Stomatitis Associated With Use of mTOR Inhibitors: Implications for Patients With Invasive Breast Cancer

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Background: The mammalian target of rapamycin (mTOR) inhibitor everolimus is approved (in combination with exemestane) for the treatment of postmenopausal women with advanced hormone receptor–positive, human epidermal growth factor receptor 2–negative breast cancer resistant to endocrine therapy. Stomatitis is among the most frequently reported dose-limiting adverse events associated with everolimus use, often requiring treatment interruption or dose reduction.

Objectives: This article aims to educate nurses on the identification and management of stomatitis associated with mTOR inhibitors in hormone receptor–positive advanced breast cancer and to assist nurses with additional management techniques to improve patient outcomes.

Methods: An evaluation of the literature highlighting the incidence, identification, and management of stomatitis in cancer was performed with a particular focus on breast cancer. In addition, the experiences of the authors’ cancer center on managing stomatitis are described.

Findings: A growing body of clinical evidence shows the benefits of adding steroid-based mouth rinses to the treatment plan. Clinical experience provides additional insight into stomatitis preventive and management strategies for patients with breast cancer receiving treatment with everolimus.

The place for targeted agents in treating cancer, including breast cancer, continues to evolve. Ensuring the safe use of targeted therapies is a critical aspect of treatment plans. Everolimus, an oral mammalian target of rapamycin (mTOR) inhibitor, has shown efficacy in combination with tamoxifen (Bachelot et al., 2012) or exemestane (Baselga et al., 2012) in postmenopausal women with advanced breast cancer resistant to endocrine therapy. Everolimus has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of postmenopausal women with advanced hormone receptor–positive (HRª), human epidermal growth factor receptor 2–negative (HER2) breast cancer in combination with exemestane after ineffective treatment with letrozole or anastrozole (Novartis Pharmaceuticals Corporation, 2015). Healthcare professionals, patients, and caregivers should be aware of safety concerns associated with mTOR inhibitors. Vigilance, preventive measures, and management of potential everolimus-associated adverse events (AEs) are essential elements of care. Oncology nurses play a vital role in meeting this important need.

Stomatitis is among the most frequently observed dose-limiting toxicities associated with mTOR inhibitors, often requiring dose interruption or reduction (de Oliveira et al., 2011; Martins et al., 2013; Rugo et al., 2014). Stomatitis occurs in as many as 79% of patients across everolimus-approved indications (Bachelot et al., 2012; Baselga et al., 2009; Bissler et al., 2013; Franz et al., 2013; Krueger et al., 2010; Motzer et al., 2010, 2014; Pavel et al., 2011;...
Ravaud et al., 2015; Yao et al., 2010, 2011; Yardley et al., 2013) (see Table 1). The BOLERO-2 study, which evaluated everolimus plus exemestane versus placebo plus exemestane in postmenopausal women with HR+ and HER2- advanced breast cancer, found that all-grade stomatitis (as a preferred term) occurred in 59% of patients receiving everolimus plus exemestane and 12% of patients receiving placebo plus exemestane (Yardley et al., 2013). Respective incidences of all-grade stomatitis (grades 1–4) and related events, including mouth ulceration, aphthous stomatitis, glossodynia, and gingival pain, were 67% and 12%, respectively (Rugo et al., 2014). Prevention and effective management of stomatitis are critical in helping patients receive therapeutic doses of everolimus and adhere to treatment recommendations. Most published literature focuses on recognition and management of chemotherapy-induced mucositis; however, focus on efficient recognition, prevention, and management of mTOR inhibitor-associated stomatitis is needed.

This article provides an overview of the incidence of stomatitis associated with everolimus use, describes its presentation and timing of onset, presents suggested management strategies, and discusses important aspects of patient education. Its intent is to serve as a practical tool for oncology nurses caring for patients with breast cancer who are receiving everolimus.

