Review
Future Oncology

Mammalian target of rapamycin inhibitor-associated stomatitis

Christine B Boers-Doets*[1], Judith E Raber-Durlacher[2,3], Nathaniel S Treister[4,5], Joel B Epstein[6,7], Anniek BP Arends[3], Diede R Wiersma[3], Rajesh V Lalla[8], Richard M Logan[9], Nielka P van Erp[10] & Hans Gelderblom[1]

[1]Department of Clinical Oncology, Leiden University Medical Centre, PO Box 9600, 2300 RC Leiden, The Netherlands
[2]Department of Oral & Maxillofacial Surgery, Academic Medical Center Amsterdam, Amsterdam, The Netherlands
[3]Department of Periodontology, Academic Centre for Dentistry Amsterdam (ACTA), Amsterdam, The Netherlands
[4]Division of Oral Medicine & Dentistry, Brigham & Women's Hospital, Boston, MA, USA
[5]Department of Oral Medicine, Infection & Immunity, Harvard School of Dental Medicine, Boston, MA, USA
[6]Samuel Oschin Comprehensive Cancer Institute & Division of Dentistry, Cedars-Sinai Medical Center, Los Angeles, CA, USA
[7]Division of Otolaryngology/Head & Neck Surgery, City of Hope National Medical Center, Duarte, CA, USA
[8]Section of Oral Medicine, MC1605, University of Connecticut Health Center, 263 Farmington Avenue, Farmington, CT, USA
[9]Oral Diagnostic Sciences, School of Dentistry, Health Sciences, University of Adelaide, Australia
[10]Department of Clinical Pharmacy, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands
*Author for correspondence: Tel.: +31 624790618 ■ c.b.boers-doets@lumc.nl

With the recent introduction of inhibitors of mammalian target of rapamycin (mTOR) in oncology, distinct cutaneous and oral adverse events have been identified. In fact, stomatitis and rash are documented as the most frequent and potentially dose-limiting side effects. Clinically, mTOR inhibitor-associated stomatitis (mIAS) more closely resembles aphthous stomatitis than oral mucositis due to conventional anticancer therapies. While most cases of mIAS are mild to moderate and self-limiting, more severe and persistent mIAS can become a dose-limiting toxicity. Small ulcerations may cause significant pain and mucosal sensitivity may occur in the absence of clinical changes. Use of clinical assessment tools that are primarily driven by ulceration size may underestimate mIAS, and assessment should include patient-reported outcomes. This article provides an up-to-date review of the clinical presentation, terminology, pathogenesis, assessment and management of mIAS and other mTOR inhibitor-associated oral adverse events. In addition, areas of future research are considered.

Mammalian target of rapamycin (mTOR) is a serine/tyrosine protein kinase that acts as a master switch for protein synthesis, cell proliferation, cell cycle progression and cell survival, integrating signals from growth stimuli to cell cycle progression [1]. Dysregulation of the PI3K/AKT/mTOR signaling pathway has been identified in several human malignancies, and investigation of this signaling network has led to the development of targeted cancer therapies [2]. One of the primary pharmacologic targets has been mTOR, which occurs in two multiprotein complexes, mTORC1 and mTORC2. mTOR inhibitors that are currently in clinical use inhibit mTORC1 through allosteric binding and demonstrate efficacy with acceptable tolerability [2]. These agents are associated with sustained, durable clinical responses in several cancer types, including, for example, advanced renal cell carcinoma and neuroendocrine pancreatic cancers [3].

The first mTOR inhibitor developed was sirolimus (Rapamune®; Wyeth-Ayerst, NJ, USA), which is used as an antirejection medication in solid and stem cell transplantation. For the treatment of cancer, two mTOR inhibitors are currently available: temsirolimus (Torisel®; Pfizer, NY, USA) and everolimus (Afinitor®; Novartis Pharmaceuticals, NJ, USA). Temsirolimus is intravenously administered and is approved for the treatment of advanced renal cell carcinoma [101]. Everolimus is an oral mTOR inhibitor that is US FDA approved for the second-line treatment of advanced renal cell carcinoma [102], neuroendocrine pancreatic cancers, and aromatase inhibitor-resistant hormone receptor-positive, HER2-/neu-negative advanced breast cancers and for tuberous sclerosis complex related renal angiomyolipomas. In addition, everolimus was recently approved for nonresectable subependymal giant cell astrocytoma [103]. A third mTOR inhibitor, ridaforolimus (deforolimus, Jenzyl® [EU], Taltorvic® [US]; Merck & Co. Inc, NJ, USA) continues to be under clinical investigation for a range of cancers [104].

Keywords

■ mTOR ■ mTOR inhibitor-associated stomatitis ■ oral mucositis ■ stomatitis ■ targeted therapy

Future Medicine part of fsg

This new class of oncology drugs has a spectrum of adverse events (AEs) that are unique as compared with conventional anticancer chemotherapy. AEs include hyperglycemia, hyperlipidemia, hypophosphatemia, hematologic toxicities and mucocutaneous eruptions. In particular, stomatitis and skin rash are documented as the most frequent and potentially dose-limiting side effects [4,5]. When mTOR inhibitors are used for immunosuppression, they are often given in combination with other immunosuppressant agents, including corticosteroids that may actually diminish and/or prevent mouth and skin AEs. Moreover, the prevalence of mouth and skin toxicity could also be decreased owing to a significant lower dose applied in transplantation medicine.

