Prevention of Stomatitis

Using dexamethasone-based mouthwash to inhibit everolimus-related stomatitis

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BACKGROUND: A common class-specific toxicity of mammalian target of rapamycin (mTOR) inhibitors is stomatitis. Some patients experience a severe form of mTOR inhibitor-associated stomatitis (mIAS) that can have a negative effect on nutritional status, compromise quality of life, and potentially lead to nonadherence, reducing the efficacy of cancer therapy.

OBJECTIVES: This article aims to address an unmet need for education about mIAS among oncology nurses and patients and to share findings about everolimus-related stomatitis from the SWISH trial.

METHODS: The authors reviewed the literature on mIAS and selected a case series of experiences to illustrate successes and clinical challenges that an oncology nurse might encounter when caring for patients with advanced breast cancer who may develop everolimus-related stomatitis.

FINDINGS: Recommendations are provided for oncology nurses to educate patients on prevention, early detection, monitoring, and management strategies to mitigate the incidence and severity of everolimus-related stomatitis.

KEYWORDS
breast cancer; everolimus; stomatitis; prevention; mouthwash; corticosteroid

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MAMMALIAN TARGET OF RAPAMYCIN (mTOR) INHIBITORS are approved for cancer treatment, including for advanced breast cancer. Class-specific adverse events (AEs) associated with mTOR inhibitors include rash, noninfectious pneumonitis, hyperglycemia, hyperlipidemia, and fatigue (Aapro et al., 2014; Rugo et al., 2014). One of the most common class-specific AEs of mTOR inhibitors is stomatitis, also referred to as mTOR inhibitor–associated stomatitis (mIAS). Among patients taking everolimus (an mTOR inhibitor) who experience mIAS, the majority report mild to moderate mIAS, with a median onset of 10 days after initiating everolimus therapy (Rugo et al., 2014; Yardley, 2014). However, a subset of patients experience severe pain and prolonged duration of mIAS that can interfere with speaking, compromise nutrition and quality of life, and potentially lead to treatment nonadherence, reducing the efficacy of cancer therapy (Boers-Doets et al., 2013; Divers & O’Shaughnessy, 2015; Meiller, Varlotta, & Weikel, 2015; Pilotte, Hohos, Polson, Hufafal, & Treister, 2011). mIAS is one of the most commonly reported AEs of everolimus in patients with advanced breast cancer. In the phase 3 BOLERO-2 trial, which evaluated the efficacy and safety of everolimus in patients with hormone receptor–positive (HR+), human epidermal growth factor receptor–negative (HER2−) advanced breast cancer, the incidence of all-grade mIAS was 67%, grade 2 or greater was 33%, and grade 3 was 8%, with a median follow-up of 18 months (Rugo et al., 2014). In a meta-analysis of phase 3 trials of solid tumors, including breast cancer, 89% of first mIAS events occurred within eight weeks of initiating everolimus therapy (Rugo, 2016). No guidelines exist to identify patients at higher risk of developing mIAS. In addition, a need for education about mIAS to better manage its effects on patients remains (Pilotte et al., 2011; Staves & Ramchandran, 2017).

Oncology nurses can play a vital role in educating patients to monitor and promptly report the signs and symptoms of mIAS, discussing preventive and therapeutic strategies to reduce the incidence, severity, and duration of mIAS, and ultimately improving clinical benefits to patients (Boers-Doets et al., 2013; Chia et al., 2015; Divers & O’Shaughnessy, 2015; Peterson, 2013; Pilotte et al., 2011). Raising awareness of mIAS enables nurses to play an expanded role in educating and empowering patients to mitigate this manageable AE on several fronts.
An evidence-based treatment strategy for preventing mIAS was evaluated in postmenopausal patients with HR+, HER2–, advanced breast cancer who received a prophylactic dexamethasone-based mouthwash concomitant with everolimus and exemestane therapy in the phase 2 SWISH (dexamethaSone mouthWash for everolImus-related stomatitiS prevention in HR+ metastatic breast cancer) trial (Rugo et al., 2017). Through participation in the SWISH trial, the current authors recognized a need to have a deeper understanding of everolimus-related stomatitis. This report aims to educate oncology nurses on the current understanding of the biology of mIAS, clinical presentation, its impact on patients, and interventions that have been evaluated to ameliorate symptoms. The authors then present a case series to share their experiences and illustrate some of the successes, nuances, and clinical challenges that nurses might encounter when caring for patients with advanced breast cancer who may develop everolimus-related stomatitis. Finally, recommendations are provided for the oncology nursing community to educate patients on prevention, early detection, monitoring, and therapeutic measures to mitigate the incidence of everolimus-related stomatitis.