### Presentation of Symptoms

Recognizing signs and symptoms of mTOR inhibitor-associated stomatitis and distinguishing them from mucositis commonly associated with chemotherapy or radiation therapy are important first steps toward efficient management. Stomatitis is a general term that refers to inflammation of the mucous membranes in the mouth (Boers-Doets et al., 2012; de Oliveira et al., 2011; Eisen et al., 2012). Ulcerative mucositis induced by radiation therapy or chemotherapy often has a fibrinous pseudomembrane with cellular debris and lacks peripheral erythema (see Figure 1). In addition, lesions have non-uniform shape and depth (Sonis, Treister, Chawla, Demetri, & Haluska, 2010). Mucositis also tends to manifest concurrently with gastrointestinal complications, such as nausea or diarrhea (Eisen et al., 2012; Pilotte, Hohos, Polson, Huftalen, & Treister, 2011; Sonis et al., 2010). Conversely, stomatitis associated with mTOR inhibitors is commonly described as aphthous-like (i.e., similar in appearance to canker sores) and

### TABLE 1. Incidence of Stomatitis in Select Everolimus Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Incidence of Stomatitis (%)</th>
<th>Comparator</th>
<th>Incidence of Stomatitis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BOLERO-2 (Yardley et al., 2013)</td>
<td>EVE + EXE</td>
<td>59</td>
<td>8/0</td>
<td>PBO + EXE</td>
</tr>
<tr>
<td>TAMRAD (Bachelot et al., 2012)</td>
<td>TAM + EVE</td>
<td>56</td>
<td>–</td>
<td>11</td>
</tr>
<tr>
<td>EVE + LET versus PBO + LET (Baselga et al., 2009)</td>
<td>EVE + LET</td>
<td>37</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>Renal Cell Carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RECORD-1a (Motzer et al., 2010)</td>
<td>EVE + BSC</td>
<td>44</td>
<td>4/1&lt; 1</td>
<td>–</td>
</tr>
<tr>
<td>RECORD-2 (Ravaud et al., 2015)</td>
<td>EVE + BEV</td>
<td>63</td>
<td>10/1&lt; 1</td>
<td>–</td>
</tr>
<tr>
<td>RECORD-3 (Motzer et al., 2014)</td>
<td>EVE</td>
<td>53</td>
<td>6/0</td>
<td>–</td>
</tr>
<tr>
<td>Pancreatic Neuroendocrine Tumor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RADIANT-1 (Yao et al., 2010)</td>
<td>EVE</td>
<td>45</td>
<td>–</td>
<td>4</td>
</tr>
<tr>
<td>RADIANT-3b (Yao et al., 2011)</td>
<td>EVE</td>
<td>64</td>
<td>–</td>
<td>7</td>
</tr>
<tr>
<td>Neuroendocrine Tumor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RADIANT-2 (Pavel et al., 2011)</td>
<td>EVE + OCT</td>
<td>62</td>
<td>–</td>
<td>7</td>
</tr>
<tr>
<td>Tuberous Sclerosis Complex</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>EVE for SEGA (Krueger et al., 2010)</td>
<td>EVE</td>
<td>79</td>
<td>–</td>
<td>4</td>
</tr>
<tr>
<td>EXIST-1 (Franz et al., 2013)</td>
<td>EVE</td>
<td>31</td>
<td>–</td>
<td>8</td>
</tr>
<tr>
<td>EXIST-2 (Bissler et al., 2013)</td>
<td>EVE</td>
<td>48</td>
<td>1/0</td>
<td>–</td>
</tr>
</tbody>
</table>

a Stomatitis included aphthous stomatitis, mouth ulceration, and tongue ulceration.

b Includes stomatitis, aphthous stomatitis, mouth ulceration, and tongue ulceration

BEV—bevacizumab; BSC—best supportive care; EVE—everolimus; EXE—exemestane; IFN—interferon alpha; LET—letrozole; OCT—octreotide; PBO—placebo; SEGA—subependymal giant cell astrocytoma; TAM—tamoxifen
manifests as superficial, discrete, oval ulcers with a white or gray center surrounded by well-marked erythematous halos or margins (Boers-Doets et al., 2012; de Oliveira et al., 2011; Divers, 2013; Ferté et al., 2011; Pilotte et al., 2011; Sonis et al., 2010). Lesions are typically 1 cm or less in diameter and confined to non-keratinized, movable mucosal areas prone to local friction, including the inside of the lips, the ventral and lateral surfaces of the tongue, and the soft palate (Ferté et al., 2011; Sonis et al., 2010). However, lesions may also appear in clusters (Sonis et al., 2010).

