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Managing cancer treatment-related stomatitis:

Current guidance in diagnosis, intervention, and interdisciplinary care

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This guide reviews recent trends in the management of cancer treatment-related stomatitis, including

- Differentiating between clinical characteristics of classic stomatitis and mTOR inhibitor associated stomatitis (mIAS)
- Identifying high-risk patients
- Assessing severity
- Recapping MASCC and NCI guidelines for the management of classic stomatitis
- Increasing awareness of effective interventions for mIAS in the absence of recognized treatment guidelines
- Building an interdisciplinary oral care protocol
- Ensuring that patients can identify early signs and symptoms

MASCC=Multinational Association of Supportive Care in Cancer.
NCI=National Cancer Institute.

Introduction

Stomatitis, a term sometimes used interchangeably with oral mucositis, is a common side effect of many anticancer therapies, including radiation, chemotherapy, and some targeted agents, in particular mTOR inhibitors. [1,2] It comprises any inflammatory condition of oral tissue, including the mucosa, dentition/periapices, and the periodontium. [1]

Classic stomatitis associated with radiation and chemotherapy has been well documented, and several management guidelines and treatment strategies have been established.[3-5] With the addition of mTOR inhibitors to the therapeutic armamentarium, a pathophysiologically distinct form of oral lesion has emerged, sometimes referred to as mTOR inhibitor-associated stomatitis, or mIAS. [3,6]

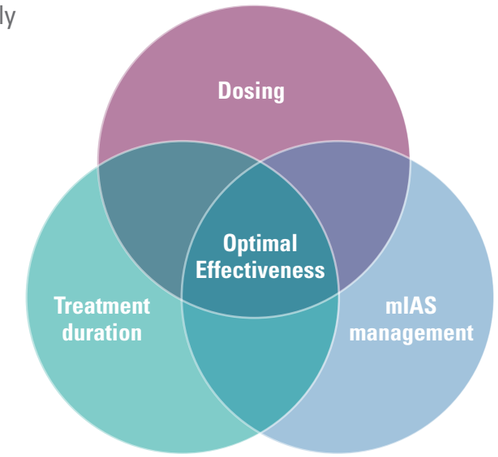

Figure 1. The relationship between treatment duration, dosing, and mIAS management.

With both classic stomatitis and mIAS, it is recommended that steps be taken early to minimize severity and thus reduce the likelihood of treatment discontinuation. [7,8] While there are no established treatment guidelines for mIAS, pathology, incidence and management strategies have been documented since its early appearance in transplant recipients receiving mTOR inhibitor therapy. Clinical experience has demonstrated that mIAS is often manageable and reversible, allowing patients to continue treatment (see Figure 1). [4,8,9]

Current trends indicate that cancer treatment-related stomatitis is manageable in most patients through identification of risk factors, early prevention, and an interdisciplinary approach to treatment, as well as patient education and awareness. [6,8] Please refer to Table 1 for the incidence of stomatitis by treatment type.

Table 1: Estimated incidence of stomatitis by treatment type.

Radiation	Chemotherapy	mTOR inhibitors
Alone **30%-69%[10]**	Alone **Up to 40%[11]**	Depending on treatment regimen **Up to 75%[8]**
In combination with radiosensitizing chemotherapy **Up to 100%[7]**	In bone marrow transplant patients **Up to 76%[10]**	

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Clinical presentation: Differentiating classic stomatitis from mIAS

Stomatitis is a frequently occurring side effect seen with many anti-cancer treatments. As has been shown, its incidence can range from 40% to 100%, depending on treatment type. [7,10,11]

Table 2 highlights the presentation, severity, course, and treatment risk associated with stomatitis/ Oral mucositis.

Table 2: Presentationof classic stomatitis/oral mucositis.

