

REVIEW ARTICLE

Mammalian Target of Rapamycin (mTOR) Inhibitors Induce Stomatitis in Patients with Metastatic Breast Cancer (Review)

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ABSTRACT

Metastatic breast cancer patients may acquire oral morbidity from therapeutic procedures. A common adverse event (AE) of the Mammalian target of rapamycin (mTOR) inhibitor is associated stomatitis (mIAS) secondary to mTOR inhibitor therapy, which have a negative impact on the quality of life, therapy adherence and health care expenses. A multidisciplinary team strategy is essential for reducing mIAS and capitalize on therapy advantages for breast cancer patients. We discuss the pathophysiology, diagnosis, and natural history of mIAS in this review. In the context of promoting a coordinated team care approach to optimizing patient care, current and new management policies are outlined for the prevention and treatment of mIAS.

Types of Studies Reviewed: We piloted different research from 2007 through 2019 using the terms “stomatitis,” “mIAS,” “mTOR,” “everolimus,” “oral care.” and “metastatic breast cancer.” We have chosen papers from peer-reviewed journals reporting controlled trials and evidence-based guidance.

Results: Cytotoxic chemical or radiation therapy causes, clinical presentation, and paradigms of therapy can distinguish mIAS from mucositis. The continuum of patient oral health care may include specific preventive and therapeutic leadership approaches.

Practical consequences: Oral health providers are at the forefront of oral health care for patients who have metastatic breast cancer and are uniquely positioned to deliver patient education, to advocate precise reporting of mIAS, and to encourage early identification, monitoring and rapid intervention to reduce the serious and time-limiting dose of this manageable AE.

Keywords: Aphthous stomatitis, Everolimus, Dexamethasone mouthwash, Mammalian target of rapamycin, Metastatic breast cancer, Mucositis, Temsirolimus, Sirolimus, Stomatitis.

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INTRODUCTION

The mammalian target of rapamycin (mTOR) regulates several forms of signaling which influence cellular mechanisms engaged in the development and survival of autoimmune inflammatory diseases, metabolism, and cancer cells.¹ The US Food and Drug Administration has to date approved three mTOR inhibitors: everolimus (EVE) for hormone receptor-positive (HR+); advanced breast cancer, human epidermal development factor (HER2), progressive pancreatic neuroendocrine tumors, advanced kidney carcinoma, and tubercle sculpting complex;² advanced renal cell temsirolimus carcinoma;^{3,4} renal transplant sirolimus.² Adverse events associated with treatment (AEs) implicate non-infectious pneumonitis, mTOR inhibitor-associated stomatitis (mIAS), diarrhea, fatigue, hyperglycemia, anemia and rash.³ The

most frequent AEs demonstrated in patients with solid tumors, especially metastatic breast cancer is mIAS, and appears to be independent of the route of administration of a mTOR inhibitor.⁴ The effect of mIAS may be negative on therapy adherence, the quality of life of patients and health care expenses.⁵ A multidisciplinary team strategy is particularly essential for balance therapy advantages with symptoms to reduce and minimize this therapeutic AE.⁶ As care for cancer patients is becoming increasingly complex in different healthcare suppliers (HCS), medical oncologists, oral oncologists, dentists and other oral HCSs are required to be acquainted with mIAS and its prevention and therapy for improved patient care.⁷ In this review, we talk about mIAS pathophysiology and explain present and new leadership approaches to promote a coordinated attitude to team care.⁸

Pathophysiology and Diagnosis of Stomatitis Associated with Mammalian Target of Rapamycin Inhibitor