Stomatitis associated with mTOR inhibitors can negatively affect patients by interfering with food and fluid intake and causing difficulty speaking (Eisen et al., 2012). The oral mucosa can become hypersensitive (e.g., to spicy foods), and patients might experience inflammation of or a burning sensation on the lips (Boers-Doets et al., 2012; Moldawer & Wood, 2010; Porta et al., 2011). Symptoms, such as mouth pain, taste distortion, and difficulty swallowing, can occur in the absence of lesions (Boers-Doets et al., 2012).

When evaluating patients for stomatitis, healthcare providers should rule out other potential causes of symptoms, including viral infections (Porta et al., 2011). Because everolimus is an inhibitor of cytochrome P450 enzymes, azole antifungal agents should not be used unless a fungal infection has been diagnosed (Novartis Pharmaceuticals Corporation, 2015).

Timing of Onset and Symptom Severity

In general, mTOR inhibitor–associated stomatitis tends to occur early, within a median of two to three weeks of treatment initiation (Boers-Doets et al., 2012; de Oliveira et al., 2011; Nicolatou-Galitis, Nikolaidi, Athanassiadis, Papadopoulou, & Sonis, 2013; Perez et al., 2013; Rugo et al., 2014). However, in some patients, later onset (within two months of treatment) has been documented (Porta et al., 2011). In BOLERO-2, median time to onset of grade 2–4 stomatitis and related events was 15 days in patients receiving everolimus plus exemestane and 24 days in those receiving placebo plus exemestane (Perez et al., 2013). The cumulative probability of stomatitis or related events after 6 and 48 weeks of treatment was 26% and 37%, respectively, in recipients of everolimus plus exemestane and 3% in recipients of placebo plus exemestane (Rugo et al., 2014).

For most patients, the severity of everolimus-associated stomatitis is most often grade 1 or 2; however, for a small percentage of cases, symptoms are more severe (Bachelot et al., 2012; Baselga et al., 2009; Bissler et al., 2013; Franz et al., 2013; Krueger et al., 2010; Motzer et al., 2010, 2014; Pavel et al., 2011; Ravaud et al., 2015; Yao et al., 2010, 2011; Yardley et al., 2013). Careful assessment of symptom severity is an important aspect of follow-up visits. The level of stomatitis-related pain is often linked to the degree to which symptoms affect patients’ daily lives and helps to determine the necessary management strategy.

Symptom Resolution and Recurrence

Symptoms of mTOR inhibitor–associated stomatitis typically resolve within a few weeks with effective management (Pilotte et al., 2011; Porta et al., 2011; Rugo et al., 2014). In BOLERO-2, for 97% of patients receiving everolimus plus exemestane, symptoms of grade 3 stomatitis and related events resolved to grade 1 or less following dose interruption or reduction after a median of 3.1 weeks, and 82% had complete resolution after a median of 7.4 weeks (Rugo et al., 2014). For placebo plus exemestane, the median time to resolution from grade 3 to grade 1 or less was 2.6 weeks (Rugo et al., 2014). In the RECORD-1 study with patients with metastatic renal cell carcinoma receiving everolimus versus placebo, most stomatitis cases resolved within three days (Porta et al., 2011). At the Texas Oncology–Baylor Charles A. Sammons Cancer Center, grade 1 or 2 stomatitis typically resolved within 72 hours after discontinuing everolimus (with use of an antibacterial mouth rinse at onset, such as chlorhexidine). In addition, if stomatitis is not associated with pain after discontinuing everolimus treatment for 48 hours and administering around-the-clock therapies
(i.e., “miracle” mouthwash with hydrocortisone), resolution occurs in less than 72 hours (Divers, 2013).