Presentation

- Presents as erythema, inflammation, lesions, ulceration, and hemorrhage in the mouth and/or throat, and characterized by irregularly shaped lesions lacking peripheral erythema.[8,11]
- Often linked to other gastrointestinal symptoms.[3]

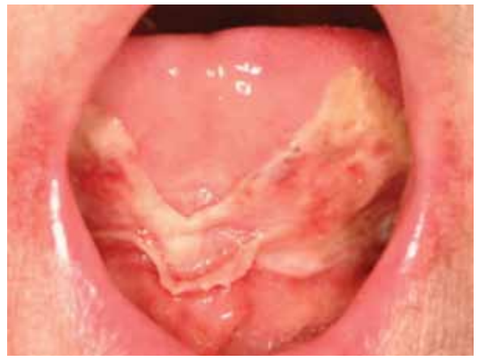

Figure 2: Stomatitis associated with cytotoxic chemotherapy

Severity and course

- Severe stomatitis occurs in approximately 10%–30% of patients with solid tumors being treated with conventional chemotherapy; that number rises up to 70% in those patients who undergo hematopoietic stem cell transplantation.[3]
- Usually appears 7 to 10 days after initiation of therapy; self-limiting when uncomplicated by infection and heals within 2 to 4 weeks after discontinuation of treatment.[1]
- Often reported as worst toxicity associated with high-dose chemotherapy or chemo-radiation and may result in significant patient morbidity.[7]

Treatment risk

- Some, but not all, chemotherapies have the same risk of stomatitis.[3]
- Classes of chemotherapy implicated in the development of stomatitis include[11]
  - Antimetabolites
  - Antitumor antibiotics
  - Alkylating agents
  - Vinca alkaloids
  - Taxanes
  - Epipodophyllotoxins

However, mIAS has been found to be distinctly different from classic stomatitis associated with radiation and chemotherapy. [3] Table 3 highlights the differences in presentation, severity, course, and treatment risk between classic stomatitis/oral mucositis and mIAS.

Table 3: Presentation of mIAS.

Presentation

- Presents as aphthous-likeulcers—discreet, focal or multifocal, and relatively shallow, surrounded by an erythematous margin. [3]
- Lesions are rarely linked to gastrointestinal events.[3]

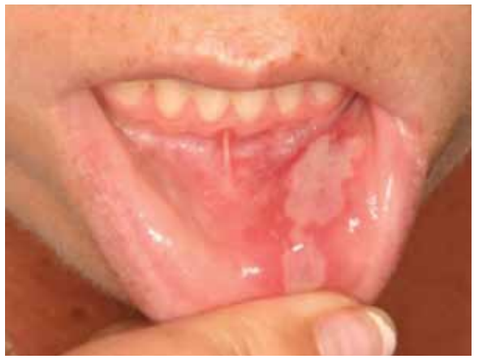

Figure 3: Stomatitis associated with mTOR inhibitor

Severity and course

- Although mIAS occurs frequently, in up to 75% of patients the oral lesions are typically only Grade 1 or 2 and usually develop during the first cycle of therapy.[4,8]
- In a retrospective study of Phase I and Phase II trials in patients receiving ridaforolimus or everolimus, the median time to development of mIAS after initiation of treatment was 10 days.[4]
- In a combined analysis of two Phase I trials, on average mIAS peaked in severity within 5 days of treatment with ridaforolimus and, in most cases, resolved spontaneously within 4 to 5 days.[3]
- mIAS is frequently reported, but generally manageable with prophylactic therapy.[8]

Treatment risk

- Consistent risk among mTOR inhibitors, including sirolimus, temsirolimus, everolimus, and ridaforolimus.[8]

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Identifying high-risk patients and assessing severity

Risk factors for stomatitis in cancer patients

To appropriately manage classic stomatitis, a careful oral assessment is important for high-risk patients.[12] Risk factors for stomatitis in cancer patients are directly associated with treatment type, dose intensity, method of administration, and patient-based variables.[1,6] Combination therapy may increase the risk and severity pf stomatitis. For example, radiation with concurrent chemotherapy or te addition of targeted therapy to a cytotoxic regimen may be confoundingfactors.[6,7] Comorbidities, nutritional deficiencies, demographics, and genetic polymorphisms may also increase the risk.[6] It is important to determine which patients may be at higher risk for stomatitis in order to prevent and manage its severity.

