Prevention and treatment options for mTOR inhibitor-associated stomatitis

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Inhibitors of mammalian target of rapamycin (mTOR) are approved for treatment of various advanced solid tumors (renal cell carcinoma, neuroendocrine tumors, breast cancer). mTOR inhibitor-associated stomatitis (mIAS), a frequent, early-onset side effect of this drug class, can be dose limiting and diminish patient quality of life. This systematic review describes clinical presentation and pathophysiology of mIAS and reviews its prevention and treatment. Published literature on mTOR inhibitors and their side effects, and their prevention and treatment were reviewed. Preventative and management strategies under evaluation in clinical trials were also reviewed. The majority of patients develop a mild form of stomatitis that does not interfere with treatment of their disease. A minority of patients can develop moderate to severe mIAS that can be managed with treatment modification or discontinuation, but these approaches may have an impact on disease outcome. mIAS is a relatively recent phenomenon, so evidence-based preventive and therapeutic measures are not yet available – although under active investigation – and current management is based largely on collective experience with chemotherapy- or radiation-induced oral mucositis and aphthous ulcers. Expert opinion and clinical experience from managing oral mucositis and apthous ulcers suggest that management of mIAS should focus on three major approaches: prevention, early aggressive treatment, and, when needed, more aggressive pain management. Early recognition and diagnosis of mIAS facilitate early intervention to limit potential sequelae of mIAS and minimize the need for mTOR inhibitor dose reduction and interruption. Funding for manuscript development was provided by Novartis Pharmaceuticals Corporation.

Mammalian target of rapamycin (mTOR), a serine–threonine protein kinase, operates in the phosphoinositide 3-kinase (PI3K)–protein kinase B (AKT)–mTOR signal transduction pathway regulating both normal and cancer cellular processes, including cell growth, proliferation, motility, survival, and protein and lipid synthesis.[1] Genetic alterations affecting this pathway, including mutations in receptor tyrosine kinases PI3K and AKT, occur frequently in human cancers,[2] supporting the rationale to develop drugs that target pathway components, such as mTOR inhibitors.

Two mTOR inhibitors are currently approved by the US Food and Drug Administration for cancer treatment: temsirolimus, for advanced renal cell carcinoma (RCC; approved 2007)[3] and everolimus, for advanced RCC (approved 2009), advanced pancreatic neuroendocrine tumors (pNET; approved 2011), and hormone receptor-positive (HR-positive), human epidermal growth factor receptor-2 (HER2)-negative advanced breast cancer (approved 2012).[4] Another mTOR inhibitor, sirolimus, is approved for use as an immunosuppressive agent and prophylactic against organ rejection after kidney transplant.[5]

Stomatitis, inflammation of the oral mucosa with contributing factors of genetic predisposition, nutritional deficiencies, infections, and immunological or hematologic dysfunction,[6] occurs frequently as a side effect associated with mTOR inhibitor treatment.[7-9] Left untreated or managed unsatisfactorily, mTOR inhibitor-associated stomatitis (mIAS) may cause patients discomfort and trouble with maintaining adequate nutritional intake and proper oral hygiene, as well as strict adherence to cancer treatment. It is therefore important for health care providers of cancer patients receiving mTOR inhibitor treatment to be knowledgeable about this side effect. The purpose of the present systematic review of published literature is to provide a better understanding of the differential diagnosis of mIAS, the pathophysiology of mIAS, preventive strategies for patients initiating mTOR inhibitor treatment, and treatment options available to manage mIAS.