Time to recurrence after stomatitis resolves has been shown to be longer with everolimus than a placebo control. In BOLERO-2, median time from resolution of the first occurrence of stomatitis to recurrence of stomatitis-related symptoms (any grade) was 35 days for everolimus plus exemestane and 23 days for placebo plus exemestane (Perez et al., 2013).

Prevention

Numerous steps can be taken to enhance patient awareness and encourage early intervention. Patients should be coached to recognize signs and symptoms of stomatitis (Pilotte et al., 2011) and be aware of how soon after initiating treatment these may develop. They should be encouraged to inform a healthcare provider (e.g., physician, oncology nurse) at the first sign of oral lesions or mouth discomfort (Moldawer & Wood, 2010; Pilotte et al., 2011). Early recognition is critical because effective treatment can minimize severity of stomatitis-related ulcers and reduce the need to decrease or discontinue everolimus (Pilotte et al., 2011).

Before initiating everolimus, a baseline oral assessment should be performed to check for gum irritation or mouth sores (Divers, 2013). Such assessments should be repeated at all subsequent visits. The level of patient baseline discomfort can be documented using a visual analog scale or other scales, such as the Oral Assessment Guide (Moldawer & Wood, 2010). Validated grading scales for stomatitis associated with use of targeted therapies are not available (Boers-Doets et al., 2012).

No data exist from randomized clinical trials to guide prevention strategies for mTOR inhibitor–associated stomatitis, and official practice guidelines have not been published. Nevertheless, precautionary measures before initiating everolimus therapy and periodically throughout treatment have been suggested in the literature and are being implemented in clinical practice (Divers, 2013; Eisen et al., 2012; Ferté et al., 2011; Moldawer & Wood, 2010; Pilotte et al., 2011). For example, patients should be encouraged to practice good oral hygiene and frequently use bland rinses, such as sterile water or normal saline (Divers, 2013; Moldawer & Wood, 2010; Pilotte et al., 2011). They should be counseled to avoid intake of agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives; consumption of spicy or acidic foods and beverages; and intake of substances that can irritate oral ulcers (Divers, 2013; Eisen et al., 2012; Pilotte et al., 2011; Porta et al., 2011). A retrospective analysis of six phase I and II studies evaluating treatment with everolimus in patients with metastatic breast or lung cancer found that use of sodium bicarbonate rinse and oral fluconazole was ineffective in preventing oral ulcers (Ferté et al., 2011).

A prophylactic strategy successfully implemented at the Texas Oncology–Baylor Charles A. Sammons Cancer Center is regular rinsing with a miracle mouthwash with hydrocortisone as soon as mTOR inhibitor therapy is initiated and throughout therapy (Divers, 2013). Numerous formulations of miracle mouthwash have been implemented in clinical practice, including those containing diphenhydramine, dimethicone suspension, viscous lidocaine, aluminum hydroxide, or magnesium hydroxide (de Oliveira et al., 2011; Eisen et al., 2012). The combination of ingredients that the authors have had success with at the Texas Oncology–Baylor Charles A. Sammons Cancer Center consists of diphenhydramine solution, tetracycline powder, hydrocortisone, and nystatin suspension (Divers, 2013). The quantities of each ingredient necessary to make 16 ounces of this formulation are described in Figure 2 (Divers, 2013). Patients are encouraged to rinse with two teaspoons of this formulation of miracle mouthwash (swish and spit four times daily), preferably 30 minutes prior to each meal (Divers, 2013). The miracle mouthwash (with hydrocortisone) must be held against all mucous membranes, including upper and lower lips and mouth vestibules, for one to two minutes. In addition, patients should gargle with the miracle mouthwash plus hydrocortisone at first signs of any stomatitis. If stomatitis develops, rinses should be continued and chlorhexidine antibacterial mouth rinse added (10 ml, swish and spit four times daily) until ulceration is healed.