Some common risk factors for stomatitis

- Age: younger or elderly patients[10]
- History of poor oral hygiene[10]
- Acute or chronic periodontal disease[10]
- Nutritional deficiencies[10]
- Compromised immune system[11]
- Oral microorganisms, including *herpes simplex* and *candida tropicalis*[7]

Assessing the severity of classic stomatitis with stomatitis/oral mucositis scales

There are a number of assessment scales available to measure the stage and severity of classic stomatitis, including the World Health Organization (WHO) toxicity scale and the NCI common toxicity criteria[6,12] (see Table 4). However, these guidelines have been designed to evaluate classic stomatitis and may potentially result in misgrading mIAS in some patients.[13]

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Table 4: WHO and NCI classic stomatitis toxicity assessment scales.[6]

WHO Oral Toxicity Scale (OTS)

Grade 0	Grade 1	Grade 2	Grade 3 (Severe)	Grade 4 (Severe)
No evidence of stomatitis	Erythema and Soreness	Ulcers, able to eat solids	Ulcers requiring liquid diet	Ulcers, with alimentation not possible

NCI Common Toxicity Criteria (NCI CTC v4.0)

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Asymptomatic/ no intervention	Moderate pain/ no interference with oral intake	Severe pain/ interfering with oral intake	Life-threatening/ urgent intervention required	Death

NCI=National Cancer Institute.

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Guidelines for managing classic stomatitis

Prevention and management of classic stomatitis differ depending on the type of therapy the patient receives: radiation, standard-dose chemotherapy, or high-dose chemotherapy with or without total body irradiation plus HSCT (see Table 5).

Table 5: MASCC-recommended interventions for managing classic stomatitis.[5,6]

Radiation Therapy	Standard-dose Chemotherapy	High-dose Chemotherapy with or without total body irradiation plus HSCT
Prevention • Use midline radiation blocks and 3-D radiation treatment. • Use benzydamine in patients with head and neck. cancer receiving moderate-dose radiation therapy. • Do not use chlorhexidine in patients with solid tumors of the head and/or neck. • Do not use antimicrobial lozenges.	**Prevention** • Use oral cryotherapy for patients receiving bolus 5-FU. • Suggested use of oral cryotherapy in patients treated with bolus doses of edatrexate. • GM-CSF use with docetaxel + doxorubicin + cyclophosphamide (TAC) has demonstrated a significant reduction in stomatitis in breast cancer patients. • Do not use acyclovir and its analogs.	**Prevention** • Use keratinocyte growth factor-1 (palifermin) 60 mg/kg per day for 3 days prior to conditioning treatment, and for 3 days posttransplantation in patients with hematologic cancers. • Use cryotherapy in patients receiving high-dose melphalan. • Do not use pentoxifyline in HSCT patients. • Use LLLT if the treatment center is able to support its use.
Management Do not use sucralfate	**Management** Do not use chlorhexidine to treat established stomatitis	N/A

MASCC=Multinational Association of Supportive Care in Cancer.
5-FU=5-fluorouracil.
HSCT=Hematopoietic stem cell transplantation.
LLLT=Low-level laser therapy.
GM-CSF=Granulocyte-macrophage colony-stimulating factor.

A stepped approach is recommended when managing classic stomatitis with topical treatments (see Table 6).[1]

Table 6: NCI-recommended interventions for managing classic stomatitis.

1. Bland rinses[1]	• 0.9% saline solution • Sodium bicarbonate solution • 0.9% saline/sodium bicarbonate solution
2. Mucosal coating agents[1]	• Amphopjel® • Kaopectate® • Hydroxypropyl methylcellulose film-forming agents • Gelclair®se
3. Topical anesthetics*[1]	• Lidocaine: viscous, ointments, and sprays • Benzocaine: sprays and gels • 0.5% or 1.0% dyclonine hydrochloride (HCl) • Diphenhydramine solution
4. Systemic analghesics*[1]	• Benzydamine HCl topical rinse • Opioid drugs: oral, IV, patches, or transmucosal
5. Growth factor (keratinocyte growth factor-1)	• Palifermin

NCI=National Cancer Institute.
*Systemic analgesics should be used when topical treatments do not sufficiently relieve patient symptoms.

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Suggested interventions for the management of mIAS.

