Original Contributions

Stomatitis associated with mammalian target of rapamycin inhibition

A review of pathogenesis, prevention, treatment, and clinical implications for oral practice in metastatic breast cancer

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ABSTRACT

Background. Patients with metastatic breast cancer may develop oral morbidities that result from therapeutic interventions. Mammalian target of rapamycin (mTOR) inhibitor–associated stomatitis (mIAS) is a common adverse event (AE), secondary to mTOR inhibitor therapy, that can have a negative impact on treatment adherence, quality of life, and health care costs. A multidisciplinary team approach is important to minimize mIAS and to maximize treatment benefits to patients with breast cancer. In this review, we discuss the pathophysiology, diagnosis, and natural history of mIAS. Current and new management strategies for the prevention and treatment of mIAS are described in the context of fostering a coordinated team care approach to optimizing patient care.

Types of Studies Reviewed. The authors conducted a PubMed search from 2007 through 2017 using the terms "stomatitis," "mIAS," "everolimus," "mTOR," "metastatic breast cancer," and "oral care." They selected articles published in peer-reviewed journals that reported controlled trials and evidence-based guidelines.

Results. mIAS can be distinguished from mucositis caused by cytotoxic chemotherapy or radiotherapy on the basis of cause, clinical presentation, and treatment paradigms. Specific preventive and therapeutic management strategies can be implemented across the continuum of patient oral health care.

Practical Implications. Oral health care providers are on the frontline of oral health care for patients with metastatic breast cancer and are uniquely positioned to provide patient education, advocate accurate reporting of mIAS, and support early identification, monitoring, and prompt intervention to mitigate the severity and duration of this manageable, potentially dose-limiting AE.

Key Words. Stomatitis; mucositis; aphthous stomatitis; mammalian target of rapamycin inhibitor-associated stomatitis; mammalian target of rapamycin; dexamethasone mouthrinse; everolimus; sirolimus; temsirolimus; metastatic breast cancer.

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The mammalian target of rapamycin (mTOR) kinase regulates several signaling pathways that affect cellular processes involved in autoimmune inflammatory disorders, metabolic disorders, and cancer cell growth and survival.[1] To date, 3 mTOR inhibitors have been approved by the US Food and Drug Administration: everolimus (EVE) for hormone receptor-positive (HR^+), human epidermal growth factor receptor-negative ($HER2^-$) advanced breast cancer, progressive neuroendocrine tumors of pancreatic origin, advanced renal cell carcinoma, and tuberous sclerosis complex[2]; temsirolimus for advanced renal cell carcinoma[3,4]; and sirolimus for renal transplantation.[5,6] Treatment-related adverse events (AEs) include mTOR inhibitor–associated stomatitis (mIAS), rash, fatigue, diarrhea, anemia, hyperglycemia, and noninfectious pneumonitis.[7] mIAS is 1 of the most frequent AEs reported by patients with solid tumors, including metastatic breast cancer,[8,9] and it appears to be independent of the administration route of the mTOR inhibitor. mIAS can have a negative impact on adherence to treatment regimen, patient quality of

life, and health care costs.[10] A multidisciplinary team approach is especially important in balancing the treatment benefits with alleviating symptoms and minimizing this treatment-related AE. With an increasing complexity of coordinating care for patients with cancer among various health care providers (HCP), there is a need for medical oncologists, oral oncologists, dental practitioners, and other oral HCPs to be familiar with mIAS and its prevention and treatment to provide enhanced patient care.[10] In this review, we discuss the pathophysiology of mIAS and describe current and new management strategies in the context of fostering a coordinated team care approach.

TREATMENT-INDUCED ORAL ULCERATIONS

Unlike mucositis caused by cytoreductive chemotherapy or radiation therapy to the head and neck, mIAS is a unique oral inflammatory condition that occurs specifically with mTOR inhibitors.[11,12] mIAS is characterized by ulceration in the oroesophageal mucosa.[13,14] These ulcerations can lead to debilitating oral pain that limits a patient's ability to eat, swallow, and speak; breakdown of the mucosal barrier can further lead to local and systemic infections.[12,14,15]