mTOR inhibition can cause an inflammatory cascade that can damage the oral mucosa.⁹ Increasing production of proinflammatory cytokines like the tumor necrosis factor- α and interleukin-2 are associated with T-cell infiltration, as well as decreased epithelial proliferation (e.g., lower interleukin-10 levels).¹⁰ Loss of epithelial obstacles and activation of a signaling pathway for the kappa b nuclear factor could play a part in oral aphthous ulceration development.¹¹ Inhibitors of the mTORs also may affect angiogenesis and the proliferation of vascular cells, thereby affecting injury.¹² The mIAS may be subject to increased socio-economic status, female sex, oral microbiomes environment changes, genetic predisposition, comorbidity and apthae history.¹¹ It is important to note with respect to oral HCSs that the diagnosis of mIAS may be confused and is frequently overestimated because of dental pain, difficulty swallowing, and frank mucositis. Differential diagnoses are, therefore, necessary to differentiate mIAS from mucositis or recurrent aphthous stomatitis.¹² Different tools for measuring the mIAS, however, each has a deficiency, have been used. Available instruments are intended to evaluate mucosity and stress lesion size and nutritional impact; these instruments can, therefore not properly assess mIAS due to the differential presentation (for instance, lower lesion size), the persistence of lesion, and effects of pain.¹³ A mIAS-specific evaluation tool was created to include pain and lesion time experienced by the patient, but this tool is non-validated and is therefore of restricted practical use in practice.¹⁴ mIAS clinical characteristics differ from cytotoxic chemotherapy-induced mucositis in terms of form, depth, and magnitude of lesions, and more strongly resemble recurrent aphthous stomatitis (i.e., canker sores) (Table 1).

The mIAS is a non-keratinization of moveable oral and oropharyngeal mucosa and is present as discrete, superficial, aphtuslike oval ulcers with a grayish-white pseudomembrane and erythematous margin.³ mIAS symptoms include bleeding, pain, sensations of burning inflammation, and dysphagia.¹⁵ In some cases, oral pain does not always match with oral erythema or ulceration presentation.¹⁶ If the suspected mIAS injury or lesions strongly similar to the aphthous ulcers and on mobile mucosa (Figure 1A-C), further diagnostic aids may not be essential after symptom evaluation and examination of clinical characteristics.¹⁷ When the clinician is uncertain

about the diagnosis, the role of the culture in these lesions is debated, given the challenge of producing cultures in a microorganism-rich setting.¹⁸ The lesions for bacterial, fungal, and virus cultures should be swabbed and placed in the right media to evaluate resistant bacteria as well as simple herpesviruses 1 and 2.¹⁹ These cultures should be obtained before antimicrobial administration, which should be administered carefully to avoid the risk of antibiotic resistance and microbiome change.²⁰ This is significant because in melanoma patients, the variety of the microbiome, which is influenced by the use of antimicrobials, was connected to enhance a reaction to cancer treatments. However, this finding in other cancers remains substantial work.¹⁹ In comparison, a study proposed that *Staphylococcus aureus* colonization, with related superantigen-driven inflammation, leads to the persistence of mycosis fungoids, with a study that discovered the eradication of *S aureus* colonization provide clinical improvement of mycosis fungoids.²¹ This is an increasingly complex area of knowledge, with cultures worth considering when confronted with an uncertain diagnosis of mIAS for bacteria, fungi, and viruses.²²

Oral Ulceration Induced by Treatment

In contrast to mucositis caused by cyto-reduction or head and neck radiation therapy, mIAS is a unique oral inflammatory condition that occurs with mTOR inhibitors specifically. The ulceration in the oroesophageal mucosa is characteristic of mIAS.²³ These ulcerations may lead to a weakening of oral pain which limits a patient's eating, swallowing and talking capability; breaking up the mucosal barrier may lead to local and systemic infections.²⁴

Table 1: Comparison of chemotherapy-induced mucositis versus mIAS.*

CHARACTERISTIC	CHEMOTHERAPY-INDUCED MUCOSITIS	mIAS
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.



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

Stomatitis Associated with Mammalian Target of Rapamycin Inhibitor and its Natural History

The natural history of mIAS is comparable, irrespective of the therapeutic agent or disease. In patients with HR+, HER2 metastatic breast cancer the natural history of mIAS has been explained.²⁵ Most of the first mIAS events occur in the 8 weeks after EVE therapy has been initiated without intervention, with most cases of grade 1 or 2.²⁶ Dose interruption or decrease in dose typically takes several weeks to resolve grade 3 or 4 mIAS grade 1 or lower.²⁷ A subset of patients can however have a prolonged life of mIAS, which can be painful and can affect oral, nutritional and lifestyle health of a patient.²⁸ This may lead to unexpected interruption of treatment, dose reduction or cessation. mIAS generally solves and does not recur in patients receiving dose reduction.²⁹ There is, however, a danger of not achieving therapeutic doses of EVE. Prevention and management of mIAS are therefore crucial to maintaining therapy concentrations and adhering to the therapy system in order to optimize clinical advantages for patients.²⁵