In the majority of cancer patients treated with mTOR inhibitors, stomatitis is reported as mild to moderate. However, even small lesions can be painful and invalidating since patients are treated continuously, rather than in cycles of determined length as in conventional chemotherapy [105,106]. As a consequence, even mild-to-moderate oral AEs may have a negative impact on health-related quality of life, leading to unplanned treatment delays or interruptions, dose reductions or ultimately to cessation of therapy [6,7]. Therefore, minimizing and managing oral AEs is important.

This article reviews the clinical presentation, terminology, pathogenesis, assessment and management of mTOR inhibitor-associated stomatitis (mIAS). In addition, other reported oral AEs that have been associated with mTOR inhibitors will be described.

Terminology

The terminology and classification of oral AEs associated with mTOR inhibitors has been inconsistent throughout different clinical trials. For example, in a review article by Bellmunt *et al.* on the AEs of temsirolimus for the treatment of renal cell carcinoma, the frequencies of mucositis, stomatitis, aphthous stomatitis and mouth ulceration were reported as distinct categories [8]. Moreover, mucosal inflammation and tongue ulceration were reported as distinct oral AEs [107,Merck, Pers. Comm.]. The terms oral mucositis and stomatitis are often used interchangeably, but they do not reflect identical processes. Oral mucositis is a Medical Subject Headings term that describes inflammation of oral mucosa resulting from chemotherapeutic agents or ionizing radiation. It typically manifests as erythema or ulcerations and may be exacerbated by local factors, such as secondary infections and trauma. Stomatitis is a less specific term that refers more generally to any inflammatory condition of oral tissues [9,108].

In a seminal paper describing the unique clinical features of oral ulcerations associated with mTOR inhibitors, Sonis *et al.* proposed the term mIAS in order to provide clarity and delineation from oral mucositis due to conventional cytotoxic chemotherapy and radiation [7]. Other authors also emphasized the importance of using consistent terminology [4,5,10,11]. Among oral medicine specialists managing patients with oral mucosal lesions associated with mTOR inhibitors, there is consensus that the term mIAS is preferable to the term oral mucositis.

Clinical presentation & prevalence of mIAS & other oral complications

The clinical presentation of mIAS typically involves solitary or multiple ulcerations resembling aphthous stomatitis, characterized as distinct, ovoid ulcers with a central gray area surrounded by a ring of erythema (Figure 1). Typically, ulcerations are small (<0.5 cm), whereas oral ulcerations caused by traditional cytotoxic chemotherapy agents (e.g., 5-fluorouracil) are typically larger, more irregular in shape, with or without surrounding erythema and without elevated borders [5,7].

Similar to conventional mucositis and aphthous stomatitis, mIAS almost exclusively affects the nonkeratinized, movable oral surfaces, including the buccal and labial mucosa, lateral tongue, soft palate and floor of mouth. Ulcerations affecting the keratinized oral mucosa (gingiva, tongue dorsum and hard palate) are more likely to have an infectious, particularly viral etiology [12]. Although mTOR inhibitors are immunosuppressive, it is not clear whether this puts patients at risk for oral infections.

mIAS lesions typically present with a rapid onset (usually within 5 days), most frequently in the first cycle of mTOR inhibitor therapy. Most often mIAS is graded as mild to moderate in severity grades 1–2, according to the oral mucositis scale of the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) [13]. Most cases improve or resolve spontaneously despite continuing mTOR inhibitor treatment [11]. However, even small ulcerations can be very painful and can interfere with a patient's ability to chew and swallow and as a result may compromise nutritional status. In some patients mIAS may persist over an extended period. A study characterizing

toxicity in patients enrolled in the Phase III RECORD-1 trial, which evaluated everolimus for the treatment of metastatic renal cell carcinoma, indicated that 42% of the patients developed stomatitis, of which 39% experienced mild-to-moderate stomatitis that resolved within 3 days [14]. However, nearly 10% required a dosage modification or treatment interruption, while nearly half required supportive therapies for symptom control. In a recent systematic review evaluating 44 studies of mTOR inhibitors, mIAS was identified as the most frequent AE overall (73.4%), the third most frequent severe AE (20.7%), accounting for 27.3% of dose reductions, and 13.1% of discontinuations, and was the most frequent dose-limiting toxicity (52.5%) [15]. In patients enrolled in ridaforolimus trials, there was a notably higher frequency of severe mIAS and related dose modifications and discontinuations compared with the other mTOR inhibitors, most likely related to the intensity of therapy [16–18,Merck, Pers. Comm.].

Mucositis induced by chemotherapy and radiotherapy to the head and neck area often leads to difficulties with swallowing (dysphagia) and need for a liquid diet. Pharyngitis and dysphagia have also been reported with ridaforolimus, but seem to occur less frequently than in conventional cancer treatments [11,14]. Throat pain has been reported in association with oral ulcerations [7,107,Merck, Pers. Comm.]. In addition, other clinically important AEs that disrupt oral function have been described relating to the use of mTOR inhibitors. These include altered taste/taste loss (dysgeusia/ageusia), oral sensitivity and pain without the presence of clinical oral lesions, and xerostomia [19,107,Merck, Pers. Comm.]. Compared with mIAS, less attention has been paid to these AEs and they have not been well described.

