investigated formally in clinical trials. mIAS generally is manageable and reversible, allowing patients to continue with mTOR inhibitor therapy. Being at the forefront of cancer care, oncology nurses are in a position to educate patients about the potential for developing mIAS and to offer strategies for preventing and treating this side effect. This article briefly reviews the role of mTOR inhibitors in cancer therapy and focuses on the characteristics and management of mIAS.

**Mammalian Target of Rapamycin in Cancer and Cancer Treatment**

mTOR is a serine or threonine kinase that has a key role in integrating intracellular signals necessary for cell growth, proliferation, metabolism, and survival (Bjornsti & Houghton, 2004; Shaw & Cantley, 2006; Yuan, Kay, Berg, & Lebwohl, 2009). Numerous pathways regulated by a range of cellular signals, including growth factors, hormones, nutrients, cellular energy levels, and stress, converge on mTOR. Specifically, mTOR is a downstream effector of the PI3K/Akt pathway, a principal pathway commonly dysregulated in many major malignancies, including colorectal, lung, and breast cancers (Chittnis, Yuen, Protheroe, Pollak, & Macaulay, 2008; Hsieh & Moasser, 2007). Signaling through the PI3K/Akt pathway is activated by several upstream cell-surface receptors known to be upregulated in tumor cells, such as estrogen and progesterone receptors, human epidermal growth factor receptor, and epithelial growth factor receptor (Carraway & Hidalgo, 2004). Aberrations in those pathways can result in the abnormal activation of proteins that lead to malignant transformation, such as cyclin D1, a key cell-cycle regulator, and hypoxia-inducible factors, which stimulate expression of angiogenic growth factors (Yuan et al., 2009) (see Figure 2).

The key role of mTOR in several signaling pathways involved in cancer-related processes makes it a desirable therapeutic target in oncology. Two mTOR inhibitors, temsirolimus (Torisel®) and everolimus (Afinitor®), have been approved for use in the treatment of renal cell carcinoma. Another mTOR inhibitor, ridaforolimus (AP23573/MK-8669, formerly deforolimus), is undergoing phase III evaluation for use as maintenance therapy in patients with metastatic soft-tissue or bone sarcomas who have had a favorable response to chemotherapy (National Institutes of Health, 2011).

**Stomatitis With Mammalian Target of Rapamycin Inhibitors**

mIAS is described as a common side effect in organ transplantation recipients undergoing immunosuppressive treatment with mTOR inhibitors (MacDonald, 2001; Mahé et al., 2005; van Gelder, ter Meulen, Hené, Weimar, & Hoitsma, 2003; Warino & Libecco, 2006). In two clinical trials, aphthous ulcerations were reported at rates of up to 60% among transplantation recipients receiving the mTOR inhibitor sirolimus (Mahé et al., 2005; van Gelder et al., 2003). In addition, those ulcers led to dose reduction or discontinuation of sirolimus in transplantation recipients. Nevertheless, clinical experience from the organ transplantation field shows that mIAS can be treated effectively, allowing patients to continue with their treatment. For example, in Chuang and Langone (2007), the use of clobetasol cream, a high-potency topical corticosteroid, resulted in early resolution of symptoms and allowed continuation of sirolimus treatment. Dose modifications also may alleviate these symptoms, as suggested by the observation that sirolimus-associated aphthous ulcerations increase in a dose-dependent manner in transplantation recipients (Chuang & Langone, 2007). Similarly, mIAS has been reported to increase in a dose-dependent manner in patients.
were treated with temsirolimus (25–250 mg/week) in a phase I trial of patients with refractory malignancies. Aphthous-like mouth ulcers were the DLT for each schedule and were reversible with dose reduction or symptomatic therapy. A dose of 40 mg once daily for five days followed by a two-day rest period was selected for additional clinical development based on its efficacy, safety, and pharmacokinetic profiles. At that dose level, no grade 3 mouth sores were reported in the trial (Mita, Britten, et al., 2008).