PATHOPHYSIOLOGY AND DIAGNOSIS OF MAMMALIAN TARGET OF RAPAMYCIN INHIBITOR–ASSOCIATED STOMATITIS

It is theorized that mTOR inhibition may trigger an inflammatory cascade that results in injury to the oral mucosa.[4,16,17] T-cell infiltration is accompanied by increased production of proinflammatory cytokines, such as tumor necrosis factor alpha and interleukin-2, and by decreased epithelial proliferation (for example, lower levels of interleukin-10).[4] Loss of epithelial barrier function and activation of the nuclear factor–kappa β signaling pathway may play a role in the development of oral aphthous ulcerations.[18] mTOR inhibitors may also impair angiogenesis and vascular cell proliferation; thus, they may have a negative impact on wound healing.[6] Possible risk factors for mIAS include higher socioeconomic status, female sex, changes to the oral microbiome environment, genetic predisposition, comorbidities, and history of aphthae.[19,20]

Of note to oral HCPs, the diagnosis of mIAS can be confounded by and is often overestimated because of pain from preexisting dental conditions, difficulty swallowing, and frank mucositis. Thus, there is a need for differential diagnosis to distinguish mIAS from mucositis or recurrent aphthous stomatitis. Various assessment tools have been used to grade mIAS, but each has a shortcoming.[6,21] Available tools are designed to assess mucositis, emphasizing lesion size and dietary impact; therefore, these tools may not adequately evaluate mIAS because of differential presentation (for example, smaller lesion size), persistence of lesions, and impact of pain.[21] The Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, was developed for oral mucositis secondary to cytotoxic chemotherapy and radiation therapy. Common Terminology Criteria for Adverse Events, Version 4.0 assesses symptoms and functional impact (that is, pain, swallowing, and ability to eat) but lacks an objective component for the extent of erythema or duration of ulcerations; thus, it may underestimate the morbidity of mIAS.[6,21] An assessment tool specific to mIAS has been developed that incorporates pain experienced by the patient and the duration of the lesions; however, this instrument has not been validated and thus has limited utility in a practice setting.[14,21]

The clinical features of mIAS are distinct from cytotoxic chemotherapy-induced mucositis with respect to shape, depth, and extent of lesions and more closely resemble recurrent aphthous stomatitis (that is, canker sores) (Table). mIAS presents as discrete, superficial, aphthous-like oval ulcers with a grayish white pseudomembrane and erythematous margin and localizes to nonkeratinized movable oral and oropharyngeal mucosa (Figures 1A-1C).[12,14] Symptoms of mIAS include pain, bleeding, inflammation, burning sensation, and dysphagia.[14] In some instances, the patient's experience of oral pain does not always coincide with presentation of oral erythema or ulceration.[19] After symptom assessment and examination of clinical features, if the putative mIAS lesion or lesions closely resemble aphthous ulcers and are on moveable mucosa, further diagnostic aids may not be necessary. If the clinician is unclear of the diagnosis, there is debate about the role of culture of these lesions, given the challenge of obtaining cultures in an inherently rich environment for microorganisms, the oral cavity. If cultures are obtained, the lesions should be swabbed for bacterial, fungal, and viral cultures and placed in appropriate media to assess for resistant bacteria, as well as herpes simplex viruses 1 and 2. These cultures should be obtained before administration of antimicrobials, which should be given cautiously, given the risk of antibiotic resistance and alteration of the microbiome. The latter is important, because the

ABBREVIATION KEY

AE: Adverse event.
EVE: Everolimus.
EXE: Exemestane.
HCP: Health care provider.
HER2$^-$: Human epidermal growth factor receptor-negative.
HR$^+$: Hormone receptor-positive.
mIAS: mTOR inhibitor-associated stomatitis.
mTOR: Mammalian target of rapamycin.
SWISH: DexamethaSone mouthWash for everolImus-related stomatitiS prevention in HR$^+$ metastatic breast cancer.

