J Oral Med Oral Surg 2019;25:11
https://doi.org/10.1051/mbcb/2018027

https://www.jomos.org

JOMOS
Journal of Oral Medicine and Oral Surgery

Educational Article

Management of mTOR inhibitors oral mucositis: current state of knowledge

Anne Sophie Calvo[1,2,*], Juliette Rochefort[1,2,3], Marie José Javelot[1], Vianney Descroix[1,2], Géraldine Lescaille[1,2,3]

[1] Oral Surgery Department, Pitié Salpetriere
[2] Faculty of Odontology, Paris Diderot
[3] Center of Immunology and Infectious Diseases (CIMI-Paris)

(Received: 28 May 2018, accepted: 28 August 2018)

Keywords: mTOR inhibitor / stomatitis / targeted anticancer treatments

Abstract – Introduction: Mucositis is a well-known side effect of classic anticancer treatments (chemotherapy and radiotherapy). Thanks to the major developments in personalizing treatments through the development of targeted treatment, various specific intraoral lesions have been described. **Purpose**: mTOR inhibitors are targeted anticancer treatments that are used to treat various cancer types. They can cause intraoral ulcerations that can be serious, and that can lead to a dose reduction or the anticancer treatment being stopped altogether. The management of these disabling and painful lesions is a major part of ensuring the efficiency of the cancer treatments. The objective of this article is to evaluate the current knowledge about the different treatments used nowadays, especially the preventive treatments. **Conclusion**: An efficient management of the lesions is a major part of the management of patients treated with mTOR inhibitors and should be carried out by the oral cavity specialists.

Introduction

Cancer treatments are known to have many adverse side-effects, particularly in the oral cavity [1]. The development of radiotherapy at the end of the nineteenth century for the treatment of upper aerodigestive tract (UADT) cancers has led to the appearance of mucositis in the 1930s. Similarly, chemotherapy treatments, which began in the 1940s with the use of nitrogen mustard gas and antifolates, were quickly associated with this complication. Therefore, it is well known that head and neck radiotherapy and most conventional cytotoxic chemotherapies can result in mucosal lesions of the gastrointestinal tract and oral mucosa. These lesions are the result of complex biological events whose biological progression was described in five distinct stages by Sonis *et al.* in 2004 [2]. The first stage is the initiation, which is directly caused by chemotherapy. The treatment results in the formation of free radicals and the oxidation reaction induces cellular, tissue, and vascular destruction. The second stage is signal upregulation. During this phase, free radicals cause DNA damage leading to increased cell death. In addition, other cellular signaling pathways are activated, resulting in the production of proinflammatory cytokines such as TNF-α, IL-1, and IL-6. Then, during the signaling and amplification phase, inflammatory reactions occur in cycles, causing a cascade of biological events that result in the biological alteration of the tissues. What follows is the ulceration phase, during which inflammatory cycles can be very severe and cause violent pain. The ulcers are deep and wide and usually covered by a pseudomembrane consisting of dead fibrinous cells. Finally, in most cases the healing phase occurs spontaneously within 2–3 weeks. The result is a renewal of epithelial proliferation and differentiation. Clinically, the tissue appears healthy but remains significantly altered.

In the last 20 years or so, new therapies have emerged in the era of personalized treatment. In fact, to increase the effectiveness of the treatment on cancer cells while decreasing their toxicity, therapies specifically targeting certain molecular pathways in each cancer have been developed: monoclonal antibodies (suffix —mab) and protein inhibitors kinases (suffix —nib). The latter are divided into tyrosine kinase inhibitors, and serine–threonine kinase inhibitors (STKI), which include mTOR inhibitors (suffix —imus).

Although many protein kinase inhibitors may be associated with oral lesions, mTOR inhibitors are the worst offenders, especially in severe forms, requiring a dose reduction or termination of the cancer treatment. These lesions differ from classic cases of mucositis.

* Correspondence: a.sophiecalvo@gmail.com

mTOR inhibitors and oncology applications

Mammalian target of rapamycin aka mTOR was discovered in rapamycin, isolated from *Streptomyces hygroscopicus* on Easter Island and was first used for its antifungal properties. One of the indications of rapamycin, also called sirolimus (Rapamune®), is related to its immunosuppressive qualities and was granted a marketing authorization in renal transplantation in 2001 to prevent transplant rejection. It currently replaces cyclosporine if contraindicated and is also used for its antiproliferative properties on vascular stents [3].