In addition to educating patients on preventive measures, discussing the critical role that everolimus plays in the breast

Based on Published Literature

- Perform a baseline oral assessment to ensure no gum irritation or mouth sores are present before initiating everolimus, and repeat assessments at all subsequent visits.
- Evaluate for herpes or fungal infection and treat as appropriate.
- Regularly rinse mouth with baking soda (or equivalent product) and “magic” or “miracle” mouthwash.
- Encourage good oral hygiene. Use a mild toothpaste (e.g., children’s) and soft-bristled toothbrush. Floss after each meal.
- Frequently use bland rinses, such as sterile water or normal saline.4
- Have regular dental examinations and proactively treat anticipated infections (e.g., periodontal diseases).
- Avoid toothpastes with sodium lauryl sulfate; agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives; spicy, acidic, or salty foods and beverages; and hard, crunchy, crusty, or hot foods and beverages that can damage the affected area or exacerbate lesions.

Based on Strategies Implemented at Texas Oncology–Baylor Charles A. Sammons Cancer Center

- Use 10 ml of miracle mouthwash with crushed hydrocortisone four times daily (swish and spit; wait 10–15 minutes after using the baking soda and salt rinse before using this formulation). Miracle mouthwash should preferably be used 30 minutes prior to each meal, with a baking soda and salt rinse 10–15 minutes after each meal.
- For a 16 oz recipe: Mix 320 ml diphenhydramine solution, 2 g tetracycline powder, 80 mg hydrocortisone (four 20 mg tablets crushed and added to solution), and 40 ml nystatin suspension, quantity sufficient with water.
- At onset of any grade of stomatitis, add chlorhexidine mouth rinse (10 ml, swish and spit four times daily) and continue mouth rinses.

4In a retrospective analysis of six phase I and II studies evaluating treatment with everolimus in patients with metastatic breast or lung cancer, use of sodium bicarbonate rinse was ineffective in preventing oral ulcers.

FIGURE 2. Suggested Stomatitis Preventive Measures

Note: Based on information from Divers, 2013; Eisen et al., 2012; Ferté et al., 2011; Moldawer & Wood, 2010; Pilotte et al., 2011; Porta et al., 2011.
cancer management plan is important. This will help to motivate patients to remain adherent to therapy and take proactive measures to prevent or manage stomatitis.

Management Strategies

Commonly Recommended Treatment Options

Package inserts are a good source of information for nurses on management of AEs. Oncology nursing drug handbooks also are invaluable to outpatient oncology nurses because they provide background on the management of stomatitis and other symptoms associated with cancer and drug side effects.

Recommendations on management of mTOR inhibitor–associated stomatitis, based on FDA labeling and published literature, are summarized in Figure 3 (Divers, 2013; Moldawer & Wood, 2010; Novartis Pharmaceuticals Corporation, 2015; Pilotte et al., 2011; Porta et al., 2011). Management of grade 1 stomatitis (i.e., mild severity and a normal diet) involves rinsing several times daily with nonalcoholic mouthwash or 0.9% salt water (Moldawer & Wood, 2010; Novartis Pharmaceuticals Corporation, 2015; Porta et al., 2011). For patients with more severe symptoms, including grade 2 (i.e., symptomatic but a normal diet) or grade 3 stomatitis (i.e., symptomatic and unable to adequately eat or drink), frequently recommended strategies include topical analgesic mouth treatments (e.g., benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, phenol) with or without topical corticosteroids (e.g., triamcinolone oral paste, clobetasol gel, dexamethasone solution) (Divers, 2013; Moldawer & Wood, 2010; Novartis Pharmaceuticals Corporation, 2015; Pilotte et al., 2011; Porta et al., 2011). If topical corticosteroids are prescribed, patients should be educated about the risk for candidiasis (i.e., thrush) (Pilotte et al., 2011). If fungal infection is diagnosed, topical antifungal agents should be applied, and all systemic imidazole fungal agents (e.g., ketoconazole, fluconazole) should be avoided (Moldawer & Wood, 2010). Patients should also be counseled to avoid agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives (Moldawer & Wood, 2010; Novartis Pharmaceuticals Corporation, 2015; Porta et al., 2011). In the presence of grade 4 stomatitis (i.e., life-threatening symptoms), the same recommendations for grades 2 and 3 stomatitis should be implemented with additional supportive interventions as appropriate (Novartis Pharmaceuticals Corporation, 2015; Porta et al., 2011).