Pathobiology

While significant progress has been made in obtaining insight into the pathobiologic mechanisms of mucositis due to cytotoxic drugs and/or ionizing radiation, mIAS is a recently recognized phenomenon and its pathogenesisis is not well understood [7]. Although it is not clear what mechanisms are involved in the development of mIAS, it is probable that these differ from what occurs in conventional oral mucositis based on differences in clinical presentation. The association with concomitant cutaneous AEs provides additional evidence to suggest a distinction between mIAS and oral mucositis induced by conventional cancer therapies [7,10]. The clinical resemblance of mIAS to aphthous stomatitis may indicate common pathobiological pathways, but also the pathobiology of aphthous stomatitis is not well understood. The etiology of recurrent aphthous stomatitis is believed to be multifactorial, including genetic, environmental, hormonal and emotional factors, in addition to trauma and irritating food and drink. Immune dysregulation is thought to play a role and several potential mechanisms have been described, including antibody-dependent cell-mediated cytotoxicity [20]. Moreover, loss of peripheral tolerance resulting in autoimmune reactions may occur and cross-reactions between a microbial antigen and a peptide within the oral epithelium may play a role [21]. Recently, it has been suggested that $CD4^+CD25^+$ Tregs are decreased and function improperly in patients suffering from recurrent aphthous stomatitis. Tregs are vital for the maintenance of peripheral tolerance throughout life and when the generation and expansion of these cells are decreased, this may result in loss of control over autoreactive T cells and consequently lead to loss of peripheral tolerance of the oral mucosa [22].

By contrast, several *in vitro* studies suggest that mTOR inhibitors increase stimulation of Tregs leading to increased peripheral tolerance, but mechanisms of action of rapamycin and its analogs are multifaceted and can exert both immunosuppressive and immunostimulatory effects [23]. Of interest is the hypothesis

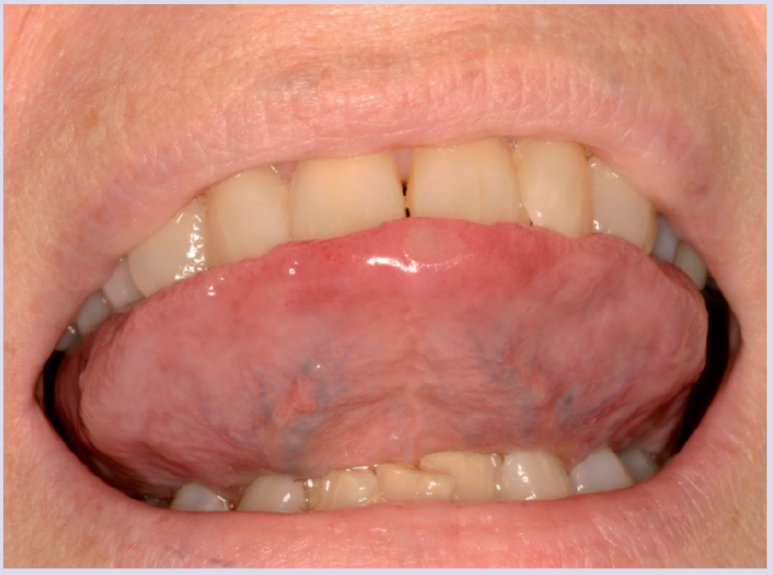

Figure 1. Typical mammalian target of rapamycin inhibitor-associated stomatitis with ulceration and an erythematous halo clinically resembling aphthous stomatitis in a patient treated with temsirolimus.

that in patients with mTOR inhibitor-induced interstitial pneumonitis, mTOR inhibitors may bind directly to tissue proteins evoking an autoimmune-like inflammatory response, mediated by conventional CD4 cells in the absence of infection [24]. Consistent with this observation, proinflammatory properties of mTOR inhibitors have also been described in various experimental models [25] and similar mechanisms may be involved in the development of mIAS.

Moreover, impaired wound healing has been suggested to play a pathobiological role in aphthous ulceration and may also be involved in the pathogenesis of mIAS. It is known that angiogenesis and vascular cell proliferation are important for wound repair, and both processes may be impeded by mTOR inhibitors [26]. Furthermore, mTOR inhibitors may induce glucose levels to increase in patients with pre-existing diabetes mellitus and in nondiabetic patients, which may also have a negative impact on wound healing.

With respect to the non-mIAS oral AEs as a response to mTOR inhibiting therapy, the potential mechanisms are even less clear. Greater characterization of these AEs and their relationship with the presence or absence of mIAS is necessary before mechanisms can be elucidated.

Assessment scales

Numerous oral mucositis grading scales have been developed over the years to grade conventional mucositis [27]. The complexity and detail of these scales varies significantly and the selection of a mucositis scale is often influenced by the reason for assessing mucositis (clinical care or research) [28]. Frequently used scales for conventional oral mucositis assessment, such as the WHO Oral Toxicity Scale and the Oral Mucositis Assessment Scale [29], were not developed to evaluate mIAS ulcerations and mIAS-associated complaints. In clinical trials of mTOR inhibitors, AEs, including mIAS, have been described primarily according to NCI-CTCAE versions 2.0 and 3.0 [19,109]. The mucositis scales of these prior versions of the NCI-CTCAE include grading of objective signs as well as subjective symptoms. However, such scales, which depend on ulceration size and extent, may underestimate the morbidity of mIAS, since even small localized ulcerations can be extremely painful and affect compliance. In this manner, the WHO scale may be a reasonable instrument for assessing mIAS. The mucositis component of the NCI-CTCAE version 4.0 is purely symptom and function driven [110]. However, this scale as well as the WHO scale emphasizes the impact of oral lesions on the subject's diet (e.g., WHO grade 3 is given when only a liquid diet can be tolerated). Since mIAS typically does not impact patients' diet to the same extent as conventional mucositis, such scales may not be sensitive enough to measure the impact of mIAS. In summary, scales developed for oral mucositis secondary to conventional chemotherapy and radiation therapy have several limitations when applied to mIAS.