**Clinical Presentation of mIAS**

Some researchers have postulated that mTOR inhibition may elicit an inflammatory process that injures the oral mucosa (de Oliveira et al., 2011; Martins et al., 2013). The pathophysiology of mIAS is clinically distinct from chemotherapy- or radiation therapy–induced mucositis. mIAS clinically resembles recurrent aphthous stomatitis (i.e., canker sores) and presents as shallow, nonconfluent ulcerations with intense erythematous margins. In contrast, mucositis presents as deep, confluent lesions without peripheral erythema (Meiller et al., 2015; Pilotte et al., 2011; Sonis, Treister, Chawla, Demetri, & Haluska, 2010; Yardley, 2014). Management strategies to prevent or treat mIAS are distinct from therapies used to treat chemotherapy-induced mucositis and include the clinical presentation and differential diagnosis of mIAS (Yardley, 2014).

**Mitigation of mIAS**

**Educational Measures**

As self-administration of cancer therapeutics grows, patients play an increasingly important role in home monitoring and reporting AEs to healthcare providers at the earliest appearance of signs and symptoms (Given, Spoelstra, & Grant, 2011). By encouraging patients to communicate the first signs of oral sensitivity or pain to a caregiver and healthcare professionals, oncology nurses can treat pain, mitigate worsening of symptoms, and guide patient decision making to minimize and manage mIAS. Oncology nurses also look to patients and caregivers to assess treatment adherence. Nurses can facilitate proactive dialogue with patients about the effect of mIAS on adherence to treatment and the value of prevention and management strategies to ameliorate mIAS (Aapro et al., 2014; Divers & O’Shaughnessy, 2015). These educational approaches may help patients adhere to treatment and, therefore, achieve therapeutic doses of an mTOR inhibitor.

**Preventive and Treatment-Based Strategies**

Various recommendations based on prophylactic measures and therapeutic interventions have been proposed to reduce the incidence and severity of everolimus-related stomatitis, but these reports of steroid-based interventions have typically been anecdotal or from a single center (Aapro et al., 2014; Divers & O’Shaughnessy, 2015; Nicolatou-Galitis, Nikolaidi, Athanassiadis, Papadopoulou, & Sonis, 2013) (see Figure 1). For milder cases or prevention of mIAS, supportive measures (e.g., nonalcoholic mouthwashes, salt water rinses, mucosal coating agents, topical anti-inflammatory agents) can be effective (Divers & O’Shaughnessy, 2015; Schütz et al., 2015; Staves & Rambachan, 2017). Nurses can also advise patients to avoid irritants that can damage the oral mucosa (e.g., alcohol-containing mouthwash products; peroxidase– or sodium lauryl sulfate–containing mouthwash products; spicy, hard, crunchy, crusty, hot, or acidic food or drink). Dental healthcare providers can play a key role in improving patient care to prevent or minimize mIAS. Nurses can encourage patients to have regular dental examinations and care by a dentist or dental hygienist, and to receive counseling on good routine oral hygiene (e.g., brushing with a soft-bristled toothbrush, flossing after meals, attending regular examinations) to prevent or minimize mIAS. Other therapeutic options include topical analgesic treatments (with or without corticosteroids), corticosteroid therapy (topical, intralesional, or systemic), dexamethasone to reduce pain and facilitate healing of oral ulcers (de Oliveira et al., 2011; Divers & O’Shaughnessy, 2015), or “miracle mouthwash,” which is a cocktail of anesthetic, antibiotic,
and steroid (Divers & O’Shaughnessy, 2015; Jones et al., 2015). Depending on the severity of mIAS, everolimus dose interruption, reduction, or discontinuation may be warranted (Divers & O’Shaughnessy, 2015; Pilotte et al., 2011).