However, other indications of mTOR inhibitors have emerged as a result of the identification of the implications of this serine–threonine intracellular protein kinase, particularly in cell development and proliferation. Its signaling pathway is in fact part of the PI3K/AKT/mTOR pathway, which may be affected in many ways upstream or downstream of this molecule in different types of cancers.

Given the immunosuppressive effects observed with rapamycin, other analogs were developed with the aim of blocking the mTOR pathway to observe the antitumor effects by blocking the cell cycle but also through decreasing the rate of vascular endothelial growth factor expression, which potentiates the process of tumoral angiogenesis. The mTOR inhibitors used in oncology are selective inhibitors administered orally: temsirolimus (Torisel®) and everolimus (Afinitor®). Ridaforolimus is also used in the United States but is not marketed in France.

Temsirolimus is indicated in renal cell carcinomas and mantle cell lymphoma while everolimus, which represents the inhibitory molecule mTOR most prescribed in France, has several indications:

- Advanced stage renal cancer following failure of antiangiogenic treatments such as antiangiogenic sunitinib (Sutent®) and sorafenib (Nevaxar®)
- Neuroendocrine tumors of pancreatic origin that cannot be resected, locally aggressive or metastatic
- HER2/neu-negative and hormone receptor-positive breast cancer in postmenopausal women. In the last case, everolimus is prescribed after treatment failure by non-steroidal aromatase inhibitors (letrozole (Femara®) or anastrozole (Arimidex®)) and is associated with a treatment with exemestane (Aromasin®).

Epidemiology of mucositis induced by mTOR inhibitors

Mucositis is one of the most common and limiting toxicities caused by mTOR inhibitors. The literature review performed by Martins *et al.* [4], which includes 44 studies involving >2,800 patients primarily treated with temsirolimus or everolimus, shows that mucositis is the most common side effect that affects 73.4% patients, with over 30% of those severe cases (20.7% grade 3 and 10% grade 4). These lesions appear to last an average of 10 days after the start of treatment, and severity of mucositis is correlated with the dose [4]. Finally, it was observed that patients receiving everolimus at the highest dose (10 mg) in combination with exemestane for metastatic breast cancer treatment are more likely to develop mucositis [5].

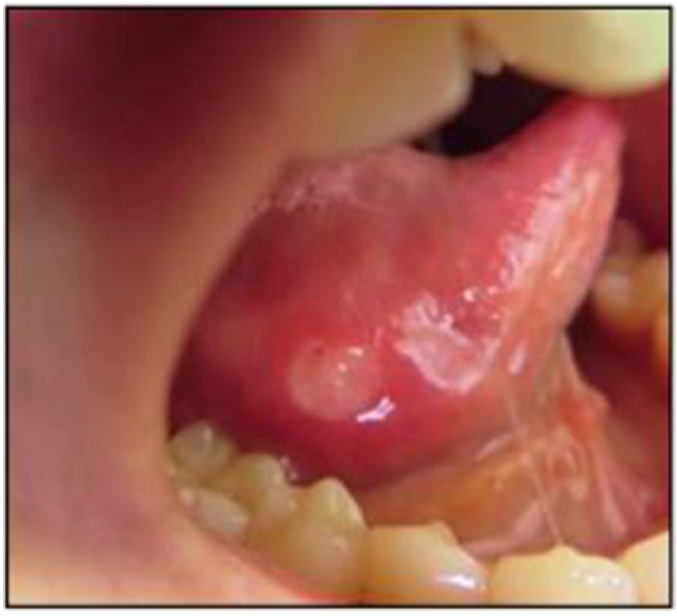

Fig.1. Everolimus-induced mucositis localized in the lateral aspect of the tongue.

Clinical presentation of mucositis induced by mTOR inhibitors

Oral lesions that appear during treatment with mTOR inhibitor called mIAS (mTOR-inhibitor-associated stomatitis) differ from mucositis caused by chemotherapy or radiotherapy [6]. They are similar to the usual singular or multiple lesions, which are often round or ovoid aphtoid lesions with certain characteristics (Fig. 1): [7]

- Usually <1 cm in diameter
- Very disabling even with a decreased size compared to lesions induced by other cancer treatments
- Preferential involvement of mucous membranes with little or no keratinization (buccal mucosa, lips, tongue, and oral floor)
- Only affects the oral cavity not the digestive tract [7–10]

To determine the severity of these ulcers, several international scales are conventionally used in oncology, using classifications from the WHO and the National Cancer Institute NCI-CTCAE 3.0 and 4.0. They are based on the functional impact more or less related to the severity and extent of the clinical lesions (Fig. 2).