Characterization of Mammalian Target of Rapamycin Inhibitor-Associated Stomatitis

mIAS seen with mTOR inhibitor therapy is consistent among sirolimus, temsirolimus, everolimus, and ridaforolimus (Mita, Mita, et al., 2008; Motzer et al., 2008; Raymond et al., 2004; Sonis et al., 2010). Sonis et al. (2010) published a preliminary characterization of mIAS lesions, using pooled data on oral events

Figure 2. Simplified mTOR Pathway Demonstrating Upstream Activation and Inhibitory Signals and Downstream Effects Mediated via mTOR

observed in two phase I studies of patients receiving ridaforolimus. Patients who developed mIAS presented with lesions that typically were discrete, ovoid, superficial, aphthous-like ulcers with grayish-white pseudomembranes and well-demarcated erythematous borders. Most lesions measured less than or equal to 1 cm in their greatest dimension and were associated with mouth pain. In some cases, the lesions appeared in a clustered distribution, similar to that seen in patients with herpetiform aphthous ulcers (not to be confused with herpes simplex virus), or as larger lesions, similar to those seen in patients with major aphthous stomatitis. mIAS lesions normally develop on nonkeratinized movable mucosa, including the inner lip, ventral and lateral tongue surfaces, and soft palate, but not on keratinized mucosal surfaces such as the palate, gingiva, or tongue dorsum. Mouth sores resulting from treatment with mTOR inhibitors have an acute onset; mIAS lesions observed in the phase I trials with ridaforolimus usually developed within five days of starting treatment, and then, in most cases, healed spontaneously without scarring during regularly scheduled treatment holidays (i.e., two-day period without treatment) or following dose reductions or delays (Sonis et al., 2010).

Mouth lesions seen with mTOR inhibitors generally differ from the mucositis commonly encountered with cytotoxic chemotherapy in terms of their clinical appearance and their association with other mouth-related and dermatologic toxicities (see Figure 3). Unlike the aphthous-like lesions seen with mTOR inhibition, mucositis observed with chemotherapy is characterized by irregularly shaped lesions that typically lack peripheral erythema. In addition, mucositis associated with cytotoxic therapy often is associated with other gastrointestinal signs or symptoms (e.g., diarrhea, nausea, vomiting, gastroenteritis, gastrointestinal hemorrhage)—a characteristic not seen in the analysis of mIAS (Sonis et al., 2010). Those differences suggest that the pathogenesis of the aphthous-like lesions seen with cytostatic mTOR inhibitors differs from the pathogenesis of mucositis seen with cytotoxic agents. Based on these differences and the distinctly aphthous-like nature of mIAS, strategies effective in managing recurrent aphthous stomatitis may be useful in managing oral ulcers encountered during mTOR inhibitor therapy, as has been demonstrated in renal transplantation recipients (Chuang & Langone, 2007; Scully, 2006).

### Oral Hygiene
- Encourage regular brushing and flossing after each meal.
- Use mild (e.g., children’s) toothpaste; avoid toothpastes containing sodium lauryl sulfate or strong flavors.
- Cleanse mouth regularly with baking soda rinses (or equivalent).
- Encourage regular dental examinations.

### Diet
- Avoid spicy or acidic foods and beverages.
- Avoid hard, crunchy, or crusty foods that can damage the oral mucosa.
- Eat foods at moderate temperatures; avoid hot foods and beverages.

### Education
- Educate patients about the likely signs and symptoms.
- Instruct patients to contact caregiver at first sign of mouth discomfort.