**SWISH Trial**

The prophylactic dexamethasone mouthwash regimen therapy used in the SWISH trial has garnered attention in preventing mIAS (Rugo et al., 2017) (see Figure 2). Dexamethasone is a glucocorticoid agonist with anti-inflammatory activity that is believed to bind to intracellular cytoplasmic receptors to inhibit transcription and protein synthesis of leukocyte infiltration at inflammatory sites and interfere with mediators of inflammation, such as prostaglandins and leukotrienes (DrugLib, 2017; Roxane Laboratories, Inc., 2007). According to trial protocol, patients were instructed to swish 10 ml of a commercially available, alcohol-free, 0.5 mg/5 ml dexamethasone solution for a minimum of two minutes to ensure contact with the entire oral cavity and then spit it out four times daily. Patients were instructed not to eat or drink for at least one hour after administering the dexamethasone mouthwash. Patients may be at potential risk of fungal infections with the use of dexamethasone. Therefore, the use of a prophylactic, topical antifungal regimen following dexamethasone mouthwash was suggested.

In addition, an educational video and materials about mIAS were used to instruct patients on monitoring for mIAS and when to contact their clinicians to report oral pain and mucosal changes. Patients were also instructed to perform good oral hygiene and routine dental care and maintenance. Patients were given a timer to ensure duration of mouthwash administration and a diary to record their usage of dexamethasone mouthwash and the ability to eat a normal diet using the Normalcy of Diet Scale (NDS), which ranks food categories from easy to eat (0 = non-oral feeding) to hard to eat (100 = normal diet, no restrictions) (List, Ritter-Sterr, & Lansky, 1990). Patients reported the highest ranking food that they were able to eat, as scored by the NDS. Patients also recorded oral pain using a visual analog scale (VAS) ranging from 0 (no pain) to 10 (severe pain) (Gould, Kelly, Goldstone, & Gammon, 2001; Sonis et al., 1999). This patient diary allowed clinicians to better assess the impact of mIAS to the patient.

In the SWISH trial, prophylactic use of dexamethasone mouthwash resulted in a greater than 10 times reduction in eight-week incidence of grade 2 or greater mIAS compared to the use in the BOLERO-2 trial (Rugo et al., 2017). Dexamethasone mouthwash was well tolerated; 95% of patients used dexamethasone mouthwash three to four times per day. A majority of patients practiced good oral hygiene and reported the ability to eat a diet with no or few restrictions and minimal pain.

**Case Presentations**

The following cases about mIAS occurrence further illustrate management and education strategies. The clinical evidence and practical management experience suggest using a prophylactic steroid-based, alcohol-free mouthwash to prevent or minimize everolimus-associated stomatitis in patients with HR+, HER2-advanced breast cancer.

**FIGURE 1.**

**NURSING RECOMMENDATIONS FOR THE PREVENTION AND MANAGEMENT OF EVEROLIMUS-ASSOCIATED STOMATITIS**

**PATIENT EDUCATION PRIOR TO INITIATION OF EVEROLIMUS THERAPY**

- Educate patients to recognize and promptly report distinguishing features, common signs and symptoms, and early onset of mIAS.
- Advise patients regarding the value and benefits of the treatment regimen in minimizing or preventing mIAS.
- Counsel patients on good routine oral hygiene (e.g., brushing with a soft-bristled toothbrush, flossing after meals, regular dental examinations by dentist).
- Educate patients on supportive care approaches to minimize irritation of lesions, reduce pain, and manage symptoms (e.g., avoidance of alcohol-containing mouthwash products; avoidance of peroxidase- or sodium lauryl sulfate-containing mouthwash products; avoidance of spicy, or hard, crunchy, crusty, hot, or acidic foods and beverages).

**PATIENT SUPPORT DURING EVEROLIMUS THERAPY**

- Encourage patients to communicate first signs of oral sensitivity or pain to caregivers and healthcare professionals.
- Guide patient decision making for pain management of mIAS.
- Communicate the value of adhering to the treatment regimen to promote improved clinical outcomes.