Pathophysiological mechanisms of mucositis caused by mTOR inhibitors

However, mucositis is a known side effect of cancer treatments caused by the toxicity to tissues, the mechanisms

Grade	NCI-CTC		WHO
	Clinical signs	Functionnal signs	
0	None		None
1	Erythema of the mucosa	Minimal symptoms, normal diet	Oral Soreness, Erythema
2	Patchy ulcerations or pseudo membranes	Symptomatic but can eat and swallow modified diet	Oral erythema, ulcers, solid diet tolerated
3	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Symptomatic and unable to adequatly aliment or hydrate oraly	Oral ulcers, liquid diet only
4	Tissue necrosis, significant spontaneous bleeding, life threatening consequenses	Symptoms associated with life threatening events	Oral alimentation impossible
5	Death	Death	Death

Fig. 2. NCI-CTCAE 3.0 and WHO classification for mucositis.

	Recurrent Aphtoid Stomatitis (RAS)	mTor ibhibitor associated stomatitis
Duration	7-10 days	< 1 week up to ≥ 2 weeks
Clinical phenotype	• Superficial ulcarations with erythemal bordures • Located in non keratinised mucosis • Pain	Idem RAS
Therapeutical response	Response to steroids adminitration, localy or systemically	Idem RAS
Pain managment	Pain managment can be completed by local anesthetics	Idem RAS

Fig. 3. Comparison between clinical characteristics of recurrent aphtoid stomatitis and mammalian target of rapamycin-inhibitor-associated stomatitis.

underlying the oral mucosal complications of mTOR inhibitor use are not understood, although several hypotheses have been proposed as direct or indirect mechanisms.

In view of a clinical aphtoid aspect, a similarity between mIAS and recurrent aphthous stomatitis (RAS) has been proposed. Peterson *et al.* in 2016 [11] (Fig. 3) hypothesized that the pathophysiological mechanisms of these lesions may be similar because of good therapeutic responses to steroids in both cases. In cases of RAS, this team also observed that the immune infiltration of the lesions combined a reduction in regulatory T cells and a strong infiltration of cytotoxic T lymphocytes, which could also be found in the mIAS. For others, the oral microbiota could cause RAS lesions and have a similar role in causing mIAS [12]. However, a study published in 2017 [13], using an *in vitro* organotypic model of mIAS suggests no link between the oral microbiota and any induced toxicity from these anticancer treatments. It was further shown that the molecule itself resulted in morphological and cytological changes in the oral mucosa. Increased apoptosis and decreased cell proliferation were observed and a release of proinflammatory cytokines derived from keratinocytes in the absence of bacteria [13].

Management of mucositis

The treatment of mucositis is primarily supportive, which is described in MASCC (Multinational Association of Supportive Care in Cancer) publications. Therefore, the standard treatment for mucositis is based on the establishment of a suitable oral hygiene routine, and the use of 1.4% sodium bicarbonate

Grade	Symptoms	Everolimus dose adjustment
1	Minimal, normal alimentation	No dose adjustment
2	Existing. The patient can eat but only soft, liquid or mixed food	Treatment interruption until the mucitis goes back to grade 1, then reintroduction. If the mucitis evolves again to grade 2, stoping treatment until grade 1, then everolimus reintroduction but at inferior dosage
3	Existing. The patient is unable to adequatly aliment or hydrate oraly	Treatment interruption until grade 1, then everolimus reintroduction but at inferior dosage
4	Severe. The patient faces life threatening consequences	Stopping everolimus and setting up an effective therapy

Fig. 4. Dose adjustment of mTOR inhibitors.

mouthwash, usually used in combination with local anesthetics, analgesics, and antiulcer medication. There is also an antifungal "magic mouthwash," which combines bicarbonate with antiseptic mouthwash that has been recognized as ineffective and is thus currently not recommended. This treatment should be adapted according to the severity of the mucositis and may require dose reduction, or a temporary interruption of the cancer treatment, and if necessary, the use of systemic treatments.

Given the clinical differences between the mIAS and classic mucositis lesions, there needs to be a specific treatment. Although there are still few clinical trials of high level of evidence, several expert groups have proposed a management of oral lesions induced by mTOR inhibitors [14–16]. We chose to detail in this article the specific aspects of this management.