#### Figure 4. Common Recommendations for Preventing or Minimizing Mammalian Target of Rapamycin Inhibitor-Associated Stomatitis

### Mammalian Target of Rapamycin Inhibitor-Induced Stomatitis During Therapy

#### Prophylactic Treatment

Oral ulcerations can be particularly painful for patients and can interfere with food and fluid intake, potentially leading to malnutrition and dehydration (Brown & Wingard, 2004). Based on the authors’ clinical observations, several steps are recommended before starting treatment with an mTOR inhibitor to prevent or minimize the severity of stomatitis (see Figure 4). Oncology nurses have an important role in educating patients on those steps before therapy is initiated and then periodically throughout treatment. Oncology nurses should encourage patients to modify their diets by avoiding spicy or acidic foods and consuming foods that are tepid rather than hot in temperature. Referral to a dietitian should be made, as medically indicated. Nurses also can promote good oral hygiene, which includes brushing with a soft-bristled toothbrush, flossing after each meal, and having regular dental examinations. Toothpastes containing sodium lauryl sulfate (SLS) and strong flavors should be avoided; rather, a milder (e.g., children’s) or SLS-free toothpaste should be recommended. Cleansing of the mouth with baking soda or Biotene® rinses four times per day should be encouraged. In addition, patients should be educated about the risk of mouth sores and their likely signs and symptoms, and instructed to contact their caregiver at the first sign of mouth discomfort.

#### Early Recognition and Treatment

Early recognition of mIAS is important because immediate and effective treatment may minimize the number and severity of ulcers as well as reduce the likelihood of discontinuation of mTOR inhibitor therapy. Patients should be reminded to avoid...
trauma to the affected region, such as from hard or crunchy foods or acidic foods and drinks that may trigger pain (Scully, 2006). Treatment may include specific medications, palliative interventions, and dose modifications (see Figure 5).

Topical high-potency corticosteroids are useful for lesion healing and pain reduction. When a topical corticosteroid is prescribed, the patient should be educated about the risk of candidiasis (i.e., thrush) secondary to topical steroid application (Scully, 2006). As mentioned, direct application of clobetasol was shown to cause prompt resolution of aphthous ulcers in renal transplantation recipients treated with sirolimus (Chuang & Langone, 2007). In cases of particularly symptomatic mIAS, clobetasol gel (0.05%), which is best absorbed in the wet oral mucosa, can be applied directly. However, dexamethasone solution (0.1 mg/mL) can be easier to use and more effective than clobetasol and may have a role in prophylaxis (Scully & Porter, 2008). Dexamethasone rinses can be initiated at the first sign of mouth sensitivity; a teaspoon (0.5 mg) should be used three times daily, with the patient instructed to swish the solution gently for five minutes and then spit it out (Scully, Gorsky, & Lozada-Nur, 2003). Patients should avoid eating or drinking for 10–15 minutes afterwards. In cases of symptomatic stomatitis, the frequency of dexamethasone rinses can be increased from twice per day to up to six times per day. Amlexanox 5% paste is a topical nonsteroidal anti-inflammatory agent useful in recurrent aphthous stomatitis (Scully, 2006), and also may be an option for symptomatic mIAS.

In addition to dexamethasone, miracle mouthwash (sometimes called “magic mouthwash”) should be used as an ancillary treatment (Bensinger et al., 2008). Several formulations of this mouthwash are available; the authors recommend one containing, in equal parts, diphenhydramine as an anti-inflammatory, viscous lidocaine as a topical anesthetic, and aluminum hydroxide or magnesium hydroxide (Maalox®) as an antacid, and it should be used every four hours as needed. Patients should be encouraged to swish the mouthwash around their entire mouth and then spit it out; alternatively, they can apply the mouthwash (or straight 2% viscous lidocaine) directly onto the ulcers with a cotton swab or cotton ball. Patients should be cautioned regarding numbness and risk of injury (e.g., tongue biting, choking) associated with using miracle mouthwash. Topical anesthetics (e.g., Orajel® Medicated Mouth Sore Swabs containing benzocaine) also may be used for palliative management to achieve pain relief and allow normal eating. In severe cases with extensive ulcers, a bioadherent oral gel (e.g., Gelclair®) may be considered.