Present Prevention and Therapy Landscape for Stomatitis Associated with Mammalian Target of Rapamycin Inhibitor in Patients with Metastatic Breast Cancer

For oral HCSs, a number of clinic or community-based recommendations can be implemented using pedagogical, supportive, preventive, and therapeutic action to reduce the incidence and severity of mIAS.³⁰ The Clinical Practices Guidelines with the European Society of Medical Oncology for the management of mIAS in cancer-receiving patients have been issued by the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer.³¹

Educational Support

Initiating EVE treatment, the symptoms and signs of mIAS, and the advantage of warning oral HCSs to first signs of mood discomfort are informed in patients on the prospective hazards of developing mIAS. Even when the risk of creating mIAS is greatest, proactive control and early acceptance of mIAS may lead to early intervention.²⁶

Options for Prevention

Experts suggest that excellent oral health care should be implemented by practice and rinsed with sodium bicarbonate mouth wash, nonalcoholic and 4 to 6 times per day as a lavage for mIAS prevention.¹⁸ Topical steroidal agents might prevent mIAS according to Anecdotal reports using of dental pastes or oral steroid rinses, patients should be knew they are at minimum risk of developing candidiasis if topical steroidal agents are used. For patients with breast cancer treated with EVE, educating oral HCPs on the results of our clinical trial experience with prophylactic use of dexamethasone mouth rinse is a chance to raise an awareness of this manageable AE.³²

Measures for Supporting Care

Some symptoms of mIAS can be regulated by support measures such as saltwater or oral washes of sodium bicarbonate.³³ Oral medical professionals can reiterate the advantages of excellent oral hygiene (oral decontamination), such as the use of a mild

toothbrush, daily flossing and routine oral cavity evaluation for diseases and lesions during EVE treatment.³⁴

Prevention Strategies of mIAS

- Create and maintain good oral hygiene routine
- Use pinched toothbrush and floss after food.
- Use oral saline or sodium bicarbonate wash.
- Visit dentist regularly (before and during treatment) to avoid irritants found in dental goods (alcohol, phenol, hydrogen peroxide).
- Minimize caries, infections and periodontal illness (chlorhexidine mouth wash).
- Carry out dental prophylaxis.
- Addressing mechanical and trauma injury.

Education for Patients

- Signs and symptoms of mIAS should be emphasized and monitored.
- Topical steroid-based mouthwash or compound steroid rinses to prevent mIAS occurrence early recognition and timely reporting of pain to health caregivers and suppliers.
- Prednisolone, Dexamethasone

Dietary Changes

- Limit acidic, spicy, difficult, crunchy or hot foods and drinks.

Approaches for mIAS Treatment

Topical analgesic or anesthetic agents for the relief of pain with or without topical corticosteroids (for example, triamcinolone):

- Tetracaine hydrochloride, menthol, phenol or butyl aminobenzoate, Lidocaine or Benzocaine.

Topical Anti-inflammatory Non-steroidal Agents

- 5% Amlexanox oral paste.

Topical Corticosteroids to Decrease mIAS Lesions

Number and Severity

- Rinse the mouth with Dexamethasone, 0.5 milligram per 5 ml.
- 0.05%, Clobetasol gel.
- 15 mg/5 mL, Prednisolone.
- 0.1% cream, Triamcinolone.

Systemic or Intralesional Corticosteroid Agents for Severe mIAS

- Triamcinolone injection.
- 5 mg; prednisolone orally.

For Severe mIAS use Systemic Analgesic Agents:

- Intravenous or Oral opioids.