The primary variables determining the morbidity of mIAS are the pain experienced by the subject and the duration of the lesions. It is important that these factors be carefully assessed in scoring mIAS. An accurate assessment of the morbidity of the toxicity will allow for informed decisions on dose modification and interruption, which have far reaching consequences. Therefore, a new scale has been developed for mIAS. This scale has a subjective component measuring pain and an objective component measuring duration of lesions. The subjective grading criteria range from 0 for no pain to 3 for a pain score of 6 or higher on a 0–10 scale. The objective grading criteria range from 0 for no visible lesion to 3 for lesion(s) persisting for more than 7 days. It is suggested that dose modification be considered only when both subjective and objective grades are 3, representing persistent lesions with significant pain, despite analgesic use [30]. These parameters (duration and pain of the lesions) have an effect upon oral and pharyngeal function.

In addition, detailed assessment of other oral and oropharyngeal AEs that may be associated with mTOR inhibitors use (e.g., swallowing problems, sensitive mucosa, dysgeusia and xerostomia) is warranted to obtain an insight of the prevalence and severity of these complaints and to assess whether these complaints are associated with mIAS or may also develop independently of clinically assessable oral ulceration. The Vanderbilt Head and Neck Symptom Survey version 2.0 measures patient-reported treatment-related symptom burden and oral health outcomes in the head and neck area and function loss within symptom subscales, including nutrition, taste, pain, voice, swallowing and mucus/dry mouth [31]. This scale may be adapted to assess such other mTOR inhibitor-associated oral complaints and their impact on patients' health-related quality of life (Table 1).

Prevention & treatment implications

Prevention and treatment of mTOR inhibitor-associated oral complications can be critical in order to maintain regimen adherence and

Table 1. Selected tools and their potential to assess mammalian target of rapamycin inhibitor-associated stomatitis.

Scale	Developed for	Scale description	Main driver of scale	Evaluation includes	Suitable for use in mIAS	Suitable for use for other mTOR inhibitor-associated oral complaints	Suitable for use for nonoral mucocutaneous adverse events	Ref.
WHO Oral Toxicity Scale	OM induced by conventional CT, RT, HSCT	Clinician-rated, combined, objective, subjective and functional parameters; 0–4 point scale	Ulceration and ability to eat and drink	Anatomical oral sites typically at risk for conventional OM and mIAS	+/- High risk for underscoring of subjective mucosal alterations	-	-	[29]
OMAS	OM due to HSCT	Clinician-rated, objective tissue scale; yes/no score	Cumulative surface of ulcerations and severity of redness	Anatomical oral sites typically at risk for conventional OM and mIAS	+/- High risk for underscoring of objective mucosal alterations, no subjective measurement	-	-	[29]
NCI-CTCAE v3.0	AEs associated with conventional CT, RT, HSCT	Clinician-rated, objective, subjective and functional parameters; 0–5 point scale	Severity of AE; need for interventions, impact on ADL	Anatomical sites typically at risk for conventional OM and mIAS	+	+	+	[109]
NCI-CTCAE v4.0	AEs associated with conventional CT, RT, HSCT	Clinician-rated, objective, subjective and functional parameters; 0–5 point scale	Severity of AE; need for interventions, impact on ADL	Oral and oropharyngeal symptoms and dietary limitation associated with conventional OM	+/- High risk for underscoring of morbidity of mIAS	+/-	+/-	[110]
VHNSS2.0	Head and neck AEs of CRT/RT for HNSCC	PRO; subjective and functional parameters; includes Likert scale for each item	Severity of AEs associated with HNSCC treatment and functional impact	Measures symptoms associated with complications in the head and neck area, no objective assessment of oral ulcers	+ No objective assessment of oral ulcers	+ Should be combined with objective evaluation	-	[31]
mIAS scale	mIAS	Clinician-rated objective component and patient-rated subjective component; 0–4 point scale	Duration of ulceration(s) attributed to mIAS and severity of associated pain	Persistence of lesions and pain	++ Specifically developed for mIAS	-	-	[30]

+: Suitable to assess mIAS; ++: Highly suitable to assess mIAS; +/-: Somewhat suitable to assess mIAS; -: Not suitable to assess mIAS; ADL: Activities of daily living; AE: Adverse event; CRT: Chemoradiotherapy; CT: Chemotherapy; HNSCC: Head and neck squamous cell carcinoma; HSCT: Hematopoietic stem cell transplantation; mIAS: mTOR inhibitor-associated stomatitis; mTOR: Mammalian target of rapamycin; NCI-CTCAEv3.0: National Cancer Institute-Common Terminology Criteria for Adverse Events version 3.0; NCI-CTCAEv4.0: National Cancer Institute-Common Terminology Criteria for Adverse Events version 4.0; OM: Oral mucositis; OMAS: Oral Mucositis Assessment Scale; PRO: Patient-reported outcome measure; RT: Radiation therapy; VHNSS2.0: Vanderbilt Head and Neck Symptom Survey version 2.0.

reduce the need for dose interruptions or reductions. To date, interventions aimed at managing mTOR inhibitor-associated oral complaints are mainly based on expert opinion and show similarities with basic oral care measures aimed at the prevention and treatment of conventional oral mucositis as well as management strategies for aphthous stomatitis (Table 2).