Method

The PubMed database was searched with the terms *mTOR inhibitor* and *stomatitis* (no date restriction); 79 articles were retrieved, and all abstracts were reviewed to select those relevant to the aims of this review article. To understand future directions for management and prevention of mIAS, a search of

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clinicaltrials.gov was performed with the terms *temsirolimus everolimus stomatitis* yielding 12 clinical trials, of which 4 were excluded: 1 trial was terminated due to slow accrual, the status of 1 trial had not been verified in >2 years, and 2 studies focused on efficacy outcomes. A search of the American Society of Clinical Oncology (ASCO) meeting abstracts database was performed to assess the availability of clinical trial data; the search was limited to 2011-2016 and terms were *stomatitis* in the title and *mTOR* in the abstract or title. Seven abstracts were retrieved; 2 discussed stomatitis prevention (1 as a "trial-in-progress" and 1 presented results of the trial); the other 5 abstracts presented meta-analyses or reviews of previous clinical studies to assess the risk, incidence, management, and resolution of mIAS.

Review findings

Incidence of mIAS in patients treated for cancer

Two recent meta-analyses quantified the rate of mIAS in patients receiving mTOR inhibitors. Shameem and colleagues[10] identified 9 randomized studies of everolimus (8 phase 3, 1 phase 2) and 2 of temsirolimus (1 each phase 2 and 3) involving a total of 4752 patients with a variety of tumor types including angiomyolipoma, breast, gastric, giant cell astrocytoma, pNET, and RCC. Patients received everolimus monotherapy (n = 1,075) or in combination with exemestane (n = 485), tamoxifen (n = 54), letrozole (n = 137), or octreotide (n = 216). Temsirolimus was administered as monotherapy (n = 208) or in combination with interferon (n = 210) or letrozole (n = 550). The incidence of all-grade stomatitis in the 11 studies ranged from 11%-63%, and the overall incidence of any grade stomatitis was 33.5% (95% confidence interval [CI], 21.9%-47.6%). The concurrent use of a second agent may have confounded these findings because, for example, stomatitis has been reported in pooled analyses and in postmarketing experience with letrozole.[11]

Rugo and colleagues[12] evaluated the incidence of stomatitis in 1455 patients participating in 5 phase 3 randomized clinical trials of everolimus in breast cancer, carcinoid tumor, pNET, and RCC. Patients received everolimus monotherapy (n = 478) or in combination with exemestane (n = 482), trastuzumab plus vinorelbine (n = 280), or octreotide (n = 215). The incidence of stomatitis in patients receiving everolimus was 59%-71%, compared with 19%-29% in 1,071 patients of the comparator arms (placebo, and placebo–trastuzumab–vinorelbine). The overall incidence of any grade stomatitis was 67%; most events were mild (grade 1/2); 9% of stomatitis events were moderate to severe (grade 3/4).

Differential clinical presentation of mIAS and severity

Oral mucositis is a common significant adverse event (AE) that occurs in patients with cancer who receive standard chemotherapy regimens and/or radiation therapy,[13] so it is important to recognize that the clinical presentation of mIAS differs from that of oral mucositis (Table 1, Figure 1[14,15]).[16] mIAS shares some similarities with aphthous ulcers (also referred to as canker sores), a common oral condition with varied causes related to systemic disorders, gastrointestinal disorders, and infections, among others .[17] In general, mIAS ulcers develop with a median onset of 10 days (range, 4-25 days) after initiation of mTOR inhibitor treatment and resolve in about 1-3 weeks after dose interruption/reduction of everolimus.[16,18,19] mIAS ulcers appear as distinct, oval

TABLE 1 Differential clinical presentation of mTOR inhibitor-associated stomatitis[14,15,18]

	mTOR inhibitor-associated stomatitis	Chemotherapy/ radiation-induced oral mucositis	Aphthous ulcers of varied etiology
General appearance	Distinct, oval lesions with central gray area surrounded by an erythematous band; clustered or coalescing lesions; usually ≤1 cm in diameter	Nonuniform shape and depth, with fibrinous pseudomembrane and cellular debris; no peripheral erythema	Ovoid lesions with inflammatory halos; minor lesions usually 0.2-0.8 cm in diameter; major lesions usually ≥1 cm in diameter
Location	Movable mucosa of the mouth and oropharynx	Movable mucosa of the mouth	Minor lesions appear on nonkeratinized mucosa of the mouth; rarely on the palate or gingiva Major lesions can affect the tongue dorsal surface and the palate, as well as buccal and lip mucosa
Cotoxicities	No more or less likely to occur with other GI events; more likely to occur with nonspecific skin rash	More likely to occur with other GI events, such as diarrhea, nausea, or vomiting	May appear in persons with systemic rheumatic, cutaneous, or hematologic diseases, GI diseases, infections, or in persons under care with certain drugs
Timing of onset	Rapid onset; peak severity within 5 days of treatment start	Rapid onset; peak severity within 10 days of chemotherapy start	Can be recurrent

