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.

Mammalian target of rapamycin (mTOR) inhibitors, a drug class used for its immunosuppressive effects in the prevention of transplantation rejection, have emerged as key components of cancer therapy (Sankhala et al., 2009; Saunders, Metcalfe, & Nicholson, 2001). Although generally well tolerated by patients with cancer, mouth ulcers or mucositis or stomatitis are the most common dose-limiting toxicities (DLTs) of these agents (Fasolo & Sessa, 2008; Hidalgo et al., 2006; Mita, Britten, et al., 2008; Mita, Mita, et al., 2008; Raymond et al., 2004; Tabernero et al., 2008; Vignot, Faivre, Aguirre, & Raymond, 2005). Mucositis is a common side effect of cancer...
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 receiving 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.

Grade 1
• Asymptomatic or mild symptoms
• Intervention not indicated

Grade 2
• Moderate pain
• Not interfering with oral intake
• Modified diet indicated

Grade 3
• Severe pain
• Interfering with oral intake

Grade 4
• Symptoms associated with life-threatening consequences
• Urgent intervention indicated

Figure 1. Severity of Oral Mucositis
Note. Based on information from National Cancer Institute, 2010.
with cancer treated with other mTOR inhibitors (Chan et al., 2005; Hidalgo et al., 2006; Mita, Mita et al., 2008; Raymond et al., 2004). Although they occur at relatively high rates—ranging from 0%–75%, depending on the treatment regimen—the oral ulcerations typically are low in severity, usually grade 1 or 2. That profile has been observed consistently in patients with advanced malignancies during treatment with the mTOR inhibitors temsirolimus, everolimus, and ridaforolimus (Mita et al., 2004; Hudes et al., 2007; Mita, Mita et al., 2008; Motzer et al., 2008; Raymond et al., 2004).

In a phase I study of weekly temsirolimus infusions in patients with advanced malignancies, the most frequent adverse events were stomatitis and dermatologic toxicities (Raymond et al., 2004). Overall, stomatitis was reported in 18 of 24 patients (75%), including 10 of 15 patients receiving temsirolimus at doses of 7.5–165 mg/m² and 8 of 9 patients receiving the highest dose tested (220 mg/m²). Only two patients had grade 3 stomatitis; one case was reversible despite treatment continuation, whereas the other case was labeled as a DLT and led to discontinuation of treatment (Raymond et al., 2004). In a phase II study, stomatitis was reported in 70% of patients with advanced refractory renal cell carcinoma who were treated with temsirolimus (25–250 mg weekly dose) (Atkins et al., 2004). Stomatitis was the second most common reason (after thrombocytopenia) for dose reduction in that trial; however, as in the phase I trial described earlier, the majority of cases were grade 1 or 2 (Atkins et al., 2004). These clinical trials of temsirolimus are examples of studies in patients with cancer that have demonstrated a high prevalence of stomatitis with a low grade of severity. Several studies further evaluating the role of mTOR inhibition in cancer treatment are being conducted and should provide more information on mIAS.

The most detailed analysis of mIAS to date was conducted using data from a phase I oral dose-escalation trial of ridaforolimus (Mita, Britten, et al., 2008). The most commonly encountered adverse events were mouth sores (79%) and rash (66%), with mouth sores including the terms oral pain, mucosal inflammation, and stomatitis. Mouth sores were described as aphthous ulcers; they increased in frequency and severity with increasing ridaforolimus doses. Most patients who received doses of 15 mg per day or higher had one to three mouth sores; most were grade 1 or 2 and, when treated symptomatically, recovery generally was complete. Several different oral schedules of ridaforolimus were evaluated in a separate 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...
Mammalian Target of Rapamycin Inhibitor-Induced Stomatitis During Therapy

Prophylactic Treatment

Oral ulcers 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...
clinical experience in patients with recurrent oral 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. Intral esional 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 intral esional (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, thiadomile 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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