Management begins with assessment and patient education on oral hygiene measures, diet modifications and pain management [4,8,20,32]. In most cases pain can be controlled with mouthwashes or locally applied products containing lidocaine or doxepin and mucosal-coating agents [33–35]. Additionally, over the counter non-narcotic analgesics may play a role, whereas prescription of opioids is seldom necessary [10,20,36]. Most often mIAS is self-limiting, but in persistent cases treatment with local or systemic corticosteroids may be considered. This is on the premise that mIAS resembles aphthous stomatitis, in which management protocols include the use of corticosteroids. Topical high-potency corticosteroid gels were reported to be effective in mIAS in a series of reports from both the solid organ transplantation and oncology literature [14,20,36]. In addition, intralesional administration of corticosteroids has been reported to be an effective treatment option [5]. In more severe and refractory cases, or when painful esophageal ulcers are present, pulsed high-dose systemic corticosteroid therapy may be indicated [10,20,36]. In severe and persistent cases, dose reductions may be considered [5], and specific strategies for dosage reduction have been described [14,37]. Dose modifications or permanent discontinuation of mTOR inhibitors should only be considered when palliative management options have failed or if the patient refuses to continue therapy.

The role of oral infections that may develop in isolation or concomitant with mIAS is not clear. Potentially, oral bacteria, viruses and fungi may contribute to the severity of oral ulceration [38,39]. Secondary candidiasis is a common side effect of topical steroid therapy. If this occurs, topical antifungal therapy should be initiated. However, it should be taken into consideration that systemically absorbed azole antifungal agents may increase the serum concentration of the mTOR inhibitor and may increase toxic effects through cytochrome P450-mediated interaction. In such cases a topical nonazole antifungal agent is preferred.

Dry mouth can be managed with increased hydration and use of taste and mechanical

Table 2. Management options for mammalian target of rapamycin inhibitor-associated oral complications.

Oral complication	Management options
Prevention	Educate patients on mTOR-associated oral complications and the importance of maintaining good oral care; pay special attention to mouthwash with saline at least four times a day Advise regular dental check-ups and dental prophylaxis Eliminate sources of trauma (e.g., sharp edges and ill-fitting prostheses) Advise to avoid hard, hot, sharp or spicy food Assess the oral cavity regularly and advise to inform caregiver at first signs and symptoms of oral complications
Management of mild-to-moderate mIAS	Increase the frequency of the mouthwash with saline, for example, every 1–2 h; if mouthwash is painful, recommend to use pain medication beforehand Assess the oral cavity regularly Diagnose and treat oral mucosal infections when present Assess severity of oral sensitivity/pain Provide pain management (e.g., viscous lidocaine 2%, coating agents, calcium phosphate solution and, when needed, systemic approaches following the WHO pain management ladder) Consider a topical NSAID (e.g., amlexanox 5% oral paste) Consider high potency corticosteroids (dexamethasone [0.1% mg/ml]; clobetasol gel or ointment [0.05%])
Management of severe mIAS	Provide adequate pain management Consider intralesional triamcinolone (weekly; total dose 28 mg) and topical clobetasol gel or ointment (0.05%) In recurrent mIAS or esophageal lesions: consider systemic corticosteroids (high-dose pulse 30–60 mg oral prednisone or prednisolone [1 mg/kg for 1 week followed by dose tapering over the second week]) Consider dose reduction of mTOR inhibitor
Complaints of dry mouth	Advise adequate fluid intake Consider sugarless chewing gum or candy, salivary substitutes or sialogogues in patients with oral dryness

This table is based, in part, on expert opinion-based recommendations provided by Pilotte et al. [10]*, de Oliveira* et al. [11] *and Scully* [21].
mIAS: mTOR inhibitor-associated stomatitis; mTOR: Mammalian target of rapamycin.

stimulation of the salivary glands with sugar-free chewing gum or candies. Palliation with mouth-wetting agents may provide temporary relief. In addition, the prescription of sialagogues can be considered in patients with hyposalivation [40]. In order to help patients coping with taste alterations, the addition of tastants to food, such as increased spices, sauces and umami flavoring, and elimination of tastes experienced as bitter or sour in the diet should be considered.

Conclusion & future perspective

mIAS and skin AEs are among the most frequent side effects of mTOR inhibitors used in anticancer treatment. However, oral complaints are probably under-reported in the literature since studies were not primarily directed to investigate oral complications and most available data originate from spontaneous patient reports in safety and efficacy studies of mTOR inhibitor agents. In addition, measurement scales and terminology differ among studies, which further complicates insight into the prevalence of these oral AEs.

Prospectively designed observational studies using well-defined terminology and appropriate assessment and grading tools are necessary to better characterize the prevalence and severity of mIAS and other associated oral complications. In addition, the prevalence of oral complications associated with mTOR inhibitors may differ between agents and different routes and schedules of administration.