GI, gastrointestinal; mTOR, mammalian target of rapamycin

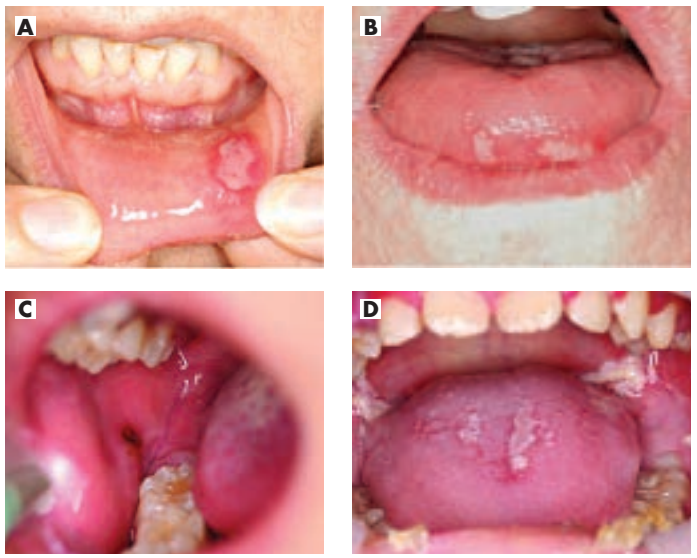

FIGURE Clinical presentation of mTOR inhibitor-associated stomatitis and chemotherapy-associated mucositis in cancer patients treated. A, Ulceration of the lower labial mucosa of a patient receiving everolimus; B, Multiple ulcers on the ventrolateral tongue of a patient receiving chemotherapy. C, Localized buccal mucositis in a patient with osteosarcoma. D, Generalized mucositis in a patient with acute myeloid leukemia.

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lesions with a central gray area surrounded by peripheral erythema. They are usually localized to the movable mucosa of the mouth and oropharynx. Although mIAS lesions are usually small, they are quite painful and may cluster.

Differential diagnosis of mIAS should be made based on physical examination and medical history, with consideration given to appearance of lesions (number, size, and location), current infection status, and current medications. Specific diagnostic testing should be conducted to confirm a coexisting or alternative cause of oral lesions.[17]

Although there are many different scales for grading mIAS severity, the most commonly used are the National Cancer Institute Common Terminology Criteria for Adverse Events (based on patient function, symptoms, and intervention needs) and the World Health Organization oral mucositis scales (based on symptoms, clinical presentation, and interference with patient function).[20-22] These scales distinguish between mild lesions (grade 1/2) and moderate to severe lesions (grade 3/4) that cause significant pain or interfere with oral intake.

Pathophysiology of mIAS

The pathophysiology mIAS is incompletely understood. The ubiquitous role of the PI3K-AKT-mTOR pathway in regulating broad cellular functions suggests that mTOR inhibition is likely to have wide-ranging effects on many biological processes. It is not known whether disruption of one or more processes – or upsetting the balance of mTOR activities – underlies the formation of mIAS.