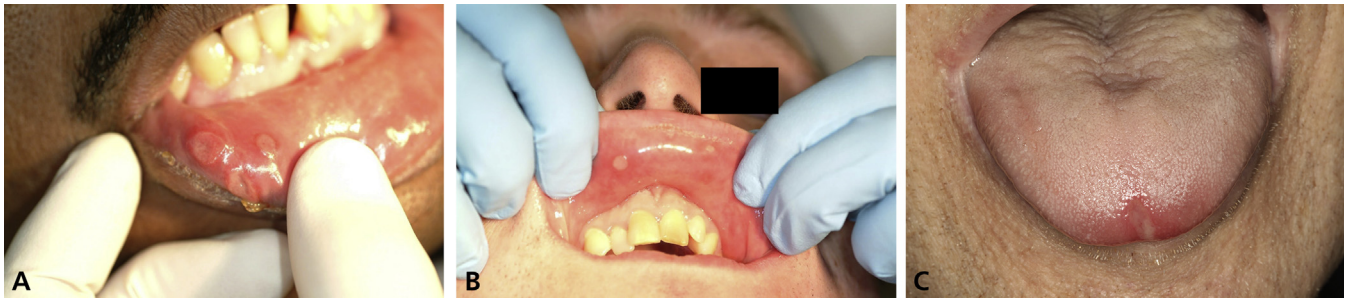

Figure 1. Clinical presentation of mammalian target of rapamycin (mTOR) inhibitor—associated stomatitis. Aphthous-like ulcers on (**A**) labial mucosa of patient treated with sirolimus, (**B**) labial mucosa of patient treated with everolimus, and (**C**) tongue of patient treated with everolimus.

Table. Comparison of chemotherapy-induced mucositis versus mIAS.*

CHARACTERISTIC	CHEMOTHERAPY-INDUCED MUCOSITIS[10,12,17,19,23,37]	mIAS[14,19,22]
Presentation	Deep, confluent lesions appear mostly on the movable buccal mucosae and lateral and ventral surfaces of the tongue, often accompanied by a fibrinous pseudomembrane with cellular debris without peripheral erythema	Shallow, nonconfluent ulcerations, well demarcated with intense erythematous margins; involves nonkeratinized oral mucosa
Duration	7-21 days	Less than 1 week to 2 weeks or more
Incidence	40%-80% for standard to high-dose chemotherapy	2%-78% (grade 3/4 AE† up to 9%)
Symptoms	Pain, bleeding, dysphasia	Pain, erythema, dysphagia, bleeding
Pain Management	Ice chips, topical or systemic analgesic agents	Steroid management may be supplemented with topical administration of local anesthetic agents
Response to Therapy	Limited response to corticosteroid agents	Local or systemic administration of steroid agents can be effective in reducing pain and promoting healing of ulcers

* mIAS: Mammalian target of rapamycin inhibitor-associated stomatitis. † AE: Adverse event.

diversity of the microbiome, which can be affected by antimicrobials, has been linked to improved response to cancer therapy in patients with melanomas, although considerable work remains to confirm this finding in other cancers.[25] In contrast, a report suggested that *Staphylococcus aureus* colonization, with associated superantigen-driven inflammation, drives persistence of mycosis fungoides, with a report that found clinical improvement of mycosis fungoides with treatment of *S aureus* colonization.[26] This is an increasingly complicated area of understanding, with cultures for bacteria, fungi, and viruses worth cautious consideration when faced with an unclear diagnosis of mIAS.

NATURAL HISTORY OF MAMMALIAN TARGET OF RAPAMYCIN INHIBITOR—ASSOCIATED STOMATITIS

Regardless of the therapeutic agent or disease, the natural history of mIAS is similar.[27] The natural history of mIAS has been elucidated in patients with HR^+, $HER2^-$ metastatic breast cancer. Without intervention, mIAS has a rapid onset within weeks of initiating EVE therapy, with most cases being grade 1 or 2; most first mIAS events occur within 8 weeks of initiating EVE therapy.[8,28,29] Resolution of grade 3 or 4 mIAS to grade 1 or less typically occurs within a few weeks with dose interruption or reduction.[7,11] However, a subset of patients may experience a prolonged duration of mIAS that can be painful and may interfere with a patient's oral health, nutritional intake, and quality of life. This can lead to unanticipated treatment interruption, dose reduction, or discontinuation.[4,6] In patients who receive dose reductions, mIAS generally resolves and does not recur.[4] However, there is a risk that therapeutic doses of EVE may not be achieved. Thus, prevention and management of mIAS are critical for patients to maintain therapeutic levels and to adhere to the treatment regimen to optimize clinical benefits.[11]

Box: Strategies for prevention and management of mIAS.*[28,30,31]

PREVENTIVE APPROACHES FOR mIAS

Establish and Maintain Good Routine Oral Hygiene
- Use soft-bristled toothbrush and floss after meals
- Use saline or sodium bicarbonate oral rinses
- Avoid irritants found in dental products (alcohol, phenol, hydrogen peroxide)