An animal model of mIAS would allow better characterization of early events and mechanisms driving its pathology. Moreover, investigations into the relationship between oral and nonoral AEs, including those of the skin, may be helpful in obtaining a better understanding of potentially shared pathobiologic mechanisms and potentially lead to improved management strategies. In addition, new insights into mIAS pathogenesis and advances made in mIAS management may improve the management of aphthous stomatitis.

An exploratory study identified polymorphisms in genes encoding for metabolizing enzymes, efflux transporters and drug targets that are associated with sunitinib-related AEs [41]. Similarly a future study aimed at identifying genetic markers of the pharmacokinetic and pharmacodynamic pathways of mTOR inhibitors that may predispose for the development of AEs might predict the risk of developing mIAS. This in combination with a better understanding of nongenetic determinants of mTOR toxicity should help to optimize drug treatment in individual patients.

New mTOR inhibitor compounds are currently under development as anticancer agents. These agents have the ability to block both mTORC1 and mTORC2. These dual inhibitors are likely to be more efficacious than presently available mTOR inhibitors that only inhibit mTORC1, and induce the activation of other signaling pathways mediated by mTORC2, resulting in proliferative and survival signals that impede their anticancer efficacy. In addition, combinations of mTOR inhibitors, conventional cytostatic therapy and agents targeting growth factor receptors, such as EGFR, may result in enhanced anticancer efficacy [42]. However, these combined treatment approaches, particularly those involving EGFR inhibitors, may increase the incidence and severity of mucosal and skin AEs [4].

A growing number of cancer patients will be treated with mTOR inhibitors, most frequently as outpatients and over a long time span. This indicates a need for awareness and early recognition of oral complications not only among oncologists and oncology nurses, but also among community healthcare specialists, such as primary care doctors and dental professionals. Healthcare professionals should educate patients on the importance of early reporting of oral complaints. A combination of basic oral care measures, pain management and topical corticosteroid therapy appears to be an effective approach to management, but well-designed prospective studies are required.

Financial & competing interests disclosure

CB Boers-Doets has been a consultant or speaker with Novartis, Pfizer, and Merck Sharp and Dohme. NS Treister has been a consultant for Merck Sharp and Dohme. JB Epstein has been a consultant for Merck Sharp and Dohme. RV Lalla has been a consultant for Merck Sharp and Dohme. RM Logan has received honoraria from and has been a speaker for Amgen. NP van Erp has been a consultant or speaker for Merck Sharp and Dohme. H Gelderblom's institution has received research funding from Novartis. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

Mammalian target of rapamycin inhibitors

- Three mammalian target of rapamycin (mTOR) inhibitors are currently used in oncology: temsirolimus, everolimus and ridaforolimus.

Terminology

- mTOR inhibitor-associated stomatitis (mIAS) is preferred to distinguish this entity from conventional chemotherapy-associated mucositis.

Clinical presentation & prevalence of mIAS & other oral complications

- Lesions are usually found on the nonkeratinized mucosa of the lips, floor of mouth, lateral tongue, buccal mucosa and soft palate. mIAS usually develops early after the administration of mTOR inhibitors and is self-limiting in most cases.

Pathobiology

- The pathobiology of mIAS is poorly understood, but may have similarities with mechanisms involved in aphthous stomatitis. These include immune mechanisms such as antibody-dependent, cell-mediated cytotoxicity and immune complex formation; this is different from what is considered to occur in conventional oral mucositis.

Other mTOR inhibitor-associated oral complaints

- These include oral pain and mucosal sensitivity, xerostomia, dysphagia, altered or loss of taste and decreased oral intake.

Assessment scales

- The development of separate assessment and grading tools for mIAS seems justified. Scales that are driven by ulceration size may under-report mIAS, since even small ulcers can be very painful. Modified versions of existing scales may be of value and should be validated for mTOR inhibitor-associated oral adverse events. An mIAS-specific assessment tool has been generated.

Prevention & treatment implications

- To date, evidence-based interventions for managing mIAS are not available. Principles of basic oral care including patient education on oral hygiene measures and avoiding hot, hard, spicy or acid foods are advised. In addition, other management strategies for aphthous stomatitis including pain management and the use of corticosteroids seem effective.

Conclusion & future perspective

- Prospective studies investigating the prevalence and clinical presentation of mIAS and other oral complications should be performed. In order to obtain meaningful outcomes, the use of well-defined terminology together with development of appropriate assessment and grading scales is mandatory. Experimental and clinical studies are required to characterize the pathogenesis of mIAS and clinical trials should be developed to evaluate interventions. Oncologists, oncology nurses, oral healthcare professionals, dermatologists, pharmacologists and basic scientists should be involved in these efforts.

Concluding remarks

- mIAS is a frequent but typically mild-to-moderate complication that is often self-limiting. When necessary, management is generally effective. The relationship with other oral adverse events is less clear but these can also typically be managed conservatively. In some cases, patients may require dose reduction.