Differences between mIAS and oral mucositis, including clinical presentation and concomitant toxicities,[16,23] suggest that the two types of oral lesions are fundamentally distinct. This distinction is supported by animal studies in which mTOR inhibition was found to almost completely prevent the appearance of oral mucositis in irradiated mice. The protective effect of mTOR inhibition is mediated through suppression of oxidative stress generated by radiation therapy.[24]

Although mIAS and recurrent aphthous ulcers share some similarities, it is not clear whether they also share a common pathophysiology. Recent studies suggest that patients with recurrent aphthous ulcers have immune dysfunction that leads to excessive immune response to normally innocuous substrates in the oral mucosa.[25] mTOR inhibition can have proinflammatory activity by promoting autophagy, a process that stimulates antigen presentation and activation of T cells that produce proinflammatory cytokines.[26] It is interesting to note that the incidence of stomatitis in patients receiving sirolimus after kidney transplant is relatively low, 3%-20%.[5] Sirolimus is administered in combination with other immunosuppressants, namely cyclosporine and corticosteroids, so it suggests that concomitant use of a steroid-based regimen may have a preventive or therapeutic effect. However, post-transplant sirolimus is typically administered at relatively low doses, which might account in part for the lower incidence of mIAS observed. Ongoing clinical studies of steroid-based mouthwashes in patients receiving everolimus should shed light on this.

Other study findings have shown that inhibition of the PI3K-AKT-mTOR signaling pathway affects skin wound healing,[27,28] which raises the possibility that mIAS may stem from a diminished capacity to repair physical injuries to the oral mucosa. More research is needed to elucidate the pathophysiology of mIAS.

Preventive measures for patients initiating mTOR inhibitor treatment

There are preventive measures for mIAS that have not yet been backed up with evidence-based findings, although several clinical studies that are underway aim to address this gap (Table 2). The hypotheses about the pathophysiology of mIAS suggest that certain preventive and therapeutic interventions might be effective against mIAS. For example, two studies are evaluating the use of steroid-based mouthwashes in patients receiving everolimus, based on the hypothesis that mIAS may arise from an inflammatory process; another study will evaluate a mucoadhesive oral wound rinse, based on the hypothesis that wound protection might prevent mIAS. Glutamine suspension is also under evaluation as it is understood to have wound-pre-

TABLE 2 Clinical trials involving stomatitis prevention strategies during treatment with an mTOR inhibitor

Title (NCT Number)	Phase	Stomatitis intervention method	Proposed enrollment	Endpoints related to stomatitis or oral mucositis
Miracle Mouthwash Plus Hydrocortisone vs Prednisolone Mouth Rinse for Mouth Sores Caused by Everolimus (NCT02229136)	2	Mouthwash with hyrdrocortisone; Prednisolone oral rinse	100	**Primary** Incidence of Gr ≥2 stomatitis **Secondary** ■ Percentage of patients requiring dose interruptions/ reductions of everolimus ■ Reduction in pain score
Open label, Phase II, Study of Stomatitis Prevention with a Steroid-based Mouthwash in Postmenopausal Women With ER+, HER2− Metastatic or Locally Advanced BC (SWISH; NCT02069093)	2	Alcohol-free mouthwash with dexamethasone 0.5 mg/5 mL	92	**Primary** Incidence of Gr ≥2 stomatitis at 2 months **Secondary** ■ Time to resolution ■ Number of times per day mouthwash regimen used ■ Dose intensity of everolimus and exemestane ■ Incidence of all grades stomatitis
Open-label, Phase II Study of Everolimus Plus Letrozole in Postmenopausal Women With ER+, HER2− Metastatic or Locally Advanced BC (BOLERO-4; NCT01698918)	2	Alcohol-free mouthwash with dexamethasone 0.5 mg/5 mL	202	**Primary** PFS (not related to stomatitis) **Secondary** Reduction in severity and duration of oral stomatitis
Mucoadhesive Oral Wound Rinse in Preventing and Treating Stomatitis in Patients With ER- or PR-Positive Metastatic or Locally Recurrent BC That Cannot be Removed by Surgery Receiving Everolimus (NCT02015559)	2	Mucoadhesive oral wound rinse (Mugard)	66	**Primary** Rate of Gr 1-4 stomatitis per NCI CTCAE 4.03 **Secondary** Rate of Gr 3/4 stomatitis
Evaluation of Oral Care to Prevent Oral Mucositis in ER Positive MBC Patients Treated With Everolimus: Phase 3 Randomized Control Trial (NCT02376985)	3	Oral care: Brushing and gargling with saline (placebo group) or Neostelin Green 0.2% mouthwash solution (dental management group)	200	Primary Incidence OM Gr≥1 **Secondary** ■ Incidence of OM Gr≥1, ≥2, ≥3, ■ Time to onset ■ Duration ■ Ratio of patients with dose interruption/ reduction of everolimus treatment due to OM
Dose EScalation Induction of EvERolimus (DESIREE; NCT02387099)	2	Dose-escalation schema	156	**Primary** Cumulative rate mucositis grade 2-4 (WHO's OTS) **Secondary** ■ Cumulative rate mucositis any grade (WHO's OTS) ■ Patients on conventional dose everolimus ■ Time to mucositis grade 2-4 (WHO's OTS) ■ Cumulative dose (everolimus) ■ Relative dose intensity (everolimus)
Randomized Trial of Glutamine in Patients With Mucositis or Esophagitis (NCT01952847)	3	Glutamine solution	180	**Primary** Severity of OM for mTOR inhibitor patients **Secondary** NA
PRednisone Plus EVerolimus in Patients With Metastatic Renal Cell Cancer After Failure of Vascular Endothelial Growth Factor Receptor-tyrosine Kinase Inhibitors (PREV; NCT02479490)	2	Prednisone 5 mg, PO	42	**Primary** Incidence of Gr ≥2 stomatitis **Secondary** NA