Based on clinical experience at the Texas Oncology–Baylor Charles A. Sammons Cancer Center (Divers, 2013), the authors recommend continuing to use the miracle mouthwash rinse for all grades of stomatitis (i.e., same formulation and dosage schedule recommended for prevention). Nurses should ensure that patients use this rinse correctly. At the authors’ institution, patients receive chlorhexidine antibacterial mouth rinse (10 ml, swish and spit four times daily) until the ulceration is healed.

Steroid-Based Mouth Rinses

Although the exact cause of mTOR inhibitor–associated stomatitis is poorly understood, presence of a T-cell–mediated inflammatory response has been suggested as an underlying factor (de Oliveira et al., 2011; Martins et al., 2013). Therefore, steroids play an important role in the treatment plan. Where steroid-based mouth rinses fit in therapy is a topic of increasing interest.

Data from studies evaluating steroid-based mouth rinses for treating mTOR inhibitor–related stomatitis are scarce. A retrospective case review of four open-label, phase I and II clinical trials evaluating mTOR inhibitor–based treatment regimens describes the clinical course of patients with stomatitis (de Oliveira et al., 2011). Seventeen patients were evaluated: 13 received everolimus and 4 received ridaforolimus. Patients received a combination of palliative topical therapies (i.e., topical anesthetics, miracle mouthwash [consisting of equal parts of lidocaine/aluminum hydroxide, magnesium hydroxide, and dimethicone suspension/diphenhydramine], and saline rinses); topical corticosteroids (clobetasol gel 0.05%, triamcinolone paste, dexamethasone 0.1 mg/ml solution), intralesional steroids, and systemic corticosteroid therapy. Fifteen patients received topical corticosteroids, typically two to four times daily. One patient received triamcinolone paste, five patients required intralesional corticosteroid therapy, and one patient received high-dose systemic prednisone. Clinical improvement was noted in 13 of 15 patients (87%), demonstrated by decreased pain and increased healing. Although results show the

All Grades
• Use the “miracle” mouthwash for prevention of stomatitis.
• Ensure that patients use mouthwashes as directed.
• At onset of any degree of stomatitis, add chlorhexidine mouth rinse (10 ml, swish and spit four times daily) and continue miracle mouthwash with hydrocortisone.

Grade 1 (patient follows a normal diet)
• Rinse several times daily with nonalcoholic mouthwash or 0.9% salt water.

Grade 2 (symptomatic but can follow a modified diet)
• Use topical analgesic mouth treatments (e.g., benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, phenol) with or without topical corticosteroids (e.g., triamcinolone oral paste, clobetasol gel, dexamethasone solution).
• Avoid agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives.

Grade 3 (symptomatic and unable to adequately eat or drink)
• Follow the same recommendations as for grade 2.

Grade 4 (life-threatening symptoms)
• Follow the same recommendations as for grade 2, and institute additional medical interventions as appropriate.

*When topical corticosteroids are prescribed, patients should be educated about the risk for candidiasis (i.e., thrush). If a fungal infection is diagnosed, topical antifungal agents should be applied; all systemic imidazole fungal agents (e.g., ketoconazole, fluconazole) should be avoided.

FIGURE 3. Recapitulation of Select Stomatitis Management Strategies

Note. Based on information from Divers, 2013; Moldawer & Wood, 2010; Novartis Pharmaceuticals Corporation, 2015; Pilotte et al., 2011; Porta et al., 2011.
usefulness of steroid-based treatments in this setting, effectiveness of individual treatment methods, such as dexamethasone solution, were not specifically reported (de Oliveira et al., 2011).

Prospective management of stomatitis with a steroid mouth rinse has also been described by Nicolatou-Galitis et al. (2013). The following treatment regimen was administered three to four times daily: 15 drops of dexamethasone solution (0.5 mg/5 ml) in 6 ml of water, with the medication kept in the patient’s mouth for two to three minutes before expectorating. After each dexamethasone use, miconazole (2%) oral gel was administered to prevent fungal infection; 5 ml of miconazole gel was kept in the mouth for one minute before expectorating. In all patients, stomatitis associated with everolimus resolved within one to two weeks of therapy (Nicolatou-Galitis et al., 2013). At the Texas Oncology-Baylor Charles A. Sammons Cancer Center, no oral cavity fungal infections have been reported with the use of miracle mouthwash plus hydrocortisone.