References

Papers of special note have been highlighted as:
- ▪ of interest
- ▪▪ of considerable interest

1. Faivre S, Kroemer G, Raymond E. Current development of mTOR inhibitors as anticancer agents. *Nat. Rev. Drug. Discov.* 5(8), 671–688 (2006).
2. Wander SA, Hennessy BT, Slingerland JM. Next-generation mTOR inhibitors: how pathway complexity informs therapeutic strategy. *J. Clin. Invest.* 121(4), 1231–1241 (2011).
3. Bukowski RM. Systemic therapy for metastatic renal cell carcinoma in treatment naive patients: a risk-based approach. *Expert Opin. Pharmacother.* 11(14), 2351–2362 (2010).
4. Watters AL, Epstein JB, Agulnik M. Oral complications of targeted cancer therapies: a narrative literature review. *Oral. Oncol.* 47(6), 441–448 (2011).
   - ▪ **Summarizes oral complications of targeted cancer therapies including mammalian target of rapamycin (mTOR) inhibitors.**
5. Li E, Trovato JA. New developments in management of oral mucositis in patients with head and neck cancer or receiving targeted anticancer therapies. *Am. J. Health Syst. Pharm.* 69(12), 1031–1037 (2012).
6. Lee WJ, Lee JL, Chang SE *et al.* Cutaneous adverse effects in patients treated with the multitargeted kinase inhibitors sorafenib and sunitinib. *Br. J. Dermatol.* 161(5),1045–1051 (2009).
7. Sonis S, Treister N, Chawla S *et al.* Preliminary characterization of oral lesions associated with inhibitors of mammalian target of rapamycin in cancer patients. *Cancer* 116(1), 210–215 (2010).
   - ▪▪ **First paper describing mTOR inhibitor-associated stomatitis (mIAS).**
8. Bellmunt J, Szczylik C, Feingold J *et al.* Temsirolimus safety profile and management of toxic effects in patients with advanced renal cell carcinoma and poor prognostic features. *Ann. Oncol.* 19(8), 1387–1392 (2008).
9. Lalla RV, Sonis ST, Peterson DE. Management of oral mucositis in patients who have cancer. *Dent. Clin. North Am.* 52(1), 61–77 (2008).
10. Pilotte AP, Hohos MB, Polson KM *et al.* Managing stomatitis in patients treated with Mammalian target of rapamycin inhibitors. *Clin. J. Oncol. Nurs.* 15(5), E83–E89 (2011).
    - ▪▪ **Informative paper with practical management recommendations for mIAS.**
11. de Oliveira MA, Martins F, Wang Q *et al.* Clinical presentation and management of mTOR inhibitor-associated stomatitis. *Oral Oncol.* 47(10), 998–1003 (2011).
    - ▪▪ **Describes the clinical presentation and management options for mIAS.**
12. Elad S, Zadik Y, Hewson I *et al.* A systematic review of viral infections

associated with oral involvement in cancer patients: a spotlight on Herpesviridea. *Support. Care Cancer* 18(8), 993–1006 (2010).

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* 17(1), 135–144 (2012).
14. Porta C, Osanto S, Ravaud A *et al*. Management of adverse events associated with the use of everolimus in patients with advanced renal cell carcinoma. *Eur. J. Cancer* 47(9), 1287–1298 (2011).
15. Kwitkowski VE, Prowell TM, Ibrahim A *et al*. FDA approval summary: temsirolimus as treatment for advanced renal cell carcinoma. *Oncologist* 15(4), 428–435 (2010).
16. Martins F, de Oliviera MA, Wang Q *et al*. A review of oral toxicity associated with mTOR inhibitor therapy in cancer patients. *Oral. Oncol.* 49(4), 293–298 (2013).
17. Chawla SP, Staddon AP, Baker LH *et al.* Phase II study of the mammalian target of rapamycin inhibitor ridaforolimus in patients with advanced bone and soft tissue sarcomas. *J. Clin. Oncol.* 30(1), 78–84 (2012).
18. Dancey JE, Monzon J. Ridaforolimus: a promising drug in the treatment of soft-tissue sarcoma and other malignancies. *Future Oncol.* 7(7), 827–839 (2011).
19. Sessa C, Tosi D, Vigano L *et al.* Phase Ib study of weekly mammalian target of rapamycin inhibitor ridaforolimus (AP23573; MK-8669) with weekly paclitaxel. *Ann. Oncol.* 21(6), 1315–1322 (2010).
20. Messadi DV, Younai F. Aphthous ulcers. *Dermatol. Ther.* 23(3), 281–290 (2010).
21. Scully C. Aphthous ulceration. *N. Engl. J. Med.* 355(2), 165–172 (2006).

▪ **Landmark paper on aphthous stomatitis.**

22. Lewkowicz N, Lewkowicz P, Dzitko K *et al.* Dysfunction of $CD4^+CD25^{high}$ T regulatory cells in patients with recurrent aphthous stomatitis. *J. Oral Pathol. Med.* 37(8), 454–461 (2008).

▪▪ **Presents provocative and new thoughts about the pathobiology of aphthous stomatitis.**