Figure 6 presents the case of a patient who developed mIAS during treatment with everolimus and was managed using some of the strategies outlined in this article. The patient had heavily pretreated metastatic osteosarcoma and enrolled in a trial of everolimus (10 mg taken once daily) in combination with figitumumab (an insulin-like growth factor-1 receptor inhibitor), administered by IV at a dose of 20 mg/kg every 21 days. The patient had a history of oral toxicity with single-agent sirolimus therapy, as well as with standard chemotherapy agents. At the initiation of mTOR inhibitor therapy, oral examination was normal, and the patient was educated on proper oral hygiene and informed to avoid dietary triggers. The patient also was advised to contact a caregiver at the first sign of oral sensitivity or discomfort. Five days after initiation of treatment, the patient began experiencing oral sensitivity and was noted to have mIAS lesions. The patient initially was prescribed oral rinses with dexamethasone, viscous lidocaine, and miracle mouthwash. IntraleSIONal therapy with triamcinolone (Kenalog®-40; total dose delivered, 28 mg) then was initiated and clobetasol gel 0.05% was prescribed for topical application. Improvements in symptoms and lesions were noted within six days after starting treatment for mIAS, with additional improvement noted a week later with continued intraleSIONal (weekly) and topical treatment. Twenty days after initiating mIAS treatment, the patient noted significant improvement in the interval of oral toxicity with continued dexamethasone rinses and topical clobetasol propionate gel 0.05%. No symptoms or visible signs of mIAS were evident about six weeks after initiating treatment for mIAS-associated lesions.

Other potential treatments exist, although none have been formally tested. For example, when ulcers affect the esophagus, topical treatment is not possible; a high-dose corticosteroid pulse—30–60 mg of oral prednisone or prednisolone (dosed at about 1 mg/kg) for one week followed by dose tapering over the second week—may be useful in severe cases based on clinical experience in patients with recurrent oral aphthous stomatitis, regardless of esophageal involvement (Scully, 2006).
That should be considered for severe cases (i.e., patients with multiple ulcers who experience pain and have significant difficulty with oral intake) (Preshaw et al., 2007). In addition, thalidomide treatment may be considered for treatment of mIAS in patients with more severe, recurrent lesions, as it has been used for the management of HIV-associated aphthous stomatitis (Kerr & Ship, 2003). Finally, other systemic agents that have been reported to be effective for prophylaxis in patients with severe recurrent aphthous stomatitis can be considered, including pentoxifylline, colchicine, and azathioprine (Scully, 2006; Scully & Porter, 2008).

**Dose Modification**

When mIAS develops and cannot be treated optimally with suggested supportive therapies, the dose of the mTOR inhibitor should be modified, as has been illustrated in clinical trials of mTOR inhibitor cancer treatment (Buckner et al., 2010; Motzer et al., 2007; National Institutes of Health, 2011). Treatment of grade 2 or higher stomatitis may include dose modification; however, standard dose reduction regimens are not yet established.

**Conclusions**

Aphthous-like stomatitis is a clinically distinct, class-specific side effect of mTOR inhibitors that likely differs in pathophysiology from mucositis commonly seen with cytotoxic chemotherapy (Sonis et al., 2010). Results from the Sarcoma Multi-Center Clinical Evaluation of the Efficacy of Ridaforolimus, a phase III trial, should provide greater understanding of mIAS (National Institutes of Health, 2011). As stomatitis can be particularly debilitating to patients, affecting their ability to eat and drink as well as their treatment adherence, preventive steps should be taken to minimize their occurrence and severity and provide prompt treatment at the first signs of mouth sensitivity and lesions. These steps will help to improve patient quality of life and ensure that patients derive optimal benefit from mTOR inhibitor therapy. Oncology nurses can have a central role in informing patients of the prevention, identification, and treatment of stomatitis. By taking proactive steps in prevention and treatment, mIAS can be managed with the goal of preventing the discontinuation of therapy.

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