**Everolimus Dose Modifications**

Depending on symptom severity, management of everolimus-associated stomatitis may require temporary treatment interruption or dose reduction. In the BOLERO-2 study, dose interruptions or reductions for any grade of stomatitis occurred in 24% of patients receiving everolimus plus exemestane versus 1% of patients receiving placebo plus exemestane (Perez et al., 2013; Rugo et al., 2014). Respective rates of treatment discontinuation because of stomatitis and related events were 3% versus less than 1% (Rugo et al., 2014).

In the retrospective review of 17 patients receiving everolimus or ridaforolimus in phase I and II clinical trials who developed mTOR inhibitor–associated stomatitis, dose reduction or treatment discontinuation was necessary for eight patients. Five patients required protocol-specified dose reductions because of grade 2 or 3 stomatitis, and they continued receiving therapy with the mTOR inhibitor. Severe stomatitis developed in two patients who required temporary treatment discontinuation; treatment was resumed at a lower dose and was tolerated. Permanent treatment discontinuation was necessary in one patient (de Oliveira et al., 2011).

The FDA-approved dose of everolimus for patients with advanced HR+, HER2− breast cancer is 10 mg per day (Novartis Pharmaceuticals Corporation, 2015). The dose should not be reduced at onset of everolimus therapy in anticipation of stomatitis (Divers, 2013). Biweekly oral assessments should be conducted during office visits (Divers, 2013; Moldawer & Wood, 2010). If no changes are noted from baseline oral assessment, everolimus should be continued. If changes develop, everolimus should be interrupted until the clinical team can properly determine the stomatitis grade and decide on an appropriate course of action (Divers, 2013). Nurses need to assess the patient and grade stomatitis appropriately. Treatment should be interrupted until pain is gone or the lesion improves, as determined by patient feedback (communication or visual aid), and treatment will be resumed after healing of first incidence of stomatitis. Everolimus dose modifications based on grade of stomatitis, per the FDA-approved label, are summarized in Table 2 (Novartis Pharmaceuticals Corporation, 2015).

**Conclusion**

mTOR inhibitors play a prominent role in the treatment of patients with breast cancer (National Comprehensive Cancer Network, 2014). Therefore, the risks of associated AEs becomes a concern if they require treatment interruption. Oncology nurses are in a prime position to educate patients and their caregivers about the possibility of stomatitis and encourage timely (at mTOR therapy initiation) and meticulous implementation of preventive strategies. The more educated the patient and the support team, the more likely the patient will properly implement the recommendations and continue with the recommended cancer treatment.

**References**


**Implications for Practice**

- Assess for and manage stomatitis in a timely manner to ensure high-quality care of patients with advanced breast cancer who are receiving treatment with everolimus.
- Prevent stomatitis by educating patients about the risk for stomatitis and coaching them on signs and symptoms before the initiation of everolimus therapy.
- Recommend preventive and management strategies for stomatitis, including steroid-based mouth rinses.

**TABLE 2. Recommended Everolimus Dose Modifications Based on Grade of Stomatitis**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Dose Adjustment</th>
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<tbody>
<tr>
<td>1</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td>2</td>
<td>Temporary dose interruption until recovery to grade 1 or less; reinitiate at the same dose. If stomatitis recurs at grade 2, interrupt dose until recovery to grade 1 or less; reinitiate at a lower dose.</td>
</tr>
<tr>
<td>3</td>
<td>Temporary dose interruption until recovery to grade 1 or less; reinitiate at a lower dose.</td>
</tr>
<tr>
<td>4</td>
<td>Discontinue and treat with appropriate medical therapy.</td>
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</tbody>
</table>

Note. Based on information from Novartis Pharmaceuticals Corporation, 2015.