**INTERVENTIONS FOR mIAS**

- Prevention: Topical corticosteroid agents (e.g., dexamethasone mouthwash)
- Grade 1: Salt water rinse, mucosal coating agents, anti-inflammatory agents
- Grade 2: Analgesic mouthwash with or without topical corticosteroids; temporary dose interruption of everolimus until resolution to grade 1 or less, then reinitiation of everolimus at same dose
- Recurrent grade 2: Temporary dose interruption of everolimus until resolution to grade 1 or less, then reinitiation of everolimus at a lower dose; analgesic mouthwash with or without topical corticosteroids
- Grade 3: Temporary dose interruption of everolimus until resolution to grade 1 or less; restart at reduced dose; analgesic mouthwash with or without topical corticosteroids
- Grade 4: Discontinue everolimus; analgesic mouthwash with or without topical corticosteroids
- Oral thrush associated with corticosteroid use: Antifungal agents

mIAS—mTOR inhibitor–associated stomatitis

Note. Based on information from Boers-Doets et al., 2013; Chia et al., 2015; Divers & O’Shaughnessy, 2015; Peterson, 2013; Pilotte et al., 2011.
Case 1
A 59-year-old woman diagnosed with stage IIIa breast cancer in 2011 was found to have a 4.1-cm mass and metastatic axillary lymph nodes at mastectomy in a community-based practice. This patient also had comorbid type 2 diabetes mellitus. She was treated with adjuvant doxorubicin plus cyclophosphamide followed by letrozole and radiation therapy for her breast cancer. In 2014, the patient had evidence of multiple bone metastases, making her a candidate for everolimus plus exemestane therapy. In 2015, she enrolled in the SWISH trial and received dexamethasone mouthwash and instructions on its administration. Nurses reviewed the participant’s guide and educational video on mIAS with the patient and counseled her on good oral hygiene, recorded NDS and VAS scores, and encouraged her to use supportive measures for pain management.

Throughout the SWISH trial, the patient reported being adherent to the mouthwash regimen, an NDS score of 90 (able to eat with no or few restrictions), and a VAS score of 0 (no pain). She tolerated the treatment regimen and had no evidence of mIAS or mouth discomfort. The patient developed a vaginal and rectal yeast infection during cycle 2 and was prescribed an eight-day course of fluconazole. After eight weeks, the patient opted to continue dexamethasone mouthwash for an additional eight weeks. She continued on everolimus plus exemestane therapy and appeared to respond to it.

This case highlights the collaborative nature between nurses and patients to mitigate the development of mIAS. Educational support by oncology nurses before initiating the treatment regimen, followed by monitoring for adherence throughout the study, may have contributed to the prevention of mIAS. This patient also seemed to be engaged in her care. Implementation of these educational, preventive, and supportive care measures may be an effective approach to reduce the likelihood that a patient will develop everolimus-related stomatitis and, therefore, remain adherent to therapy.

Case 2
A 35-year-old woman was diagnosed with breast cancer in 2010 and metastatic disease (including skull, femur, and liver) in 2014 in an academic setting. The patient received prior radiation and hormonal therapy. In 2015, she enrolled in the SWISH trial and initiated everolimus plus exemestane therapy with dexamethasone mouthwash. The oncology nursing team provided an educational video on mIAS, a soft-bristled toothbrush, and a timer before initiating the therapeutic regimen. The research team emphasized the importance of good oral hygiene, prompt reporting of the onset of oral pain, supportive measures, and the therapeutic benefit of maintaining the dose of everolimus even with the onset of mIAS. She experienced grade 2 mIAS within four weeks of initiating the treatment regimen (NDS score of 90; VAS score of 7). Therefore, her everolimus dose was reduced from 10 mg to 5 mg. The patient reported that she used mouthwash four times daily and followed good oral care. However, her care team was not confident regarding her adherence to dexamethasone mouthwash; she completed her diary during clinic visits rather than recording mouthwash usage and NDS and VAS scores daily at home. Nonetheless, the patient repeatedly expressed concerns that the mouthwash was ineffective despite her grade 2 mIAS resolving to grade 1 and an improved NDS score of 100 and VAS score of 2 at 12 weeks of dexamethasone mouthwash and concurrent everolimus plus exemestane therapy.