Visit Dentist Regularly (Before and During Treatment)
- Minimize infections (chlorhexidine mouthrinse), caries, periodontal disease
- Perform dental prophylaxis
- Address mechanical injury and trauma

Dietary Modifications
- Limit foods and beverages that are acidic, spicy, hard, crunchy, or hot

Patient Education
- Emphasize awareness and monitoring for signs and symptoms of mIAS
- Early recognition and prompt reporting of pain to caregiver and health care providers

Use of Topical Steroid-Based Mouthrinses or Compounded Steroid Rinses To Prevent Incidence of mIAS
- Dexamethasone, prednisolone

TREATMENT APPROACHES FOR mIAS

Topical Anesthetic or Analgesic Agents With or Without Topical Corticosteroid Agents (for Example, Triamcinolone) for Pain Relief
- Lidocaine, benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol

Topical Nonsteroidal Anti-Inflammatory Agents
- Amlexanox, 5% oral paste

Topical Corticosteroids to Reduce the Number and Severity of mIAS Lesions
- Dexamethasone mouthrinse, 0.5 milligrams per 5 milliliters
- Clobetasol gel, 0.05%
- Prednisolone, 15 mg/5 mL
- Triamcinolone, 0.1% cream

Intralesional or Systemic Corticosteroid Agents for Severe mIAS
- Triamcinolone injection
- Oral prednisone, 5 mg; prednisolone

Systemic Analgesic Agents for Severe mIAS
- Oral or intravenous opioids

* mIAS: Mammalian target of rapamycin inhibitor–associated stomatitis.

CURRENT PREVENTION AND TREATMENT LANDSCAPE FOR MAMMALIAN TARGET OF RAPAMYCIN INHIBITOR–ASSOCIATED STOMATITIS IN PATIENTS WITH METASTATIC BREAST CANCER

For oral HCPs, a variety of recommendations can be implemented in the clinic or community setting on the basis of educational, supportive care, prophylactic, and therapeutic measures to reduce the incidence and severity of mIAS (Box).[2,11,27] The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer published clinical practice guidelines with the European Society of Medical Oncology for managing mIAS in patients with cancer receiving mTOR inhibitors.[30]

Educational support

Patients can be educated on the potential risks of developing mIAS when initiating EVE therapy, the signs and symptoms of mIAS, and the benefit of alerting oral HCPs at the first sign of mouth discomfort. Proactive monitoring and early recognition of mIAS can lead to early intervention during a time when the risk of developing mIAS is highest.

Supportive care measures

Some symptoms of mIAS may be controlled by supportive care measures such as saltwater or sodium bicarbonate oral rinses.[6,11,27] Oral health practitioners can reiterate the benefit of good oral hygiene (oral decontamination) measures such as using a soft toothbrush with mild dentifrice, daily flossing, and routine assessment of the oral cavity for infections and lesions for the duration of EVE therapy. It is also important to have a discussion with patients about nutritional considerations, including the avoidance of hot, sour, salty, acidic, hard, and crunchy food and agents that contain hydrogen peroxide, iodine, alcohol, sodium lauryl sulfate, thyme, or tobacco, and to encourage use of cooling measures such as sucking on ice.[11,27]

Preventive options

Expert opinion suggests that patients should implement good oral health care practices and rinse with a nonalcoholic, sodium bicarbonate–containing mouthrinse 4 to 6 times daily as a lavage to prevent mIAS.[31] Anecdotal reports about the use of steroid-based oral rinses or dental pastes suggest that topical steroidal agents could prevent mIAS. If topical steroidal agents are prescribed, patients should be aware they are at a low risk of developing candidiasis.[11,27] Educating oral HCPs on the findings of our clinical trial experience with prophylactic use of a dexamethasone mouthrinse for patients with breast cancer treated with EVE is an opportunity to create awareness of this manageable AE.