BC, breast cancer; ER+, estrogen receptor positive; Gr, grade; HER−, HER2 negative; MBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; NA, not applicable; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; OM, oral mucositis; OTS, oral toxicity scale; PFS, progression-free survival; PO, orally; PR, progesterone receptor; WHO, World Health Organization

ventative and tissue-repair properties, and another study is focused on dentist-guided oral management. Recent results of one of these trials (SWISH),[29] reported that preventative care with a dexamethasone mouthwash 3-4 times a day significantly minimized or prevented the incidence of all grades of stomatitis in women receiving everolimus plus

TABLE 3 Strategies for prevention and management of mTOR inhibitor-associated stomatitis

Preventive Measures for mTOR Inhibitor-Associated Stomatitis[13,32,41]

Measure	Evidence[a] or rationale
Dental care	
Maintain good routine oral care	■ Insufficient scientific evidence; generally accepted principles ■ Control oral microbial flora ■ Prevent soft-tissue infections
Visit dentist regularly (before and during treatment)	■ Reduce risk of dental complications, such as caries and gingivitis
Floss/brush regularly; use soft toothbrush, mild (children's) toothpaste or toothpaste without sodium lauryl sulfate	■ Toothbrushing significantly reduced the number of patients on chemotherapy presenting with oral lesions[43] ■ Reduce risk of mechanical/chemical injury in mouth
Use baking soda (or equivalent) mouth rinses	■ Recommended for all cancer patients ■ Prevent dry mouth ■ Avoid mouthwashes that contain alcohol, hydrogen peroxide, iodine, or thymol
Diet	
Modify diet	■ Maintain healthy oral mucosa
Avoid spicy or acidic foods/beverages, hard/crusty, and hot temperature foods	■ Reduce risk of irritation, mechanical injury, or burns in the mouth
Patient education	■ Empower patients to recognize early signs of mIAS
Establish oral care plan	■ Implementation of an oral care plan reduced oral mucositis and increased oral comfort in patients with cancer on chemotherapy or radiation therapy[33-40]
Emphasize awareness/recognition of early signs of mIAS; encourage patients to report potential problems to healthcare providers	■ Interventions, if needed, can be started early

Treatments for mTOR inhibitor-associated stomatitis[13,15,32,41,44]