This case illustrates some of the challenges of treating a suspected nonadherent patient and the need to identify and manage symptoms of mIAS before they become painful and limit treatment. Possible factors that can contribute to patient nonadherence include forgetfulness, disease complexity, sociocultural issues, and living alone (Ault & Allen-Bard, 2012). After identifying patients most at risk for nonadherence, nurses can play a proactive role in reducing potential barriers to adherence by counseling patients on the value of the regimen early and often and reiterating good oral hygiene and supportive measures throughout the treatment program. Prompt detection of mIAS is not to be underestimated; early recognition is critical to minimizing the severity of mIAS and reducing the need for dose modification (Pilotte et al., 2011). Fostering a collaborative relationship before initiating everolimus may uncover specific needs, concerns, motivations, and preferences to tailor communication for each patient. Nurses can ask patients about the quantity and quality of information they need and whether the information is useful and addresses their needs (Seah, Lin, Curley, Weiner, & Partridge, 2014). To empower patients to fully participate in achieving beneficial outcomes, oncology nurses can emphasize the importance of adherence and regular self-monitoring to help patients understand the consequences of inaction and aggressively manage treatment-related side effects with supportive and therapeutic approaches (Cornelson, Jabbour, & Welch, 2012). Patients who are vigilant in recognizing symptoms and proactive...
in the decision-making process about interventions are more likely to have better treatment outcomes (Coleman, 2014).

Case 3
A 65-year-old woman was diagnosed with de novo metastatic (bone and liver) breast cancer in 2011 in an academic setting. Her liver disease resolved with cytotoxic and hormonal therapy. She was then on hormonal and denosumab maintenance therapy until 2013, followed by a vaccine trial for two years. Upon disease progression in 2015, the patient was enrolled in the SWISH trial and responded to everolimus plus exemestane therapy. Upon the patient’s receipt of the guide and video on mIAS, the nurse counseled the patient on good oral hygiene and recorded NDS and VAS scores and supportive measures for pain associated with mild mIAS. The patient experienced grade 1 mIAS (NDS score was 100; VAS score was 2) five days after initiating treatment that resolved within four weeks of initiating a salt water rinse regimen 10–15 minutes prior to using the dexamethasone mouthwash, per study protocol. The patient experienced no further symptoms or visible evidence of everolimus-related stomatitis, reported good oral health (NDS score was 100; VAS score was 0), and was adherent to dexamethasone mouthwash for 16 weeks.

This case is consistent with other studies in the early onset of mIAS (de Oliveira et al., 2011; Rugo, 2016) and reiterates the importance of educating patients to immediately report any signs or symptoms of mIAS. Immediate and effective treatment can reduce pain, allow patients to maintain oral function, and lessen the frequency and severity of mIAS, reducing the chances of discontinuation of mTOR inhibitor therapy (de Oliveira et al., 2011; Pilotte et al., 2011). Dexamethasone has previously been shown to be helpful in reducing pain associated with everolimus-related stomatitis and facilitating resolution and healing (Nicolatou-Galitis et al., 2013).

Discussion
Oncology nurses are on the frontline of cancer care and have an opportunity to serve as educators of dose-limiting toxicities and offer recommendations for preventing and managing AEs, such as mIAS (Boers-Doets et al., 2013; Chia et al., 2013; Divers & O’Shaughnessy, 2015; Peterson, 2013; Pilotte et al., 2011). Before initiating everolimus therapy, nurses can educate patients to recognize distinguishing features, common signs and symptoms, and early onset of mIAS, and can counsel patients on the value and benefits of a treatment regimen that minimizes or prevents mIAS. An effective approach is to couple a discussion of the potential impact of mIAS on dose interruption or reduction with videos and images illustrating the signs and symptoms of mIAS and emphasizing good oral hygiene and maintenance of dental health. Throughout the disease course, nurses play a key role by guiding patient decision making for pain management; promoting awareness of the onset, prevention, and management of mIAS; and reiterating the value of adhering to the treatment regimen to improve clinical outcomes.