EFFICACY OF DEXAMETHASONE MOUTHRINSE IN REDUCING THE INCIDENCE AND SEVERITY OF MAMMALIAN TARGET OF RAPAMYCIN INHIBITOR–ASSOCIATED STOMATITIS

The completed phase 2, US-based, multicenter, single-arm SWISH (dexamethaSone mouthWash for everolImus-related stomatitiS prevention in HR$^+$ metastatic breast cancer) trial established the efficacy and safety of prophylactic use of dexamethasone mouthrinse in preventing or minimizing mIAS in postmenopausal women who receive EVE plus exemestane (EXE) for HR$^+$, HER2$^-$ advanced or metastatic breast cancer.[28] The study reported a greater than 10-fold reduction in the 8-week incidence of grade 2 or greater mIAS (the primary end point) compared with patients in the Breast Cancer Trials of Oral Everolimus-2 study (a similar group of patients treated in a previous study who did not receive dexamethasone solution); 2.4% (n = 2; 95% confidence interval [CI], 0.29% to 8.24%; $P < .001$) versus 33% (n = 160; 95% CI, 28.9% to 37.2%) in patients in the Breast Cancer Trials of Oral Everolimus-2 study and 27.4% at 8 weeks.[7,28] Most patients also reported an ability to maintain a diet with no or few restrictions and to experience minimal or no pain.[28] Limitations of the SWISH study included the use of historical controls and the nonrandomized study design. In the absence of a placebo control, the impact of lesions with a short duration or lesions that resolve spontaneously cannot be assessed and may affect the conclusions. Interim results on the incidence and severity of mIAS from a clinical study of 47 patients treated with EVE, an aromatase inhibitor, and prophylactic hydrocortisone-based or prednisolone oral solution for 12 weeks are consistent with that of the SWISH trial.[31]

The prophylactic regimen used in the SWISH trial was 10 milliliters of a commercially available alcohol-free dexamethasone oral solution 0.5 milligram per 5 mL (Roxane Laboratories/West Ward Pharmaceuticals, 00054-3177-57 [240 mL]; 00054-3177-63 [500 mL]) concurrent with initiating EVE-EXE treatment. Administration required swishing for 2 minutes to allow the mouthrinse to contact the entire oral mucosal surface before expectorating. No food or drink was allowed for 1 hour after administering the mouthrinse. The mouthrinse was administered 4 times daily for the first 8 weeks of initiating EVE-EXE therapy (the period of highest risk of developing mIAS). For the prevention of potential oral fungal infection, a prophylactic topical antifungal with nystatin four times daily or other antifungal regimen after dexamethasone mouthrinse was encouraged. Caution is advised with continued use of nystatin because of sucrose contact. A unique aspect of the study design was to incorporate educational tools about stomatitis and instruction for patients to self-monitor for stomatitis and when to report oral pain and mucosal changes. Patients were also instructed to perform good oral hygiene, including brushing teeth 2 or more times daily with a soft-bristled toothbrush, daily flossing, and routine dental care and maintenance with their dentist. We think the results of the SWISH study highlight the importance of integrating patient education

Figure 2. Multidisciplinary management of mammalian target of rapamycin (mTOR) inhibitor-associated stomatitis (mIAS) in cancer patients.[11,15,21,27,36] This model describes a multidisciplinary strategy and collaborative approach between the oral health care team and other health care providers (HCPs) for management of mIAS in cancer patients. AE: Adverse event. EVE: Everolimus.

with early detection of mIAS and prophylactic use of dexamethasone mouthrinse to prevent (or minimize) mIAS.

Treatment approaches

Once mIAS develops, treatment strategies are based on the severity of symptoms.[32] For patients with milder cases of mIAS or to minimize infection, oral health practitioners can recommend the use of nonalcoholic mouthrinses or salt water or sodium bicarbonate rinse up to an hourly basis.[16,33] Expert opinion recommendations include the use of protectants that coat the oral mucosa such as mucoadhesive gels or topical analgesic agents (for example, viscous lidocaine) for pain management, prophylactic antibiotic agents to minimize secondary infections, topical agents (for example, amlexanox 5% oral paste) to reduce inflammation, and steroid-based mouthrinses or topical steroid agents for treatment of mIAS.[30]

For patients with greater than grade 2 mIAS who experience persistent or severe pain, palliative approaches may not be beneficial. There is a growing body of evidence from the real-world setting that the incidence of greater than grade 2 mIAS remains relatively high with this supportive care approach.[33] Pain associated with mIAS may be treated with topical analgesic agents (with or without corticosteroid agents),[11,16] systemic analgesic agents for severe pain,[30] or "miracle" mouthrinse formulations that consist of an analgesic, antibiotic/antifungal, and steroid cocktail that is used at most cancer centers.[11,27,31,34] However, this broad-spectrum cocktail approach can be ineffective in altering the duration or severity of lesions; thus, it is not recommended.[24] High potency, topical, intralesional, or systemic corticosteroid therapy (dexamethasone mouthrinse, 0.1 mg/mL; clobetasol gel, 0.05%) may be used for treatment of severe disease and may ameliorate pain,

improve healing of mIAS, or reduce the need for dose reductions or interruptions of EVE.[16,22] However in some instances, a patient may benefit from EVE dose delay, reduction, or discontinuation,[6,7,11] particularly in patients for whom debilitating pain can have a negative impact on quality of life and adherence to treatment.