Due to the recent introduction of mTOR inhibitors to the treatment paradigm, there are no currently established guidelines for the management of mIAS, but some management approaches have been documented.[6,8] These include topical or systemic medications, palliative measures, and dose reduction.[8]

High -dose prednisone or prednisolone may be used for mIAS esophageal ulcers.[8] For recurrent mIAS in patients still on cancer protocol, intensive topical corticosteriods may be used and systemic therapies including pentoxifylline, colchicines, and azathioprine may be considered.[8] For Grade ≥2 mIAS, the following may be considered:

- Dose reduction of mTOR inhibitor as necessary[8]
- Intralesional corticosteriod injection based on size of ulcer and degree of pain[4]
- High-dose systemic prednisone for severe pain after failed treatment with localized therapy and mTOR dose reduction[4]

Please refer to each medication's prescribing information for further guidance on mIAS management.

Topical treatments

- Topical high-potency corticosteroids
  - 0.1 mg/mL dexamethasone
  - 0.05% clobetasol gel
- Topical nonsteroidal anti-inflammatory
  - 5% amlexanox oral paste
- Topical anesthetic
  - Miracle mouthwash
  - 2% viscous lidocaine

For mIAS esophageal ulcers

- High-dose prednisone or prednisolone

Grade ≥2 mIAS

- Dose reduction of mTOR inhibitor as necessary
- Intralesional corticosteroid injection based on size of ulcer and degree of pain
- High-dose systemic prednisone for severe pain after failed treatment with localized therapy and mTOR dose reduction

Recurrent mIAS in patients still on cancer protocol

- Intensive topical corticosteroids
- Systemic therapies: pentoxifylline, colchicines, azathioprine, for example

Growth factor (keratinocyte growth factor-1)

- Palifermin

Building an interdisciplinary preventative oral care protocol for classic stomatitis and mIAS.

Oral cae protocols developed by a multidisciplinary team may reduce the severity of stomatitis.[6,7] These protocols should include educational materials for both patients ad health care providers.[7,8]

Good clinical practice recommendations begin with referral to a dental professional.[7,8] Recommendations for patients include:

- Use a soft toothbrush that is replaced regularly
- Brush and floss regularly, after meals
- Use mild toothpaste and avoid those that contain sodium lauryl sulfate or strong flavor
- Frequent use of nonmedicated oral rinses such as saline or baking soda rinses
- Avoid alcohol-based rinses
- Follow appropiate denture care

Referral to a dietitian is also recommended.[8] Additionally, the following should be avoided by patients in an attempt to prevent classic stomatitis and mIAS:

- Spicy or acidic foods and beverages
- Hard or crunchy foods that have the potential to damage the oral mucosa
- Hot beverges and foods (tepid foods are recommended)

A regular oral pain assessment should incorporate nurse-and patient-utilized tools to evaluate the dimentions of stomatitis before and during treatment. [8,14] Such evaluations should consider the level of function, pain, and state of the oral cavity[10] and should incorporate education on risk factors and symptoms identification.[8]

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Educating patients about stomatitis before and during anticancer treatment

It is important that health care providers inform patients about the signs and symptoms of stomatitis before they begin treatment.[8] Patient oral hygiene standardsshould be assessed and patients should be educated pn an appropriate oral care protocol.[11] They should also be reminded to contact their health care professional if they experience any signs or symptoms of stomatitis, including[8,12]:

- Mouth inflamation or pain
- Mouth ulcers
- sore oral membrane
- Oral membrane ulcers
- Oral bleeding
- Blood in saliva

Future directions

Despite advances in the prevention and treatment of cancer-related stomatitis, it remains a common side effect of radiation, chemotherapy, and some targeted therapies.

There are several established guidelines for the treatment of classic stomatitis, but with the increased incorporation of mTOR inhibitors in the treatment paradigm, establishing standard guidelines for the identification, management, and prevention of mIAS is of great importance. In the meantime, documented approaches for the treatment of mIAS include topical or systemic medications, palliative measures, and dose reduction.[8] These approaches provide an important starting point for the control of this clinically significant reaction.