23. Weichhart T, Saemann MD. The multiple facets of mTOR in immunity. *Trends Immunol.* 30(5), 218–226 (2009).
24. Morelon E, Stern M, Israel-Biet D *et al.* Characteristics of sirolimus-associated interstitial pneumonitis in renal transplant patients. *Transplantation* 72(5), 787–790 (2001).
25. Saemann MD, Haidinger M, Hecking M *et al*. The multifunctional role of mTOR in innate immunity: implications for transplant immunity. *Am. J. Transplant.* 9(12), 2655–2661 (2009).
26. Bjornsti MA, Houghton PJ. The TOR pathway: a target for cancer therapy. *Nat. Rev. Cancer* 4(5), 335–348 (2004).
27. Sonis ST, Elting LS, Keefe D *et al.* Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. *Cancer* 100(9 Suppl.), S1995–S2025 (2004).
28. Brennan MT, von Bültzingslöwen I, Schubert MM *et al*. Alimentary mucositis: putting the guidelines into practice. *Support. Care Cancer* 14(6), 573–579 (2006).
29. Sonis ST, Eilers JP, Epstein JB *et al*. Validation of a new scoring system for the assessment of clinical trial research of oral mucositis induced by radiation or chemotherapy. Mucositis Study Group. *Cancer* 85(10), 2103–2113 (1999).
30. Boers-Doets CB, Lalla RV. The mIAS scale: a scale to measure mTOR inhibitor-associated stomatitis. *Support. Care Cancer* 21(S1),S140 (2013).
31. Cooperstein E, Gilbert J, Epstein JB *et al*. Vanderbilt Head and Neck Symptom Survey version 2.0: report of the development and initial testing of a subscale for assessment of oral health. *Head Neck* 34(6), 797–804 (2012).
32. Bhojani N, Jeldres C, Patard JJ *et al*. Toxicities associated with the administration of sorafenib, sunitinib, and temsirolimus and their management in patients with metastatic renal cell carcinoma. *Eur. Urol.* 53(5), 917–930 (2008).
33. Keefe DM, Schubert MM, Elting LS *et al*. Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer* 109(5), 820–831 (2007).
34. Bensinger W, Schubert M, Ang KK *et al.* NCCN Task Force report. prevention and management of mucositis in cancer care. *J. Natl Compr. Canc. Netw.* 6(Suppl. 1), S1–S21 (2008).
35. Hudes GR, Carducci MA, Choueiri TK *et al*. NCCN Task Force report: optimizing treatment of advanced renal cell carcinoma with molecular targeted therapy. *J. Natl Compr. Canc. Netw.* 9(Suppl. 1), S1–S29 (2011).
36. Campistol JM, de Fijter JW, Flechner SM *et al*. mTOR inhibitor-associated dermatologic and mucosal problems. *Clin. Transplant.* 24(2), 149–156 (2010).
37. Hutson TE, Figlin RA, Kuhn JG *et al*. Targeted therapies for metastatic renal cell carcinoma: an overview of toxicity and dosing strategies. *Oncologist* 13(10), 1084–1096 (2008).
38. van der Beek MT, Laheij AM, Raber-Durlacher JE *et al*. Viral loads and antiviral resistance of herpesviruses and oral ulcerations in hematopoietic stem cell transplant recipients. *Bone Marrow Transplant.* 47(9), 1222–1228 (2012).
39. Laheij AM, de Soet JJ, von dem Borne PA *et al.* Oral bacteria and yeasts in relationship to oral ulcerations in hematopoietic stem cell transplant recipients. *Support. Care Cancer* 20(12), 3231–3240 (2012).
40. Jensen SB, Pedersen AM, Vissink A *et al.* A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: management strategies and economic impact. *Support. Care Cancer* 18(8), 1061–1079 (2010).
41. van Erp NP, Eechoute K, van der Veldt AA *et al*. Pharmacogenetic pathway analysis for determination of sunitinib-induced toxicity. *J. Clin. Oncol.* 27(26), 4406–4412 (2009).
42. Dufour M, Dormond-Meuwly A, Demartines N *et al*. Targeting the mammalian target of rapamycin (mTOR) in cancer therapy: lessons from past and future perspectives. *Cancers* 3(2), 2478–2500 (2011).

▪▪ **Provides an in-depth insight into the mechanisms of mTOR inhibitors used in cancer treatment.**

Websites

101. US FDA. (1-6-2007) FDA approval for temsirolimus. www.cancer.gov/cancertopics/druginfo/fda-temsirolimus (Accessed 20 October 2010)
102. US FDA. (11-1-2010) Everolimus. www.fda.gov/AboutFDA/CentersOffices/CDER/ucm127799.htm (Accessed 20 October 2010)
103. National Cancer Institute. (4-9-2012) FDA approval for everolimus. www.cancer.gov/cancertopics/druginfo/fda-everolimus (Accessed 22 October 2012)
104. National Cancer Institute. www.cancer.gov/clinicaltrials (Accessed 12 September 2012)
105. Novartis Pharmaceuticals Corporation. (5-9-2011) Novartis drug Afinitor® gains EU approval to treat patients with advanced pancreatic neuroendocrine tumors. www.novartis.com/newsroom/media-releases/en/2011/1543887.shtml. (Accessed 1 June 2011)

106. Pfizer. (2010) Full prescribing information temsirolimus (TORISEL). www.pfizerpro.com/content/showlabeling.asp?id=490 (Accessed 12 November 2010)

107. Novartis Pharmaceuticals Corporation. (2010) Full prescribing information everolimus (AFINITOR®). www.pharma.us.novartis.com/product/pi/pdf/afinitor.pdf (Accessed 15 November 2010)

108. National Cancer Institute. (17-5-2012) Oral complications of chemotherapy and head/neck radiation (PDQ®) www.cancer.gov/cancertopics/pdq/supportivecare/oralcomplications/HealthProfessional/page5 (Accessed 22 October 2012)

109. National Cancer Institute. (9-8-2006) Common terminology criteria for adverse events v3.0 (CTCAE) www.eortc.be/services/doc/ctc/ctcaev3.pdf (Accessed 11 September 2009)

110. National Cancer Institute Cancer Therapy Evaluation Program. (15-12-2010) Common terminology criteria for adverse events and common toxicity criteria [v4.0]. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_v40 (Accessed 1 June 2011)