Similar treatment strategies for mIAS have been adopted in other disease areas, for which potential long-term use of an mTOR inhibitor is indicated. A small study of patients who received a renal transplant and were taking sirolimus highlights an effective treatment strategy for mIAS. Chuang and Langone[24] reported that clobetasol cream ameliorated aphthous ulceration, led to symptom improvement, and obviated the need for dose reductions. Maintaining an effective therapeutic range of sirolimus minimized the patient's risk of experiencing acute rejection.[24] Among patients with solid tumors, a comparative systematic review and meta-analysis of mTOR inhibitors reported significantly increased risk of developing mIAS and suggested practical treatment approaches that are consistent with evidence-based guidelines for mIAS.[29,30,35]

MULTIDISCIPLINARY APPROACH FOR MANAGEMENT OF MAMMALIAN TARGET OF RAPAMYCIN INHIBITOR–ASSOCIATED STOMATITIS

Patients with metastatic breast cancer interact with HCPs who manage different aspects of their disease and treatment program; therefore, coordinated care among the HCPs is important for providing optimal patient care and for minimizing or preventing treatment adverse effects of mTOR inhibitors (Figure 2). General dental practitioners and other experienced oral specialists are on the frontline of oral health care for patients with cancer and uniquely positioned to provide patient education that supports good oral hygiene, early identification, monitoring, and accurate reporting of mIAS for prompt intervention and mitigation of the severity and duration of this manageable, potentially dose-limiting AE.

Oral practitioners can monitor the oral cavity, identify and treat mIAS early on, and manage pain associated with mIAS. A thorough examination of the oral cavity, including lips, tongue, gingivae; palpation of visible lesions; and evaluation of function (that is, swallowing, talking) are advised. Specific areas of concern that may lead to oral morbidities are changes in mucosal integrity or cleanliness. The oral cavity should also be assessed to identify, eliminate, and treat sources of oral trauma and irritation that may complicate treatment of mIAS (for example, infections, tissue injury, caries, periodontal disease, endodontic disease, mucosal lesions, and trauma from poorly fitted prostheses or teeth that require extraction).[15] Medical oncologists can describe the disease condition, treatment options, and biology and management of mIAS with patients. Before initiating and throughout treatment, oncology nurses can educate patients about the importance of maintaining good oral health and prompt reporting of oral pain to a HCP or caregiver and to recognize clinical features of mIAS. Pharmacists can discuss correct administration of medications, possible drug interactions, and monitoring for adverse effects. Patient self-care is not to be underestimated in terms of reducing morbidities, especially when patients receive educational tools and supportive follow-up from oral HCPs. Patients need to exercise good oral hygiene, avoid foods that create trauma in the oral cavity, and immediately report oral pain or other signs and symptoms of mIAS to the health care team.[15] Increased knowledge and awareness of the symptoms of mIAS will provide treatment teams with tools to individualize treatment plans and to initiate supportive measures to alleviate symptoms.[23] The success of this multidisciplinary approach depends on proactive and coordinated dialog between oral HCPs (dentists, hygienists), nurses, pharmacists, medical oncologists, and patients and caregivers to support optimized clinical outcomes by reducing the likelihood of dose reduction, interruptions, or discontinuation while delivering high-quality supportive patient care in routine oral practice.

CONCLUSIONS

mIAS is 1 of the most common AEs associated with mTOR inhibitors. With a growing understanding of mIAS in metastatic breast cancer, an opportunity exists to leverage findings about EVE treatment to other disease areas that use an mTOR inhibitor treatment approach. The incidence and severity of mIAS can be effectively managed with patient education and various treatment strategies, including prophylactic use of dexamethasone mouthrinse. A multidisciplinary, supportive care approach should include patient education about good oral health, vigilance, early detection,

and pain management. Ultimately, these approaches of oral health care may translate to improved care and better outcomes in patients with diseases, for which potential long-term use of mTOR inhibitors are indicated.

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