References:

1. National Cancer Institute. Oral complications of chemotherapy and head/neck radiation. Available at: http://www.cancer.gov/cancertopics/pdq/supportivecare/oralcomplications/HealthProfessional/page5. Accessed April 13, 2012. **2.** Vignot S, Faivre S, Aguirre D, Raymond E. mTOR-targeted therapy of cancer with rapamycin derivatives. Ann Oncol. 2005;16:525-537. **3.** Sonis S, Treister N, Chawla S, Demetri G, Haluska F. Preliminary characterization of oral lesions associated with inhibitors of mammalian target of rapamycin in cancer patients. Cancer. 2010;116:210-215. **4.** de Oliveira MA, Martins FM, Wang Q, et al. Clinical presentation and management of mTOR inhibitor-associated stomatitis. Oral Oncol. 2011;47:998-1003. **5.** Rubenstein EB, Peterson DE, Schubert M, et al. Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. Cancer. 2004;100:2026-2046. **6.** Peterson DE, Bensadoun R-J, Roila F. Management of oral and gastrointestinal mucositis: ESMO clinical practice guidelines. Ann Oncol. 2011;22:vi78-vi84. **7.** Barasch A, Epstein JB. Management of cancer therapy-induced oral mucositis. Derm Therapy. 2011;24:424-431. **8.** Pilotte AP, Hohos MB, Polson KMO, Huftalen TM, Treister N. Managing stomatitis in patients treated with mammalian target of rapamycin inhibitors. Clin J Onc Nursing. 2011;15:E83-E89. **9.** De Masson A, Fouchard N, Méry-Bossard L, Dauedorffer JN. Cutaneous and mucosal aphthosis during temsirolimus therapy for advanced renal cell carcinoma: review of cutaneous and mucosal side effects of mTOR inhibitors. Dermatol. 2011;223:4-8. **10.** Naidu MUR, Ramana GV, Rani PU, Mohan IK, Suman A, Roy P. Chemotherapy-induced and/or radiation therapy-induced oral mucositis—complicating the treatment of cancer. Neoplasia. 2004;6:423-431. **11.** Wojtaszek C. Management of chemotherapy-induced stomatitis. Clin J Oncol Nursing. 2000;4:263-270. **12.** Harris DJ. Cancer treatment-induced mucositis pain: strategies for assessment and management. Therapeutics Clin Risk Management. 2006;2:251-258. **13.** Boers-Doets CB, Epstein JB, Raber-Durlacher JE, et al. Oral adverse events associated with tyrosine kinase and mammalian target of rapamycin inhibitors in renal cell carcinoma: a structured literature review. Oncologist. 2011;16:1-10. **14.** Harris DJ, Eilers JG, Cashavelly BJ, Maxwell CL, Harriman, A. ONS PEP resource: Mucositis. In L.H. Eaton & J.M. Tipton (Eds.), Putting evidence into practice: Improving oncology patient outcomes. Pittsburgh, PA: Oncology Nursing Society. 2009.

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Managing cancer treatment-related stomatitis:

Definitions:

- Stomatitis and oral mucositis, sometimes used interchangeably, comprise any inflammatory condition of oral tissue, including the mucosa, dentition/periapices, and the periodontum.[1]
- mTOR inhibitor-associated stomatitis (mIAS) is represented by a pathologically distinct form of lesion characterized as apthous-like ulcers that are discrete, focal or multifocal, relatively shallow, and surrounded by an erythematous margin.[2]

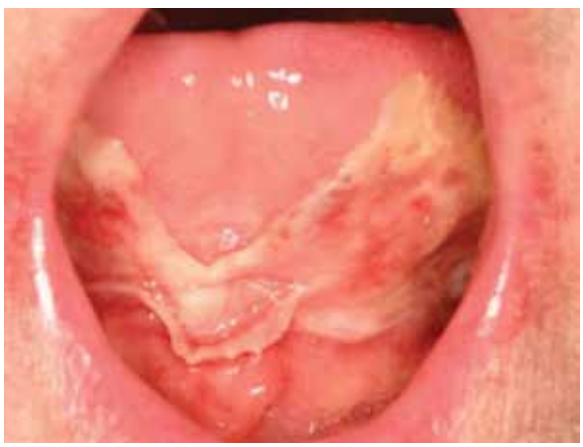

Figure 1A: Classic stomatitis

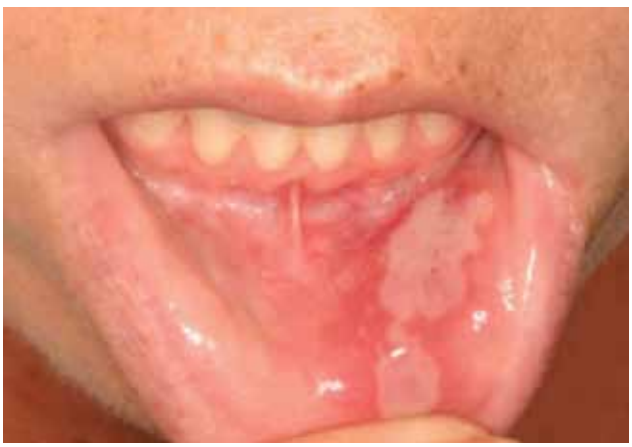

Figure 1B: mIAS.