This case series highlights the clinical course, management, and outcomes of everolimus-related stomatitis and exemplifies typical situations that nurses may encounter, which are consistent with findings from a previous study describing the clinical features and management strategies to reduce pain and facilitate healing of mIAS (Nicolatou-Galitis et al., 2013). The findings from the authors’ clinical centers (University of Texas MD Anderson Cancer Center and Oncology Consultants, P.A., both in Houston, Texas) align with the overall results of the SWISH trial with respect to demographics, onset, and severity of mIAS (Rugo et al., 2017). In the current authors’ experience, prophylactic use of dexamethasone mouthwash can be effective in preventing mIAS within the first eight weeks of initiating everolimus plus exemestane therapy. Therefore, a similar management strategy among patients currently treated at the authors’ clinical centers has been adopted. At one center, physicians prescribe dexamethasone solution to everolimus-treated patients, and nurses provide instructions on prophylactic use and good oral care. Nurses emphasize the importance of using steroid mouthwash for the first eight weeks of everolimus treatment and encourage patients to continue using mouthwash even if they are not experiencing mIAS. The second center participated in the TRINITY-1 study evaluating the efficacy and safety of ribociclib plus everolimus plus exemestane. Every patient received steroid mouthwash for eight weeks along with education regarding its clinical benefit. The authors’ initial observations from these centers reiterate the need for patient education from the first visit onward to guide decision making for the prevention and management of mIAS. This preventive approach can support better patient outcomes, enhance quality of life, and improve the management of advanced breast cancer by maintaining adherence and reducing the need for dose modifications of everolimus.

As the case series illustrates, potential suboptimal adherence to the treatment regimen can be a challenge for the oncology team (Boers-Doets et al., 2013; Chia et al., 2013). Therefore, nurses should emphasize to patients the value and benefit of adhering to the concurrent treatment regimen. Another challenge is to tailor education and management strategies to meet an individual patient’s needs. This can be accomplished by

IMPLICATIONS FOR PRACTICE
- Address potential communication barriers by facilitating proactive dialogue and educating patients on the importance of early identification of mTOR inhibitor–associated stomatitis (mIAS) by encouraging patients to self-monitor and report oral pain for prompt intervention.
- Raise awareness about the potential negative impact of mIAS on adherence, and provide suggestions for supportive care measures.
- Emphasize the value of prevention, such as dexamethasone mouthwash, and management strategies to reduce the severity and duration of mIAS and potentially improve quality of life and provide clinical benefits to patients.
identifying patients most at risk of nonadherence and fostering collaborative relationships by listening to their needs, concerns, preferences, and motivations to create an education program that resonates with each patient. A need remains for effective practical approaches among the oncology community to improve safety, adherence, quality of life, and potential treatment outcomes for patients receiving everolimus plus exemestane therapy for advanced breast cancer (Chia et al., 2015). Nurses can address potential communication barriers by facilitating proactive dialogue and educating patients on the importance of early identification of mIAS and its negative impact on adherence and treatment efficacy. Oncology nurses can play a pivotal role in encouraging patients to self-monitor and report oral pain for prompt intervention and discussing the value of prevention and management strategies to reduce the severity and duration of mIAS and improve patient quality of life.

In addition to proactive monitoring of mIAS, nurses should emphasize good routine oral hygiene and suggest supportive care approaches to minimize irritation of lesions, reduce pain, and manage symptoms. Mapping out these options with patients provides critical information, so they can develop an optimized treatment plan for managing mIAS while treating advanced breast cancer.

Limitations
Some limitations to the SWISH trial exist. Dexamethasone mouthwash was evaluated in patients with metastatic breast cancer; findings may not be applicable to other cancer populations. This study did not have a control arm or comparator group.

Conclusion
This article aims to raise awareness of mIAS among oncology nurses and highlights the need for patient education, early and accurate detection of mIAS, and implementation of dexamethasone mouthwash for preventing or minimizing mIAS, particularly during the first eight weeks of initiating everolimus-based therapy. Active dialogue among nurses, patients, and caregivers and early intervention may lead to optimized clinical outcomes by reducing the likelihood of dose reduction, interruption, or discontinuation and, therefore, achieving therapeutic doses of everolimus and delivering high-quality care to patients. Educating patients on the identification and early intervention of mIAS and guiding informed decision making about prophylactic measures and therapeutic interventions will further strengthen the critical role of nurses in supporting patient quality of life and adherence to therapy. Nurses and related healthcare professionals can play a crucial role as educators in recognizing, minimizing, preventing, and managing mIAS. Should future studies determine the efficacy of mTOR inhibitors in patients with other diagnoses, the authors’ learnings could potentially be applied to indications beyond advanced breast cancer.

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