Dexamethasone Mouthwash Efficacy in Minimizing the Frequency and Harshness of Stomatitis Associated with Mammalian Target of Rapamycin Inhibitor

The completed phase 2 research identified the effectiveness and protection of the prophylactic use of dexamethasone mouthwash in the prevention or minimization of mIAS in postmenopausal women receiving EVE plus exemestane (EXE) for advanced or metastatic breast cancer of HR⁺, HER2⁽³⁵⁾.

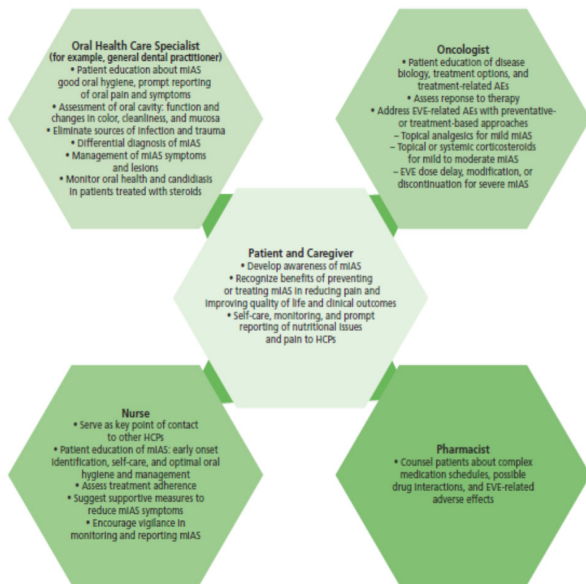


Figure 2: Multidisciplinary lines for controlling stomatitis associated with mammalian target of rapamycin inhibitor.

Multidisciplinary Lines for Controlling Stomatitis Associated with Mammalian Target of Rapamycin Inhibitor

Patients with metastatic breast cancer communicate with HCSs who handle different aspects of their disease and treatment program; thus, coordinated care between HCSs is important to ensure optimal patient care and reduce or avoid the adverse effects of mTOR inhibitors on treatment (Figure 2).³⁶ General dentists and other professional oral specialists are at the forefront of oral health care for cancer patients and are in a unique position to provide patient education which promotes good oral hygiene, early detection, tracking and accurate reporting of mIAS for timely treatment and mitigation of the extent and length of this manageable, potentially dose-limiting AE.³⁴ Oral practitioners should observe the oral cavity early on, diagnose and treat mIAS, and manage mIAS-related pain. It is recommended that the oral cavity be thoroughly examined, including tongue, lips, gingivae; palpation of apparent lesions; and function assessment (i.e. swallowing, speaking).³⁷ The oral cavity should also be examined to recognize, remove and manage causes of oral trauma and pain that may hinder mIAS care (e.g. infections, tissue damage, caries, periodontal disease, endodontic disease, mucosal lesions, and trauma from poorly fitted prostheses or teeth requiring extraction).³⁸ Medical oncologists will explain to patients the state of the disease, treatment options, and mIAS biology and management. Until beginning and throughout treatment, oncology nurses should inform patients on the importance of maintaining good oral health and timely oral pain reporting to an HCS or caregiver and understanding the medical characteristics of mIAS.¹⁶ Pharmacists should address proper medication management, potential drug reactions, and adverse effect monitoring.²⁶ In terms of reducing morbidity, self-care for patients should not be overlooked, particularly when patients receive educational tools and oral HCS aid. Patients should

maintain good oral hygiene, avoid foods that cause damage in the oral cavity, and report immediately to the health care team oral pain or other signs and symptoms of mIAS.³⁹ Improved knowledge and awareness of mIAS symptoms will provide care teams with resources for individualizing treatment plans and implementing symptom management support measures.³⁰

CONCLUSION

mIAS is one of the most popular AEs associated with mTOR inhibitors. With an increasing knowledge of mIAS in metastatic breast cancer, an prospect exists to control findings about EVE management of other disease areas that depend on mTOR inhibitor. Through patient education and different treatment approaches, including prophylactic use of dexamethasone mouthwash, the frequency and extent of mIAS can be effectively managed. Patient education on good oral health, vigilance, early detection and pain management should be part of a multidisciplinary, supportive care approach. Overall, these oral health care strategies can turn into improved treatment and better outcomes in disease patients, suggesting possible long-term use of mTOR inhibitors.

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