Signs and symptoms

(see Figures 1A and 1B) [6,7]*:*

- Mouth inflammation or pain
- Mouth ulcers
- Sore oral membrane
- Oral membrane ulcers
- Oral bleeding
- Blood in saliva

Risk factors:

- Age: younger or elderly patients[3]
- History of poor oral hygiene[3]
- Acute or chronic periodontal disease[3]
- Nutritional deficiencies[3]
- Compromised immune system[4]
- Oral microorganisms, including *herpes simplex* and *candida tropicalis*[5]

Managing cancer treatment-related stomatitis

Severity and course:

- Classic stomatitis:
  - Severe stomatitis usually appears 7 to 10 days after initiation of therapy, is self-limiting when uncomplicated by infection, and heals within 2 to 4 weeks after discontinuation of treatment.[1]
- mIAS:
  - Although mIAS occurs frequently, in up to 75% of patients the oral lesions are typically only Grade 1 or 2 and usually develop during the first cycle of therapy.[6,8]
  - In a retrospective study of Phase I and Phase II trials in patients receiving ridaforolimus or everolimus, the median time to development of mIAS after the initiation of treatment was 10 days.[8]
  - In a combined analysis of two Phase I trials, on average mIAS peaked in severity within 5 days of treatment with ridaforolimus and, in most cases, resolved spontaneously within 4 to 5 days.[2]

NCI-recommended interventions for managing classic stomatitis:

- Bland rinses[1]
- Mucosal coating agents[1]
- Topical anesthetics[1]
- Systemic analgesics[1]
- Growth factor (keratinocyte growth-factor-1)[1]

Suggested interventions for the management of mIAS:

- High protein corticosteroids, including 0.1mg/mL dexamethasone and 0.05% clobetasol gel[6]
- Nonsteroidal anti-inflammatory such as 5% amlexanox oral paste[6]
- Anesthetics including Miracle mouthwash and 2% viscous lidocaine[6]

For additional information and guidance on the management of stomatitis, please see the companion guide, "Managing Cancer Treatment-related Stomatitis."

References:
1. National Cancer Institute. Oral complications of chemotherapy and head/neck radiation. Available at: http: www.cancer.gov/cancertopics/pdq/supportivecare/oralcomplications/HealthProfessional/page5. Accessed April 13, 2012. **2.** Sonis S, Treister N., Chawla S, Demetri G, Haluska F. Preliminary characterization of oral lesions associated with inhibitors of mammalian target of rapamycin in cancer patients. Cancer. 2010;116:210-215. **3.** Naidu MUR, Ramana GV, Rani PU, Mohan IK, Suman A, Roy P. Chemotherapy-induced and/or radiation therapy-induced oral mucositis—complicating the treatment of cancer. Neoplasia. 2004;6:423-431. **4.** Wojtaszek C. Management of chemotherapy-induced stomatitis. Clin J Oncol Nursing. 2000;4:263-270. **5.** Barasch A, Epstein JB. Management of cancer therapy-induced oral mucositis. Derm Therapy. 2011;24:42-431. **6.** Pilotte AP, Hohos MB, Polson KMO, Huftalen TM, Treister N. Managing stomatitis in patients treated with mammalian target of rapamycin inhibitors. Clin J Oncol Nursing. 2011;15:E83-E89. **7.** Harris DJ. Cancer treatment0induced mucositis pain: strategies for assessment and management. Therapeutics Clin Risk Management. 2006;2:251-258. **8.** de Oliveira MA, Martins FM, Wang Q, et al. Clinical presentation and management of mTOR inhibitor-associated stomatitis. Oral Oncol. 2011;47:998-1003.

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