Treatment approach	Possible advantages	Possible disadvantages
Mild mIAS[b]		
Topical anesthetics or analgesics: viscous lidocaine; benzocaine; milk of magnesia; kaolin; pectin; benzydamine; morphine	■ Possibility of immediate local pain relief	■ Lack of evidence regarding efficacy/ tolerability ■ Potential for amide analgesics to be absorbed systemically through damaged mucosal surfaces to affect cardiovascular and central nervous systems
Mucosal coating agents: Gelclair; MuGard	■ MuGard currently under clinical study as preventive/ therapeutic intervention	■ Insufficient evidence at this time
Antimicrobial agents: chlorhexidine mouthwash	■ May be used as part of an oral care protocol	■ No evidence of greater efficacy vs salt and soda rinses or 'magic' mouthwash
Topical corticosteroids: clobetasol cream (twice daily application); dexamethasone solution (2-6 times daily rinse)	■ May promote lesion healing, offer pain relief ■ Rapid, complete resolution of oral lesions in patients on sirolimus following kidney transplant using clobetasol; well tolerated; effective on reappearance of oral lesions ■ Ease of use of dexamethasone mouth rinses; possibility of initiating at first sign of mouth sensitivity	■ Possibility of oral candidiasis
Other topical anti-inflammatories: Amlexanox paste (4 times daily for 2 weeks or until lesions heal); 'miracle' or 'magic' mouthwash (diphenhydramine, viscous lidocaine, and aluminum hydroxide or magnesium hydroxide; once every 4 hours as needed)	■ Reduction in lesion size and benefit of early use of amlexanox in patients with recurrent aphthous ulcers	■ Stinging sensation with use of amlexanox ■ Variable formulations for miracle or magic mouthwash ■ Possible numbness, risk of injury with miracle or magic mouthwash

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Treatment approach	Possible advantages	Possible disadvantages
Moderate to severe mIAS[c]		
Intralesional steroids: triamcinolone acetonide	■ Potential immediate symptomatic improvement ■ No adverse events reported by 5 patients who received a total of 18 injections of 8-24 mg doses[18]	■ Can produce atrophic effect ■ Risk of systemic effects, especially with repeated injections
Systemic analgesics: oral or intravenous opioids; PCD of morphine	■ Oral or intravenous opioids should be tried before moving onto PCD morphine ■ PCD may require lower doses, vs other opiates, to achieve similar pain control ■ PCD may be more tolerable than other opiates Pediatric use of PCD is feasible	■ Little evidence supports use in patients other than those with oral mucositis undergoing HSCT
Systemic corticosteroids: oral prednisone or prednisolone (Montelukast may be an option if systemic corticosteroids are contraindicated)[45]	■ Considered first-choice treatment for acute, severe recurrent aphthous ulcers	■ No evidence of greater efficacy of systemic over topical corticosteroids, but increased risk of adverse effects
Systemic immunomodulator: thalidomide	■ Lower incidence of recurrent aphthous ulcers vs placebo	■ High risk of serious adverse events (eg, neuropathy and teratogenesis) Not FDA-approved for treatment of oral lesions

FDA, US Food and Drug Administration; HSCT, hematopoietic stem cell transplant; mIAS, mTOR inhibitor-associated stomatitis; PCD, patient-controlled delivery

[a]If available. [b]Grade 1 or 2 mIAS is considered mild. [c]Grade 3 or 4 mIAS is considered moderate to severe.

exemestane therapy for advanced/metastatic breast cancer compared with the incidence of stomatitis observed in a previously published phase 3 trial (BOLERO-2)[30,31] of everolimus plus exemestane in the same patient population. Results from several other studies are expected soon.

Current approaches to mIAS prevention are based largely on clinical experience with chemotherapy- or radiation-induced oral mucositis (Table 3).[13,32] Preventive measures use three main strategies: establish and maintain good routine oral care; modify diet to avoid potentially damaging foods; and improve patient education about mIAS. In regard to patient education, numerous studies have reported that establishing an institutional protocol for oral care helped reduce the incidence of chemotherapy- or radiation-induced oral mucositis.[33-40] An ongoing clinical study that will randomize patients to receive oral care education from oral surgeons or instruction on brushing only (NCT02376985) is investigating whether having an oral care protocol holds for patients with mIAS. The hypothesis is that focusing attention on oral care and educating patients to recognize the onset of mIAS facilitates early detection and promotes early intervention.

Therapeutic measures for patients with mIAS

Therapeutic measures for mIAS are based largely on experience with chemotherapy- or radiation-induced oral mucositis or recurrent aphthous ulcers (Table 3) and vary in part by the severity of lesions. Treatments for mild mIAS aim to ameliorate symptoms (eg, topical analgesics for pain), protect the oral mucosa (eg, mucoadhesive gels or viscous solutions that coat the oral cavity), prevent potential sequelae (eg, prophylactic antibiotics to avoid secondary infections), and reduce inflammation/immune response (eg, steroid-based mouth rinses, topical steroids, or topical anti-inflammatory agents). Treatments for mild mIAS are generally local rather than systemic.

Treatment options for moderate to severe mIAS include systemic approaches that generally carry increased risk of AEs and, therefore, should be reserved for patients with multiple lesions, uncontrolled or poorly controlled pain, or greatly diminished oral food intake (Table 3).[41] When mIAS cannot be controlled with the interventions described, the dose of the mTOR inhibitor can be reduced with the recognition that dose modification of anticancer therapy may affect disease outcomes.[29] The experience of reduction or interruption of treatment with everolimus in the BOLERO-2 trial as a strategy for management of AEs is discussed in a recent review.[29] Prescribing information for both temsirolimus and everolimus specify that grade 3 AEs be treated with temporary dose interruption, and with resolution (temsirolimus: grade ≤2; everolimus: grade ≤1), treatment may be resumed at lower doses (temsirolimus: reduce by 5 mg/week; no lower than 15 mg/week; everolimus: reduce by half the previously admin-

istered dose).[3,4] Grade 4 events due to treatment with temsirolimus may also be treated with dose interruption/reduction; the everolimus prescribing information advises treatment discontinuation for grade 4 stomatitis.

Summary and discussion

mTOR inhibitors can be effective treatments for patients with advanced cancer, specifically for advanced RCC, advanced pNET, and HR+, HER2-negative advanced breast cancer. Although mIAS may occur in many patients, it is usually grade 1 or 2 in severity. mIAS has an early onset, usually within the first 2 weeks of treatment[16,19,42] and a relatively rapid resolution, usually within 3 weeks.[16,19] Thus, most cases of mIAS are self-limiting.

The relatively recent emergence of mIAS poses short-term challenges regarding diagnosis, assessment, prevention, and treatment. Several clinical studies are underway to evaluate a range of interventions for their preventive and therapeutic efficacy in mIAS. Furthermore, our growing understanding of the underlying pathophysiology of mIAS can guide how mIAS is managed and what interventions patients receive.

Although mIAS is believed to differ from chemotherapy- or radiation-induced oral mucositis and aphthous ulcers, much can be learned from the treatment of both of these. Several strategies have been proposed to limit the occurrence of mIAS (Table 3). First, establish an oral care protocol. Educate patients who are initiating treatment with an mTOR inhibitor on implementation of the oral care protocol and emphasize adherence. Second, educate patients on the symptoms and timing of mIAS. Patients may hesitate to report mild symptoms or assume they are innocuous, so be clear that reporting all symptoms is important to allow timely clinical evaluation. Early recognition of mIAS facilitates early intervention and can prevent dose modification and interruption. Third, implement the preventive and treatment measures described. Many of the preventive measures can be incorporated into an oral care protocol.

The advent of mTOR inhibitors has clinically benefited many patients with cancer. Although side effects, like mIAS, may develop during treatment, they should not be considered insurmountable. Through education, vigilance, and aggressive management, health care providers and patients can work together to help patients maintain their quality of life while continuing to optimally address their disease.

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