Dose reduction or discontinuation of mTOR inhibitor treatment

A dose adjustment table is provided by the pharmaceutical company if there are adverse effects. In the case of oral lesions, adjustments are made on the basis of functional repercussions (Fig. 4). The reasons for the changes in the treatment regimens were studied in several cohort studies. According to Martins *et al.* dose reduction was required in 19.2% patients treated with mTOR inhibitors. The main causes of this dose reduction were thrombocytopenia (37.2%) and mucositis (27.3%) [5]. In the BOLERO-2 study, 24% patients treated with everolimus in combination with exemestane required a dose reduction or treatment interruption because of mucositis of any grade.

Drug management

Anti-inflammatory drugs

A single-center retrospective analysis shows that 87% patients treated with mTOR inhibitors (everolimus or ridaforolimus) showed an improvement in symptoms after local or systemic corticosteroid treatment [11,18]. Another recent study (SWISH trial) including 86 patients in a multicenter single-arm phase-2 trial showed that the use of preventive topical corticosteroids leads to a very significant reduction in the incidence of grade-2 mucositis as part of a treatment with exemestane and everolimus (incidence of 2.4% against 33% in BOLERO-2 study) [19]. After informing patients about oral hygiene, the protocol started with a mouthwash solution of 10 mL of dexamethasone at a concentration of 0.5 mg/5 mL, from the first dose of everolimus, at a rate of four mouthwashes a day for 8 weeks minimum, then at the practitioner's discretion. The solution was kept in the mouth for 2 min without any food or liquid intake for 1 h. Apart from the effects on the reduction of local toxicities, dexamethasone mouthwashes were well tolerated by patients, and only two patients developed a fungal infection. Another advantage is that the cancer treatment could therefore be continued in patients without any dose modifications.

In France, the products available for the topical application of steroidal anti-inflammatory drugs are mainly prednisolone (Solupred®) 60 mg dose in half a glass of water for use as a mouthwash three times a day and clobetasol 0.05% gel (Dermoval® gel). Dexamethasone comes in vials of 20 mg/5 mL or 4 mg/1 mL for use in mouthwashes and methylprednisolone 1 g (Solumedrol® 1 g) in powder form and dissolved in solution for injection using a syringe. The preventive and curative chlorohexidine antiseptic mouthwash prescription has not shown efficacy for this condition [17]; hence, the anti-inflammatory drugs seem to be a more promising approach.

Other absorptions: low-frequency laser possibilities

The term laser is an acronym for light amplification by stimulated emission of radiation. There are different laser types according to the desired effect, exposure time, and the power density. The cellular effects are dependent on the wavelength, energy dose, mode of emission, and duration of beam application to tissues. It has been shown in numerous publications that the low-power laser (LLLT for low-level laser therapy) is effective in treating mucositis at wavelengths ranging 633–685 or 780–830 nm and at power strengths

Early diagnosis
- Therapeutical education of patients with early symptoms
- Education on how to contact the hospital when the mouth discomfort appears
- Education on hox to contact the hospital when lesions that interfere with the alimentation appears

Mouth care and dental hygiene:
- Intructions given to the patient on how to:
  - Regularly brush the teeth with a soft brush. Floss after each meal
  - Regularly rince the mouth with water or baking soda
  - Avoid alcoholic mouth wash and toothpastes with sodium lauryl sulfate
  - Avoid mouthwash with oxigenated water
  - Avoid spicy and acid food, or the one that can hurt the mucosis. Prefer tepid food to warm food.
- Consider using artificial saliva
- Insist on the necessity of regular visits to the dentist
- Anticipated treatment of infection as gum desease

Evaluation of the oral comorbidity
- Evaluation of fongic, viral and bacterial infections
- If needed, adminitrate antifungal, antiviral or antibiotics

Fig. 5. Suggested strategies to prevent or manage mTOR-inhibitor-associated stomatitis [10].

D-x: Oral chack up befor the everolimus therapy starts.
Therapeutical education

D-0: Introduction of everolimus + preventive traetment with a mouthwash:
60mg prednisolone in half a glass of water. 3-4 times/day

D-15: Dentist apointment
Clinical data collection
Treatment by LLLT laser if mucusitis > grade2 CTCAE

D-18: Phone call to the patients with mucisitis > garde 2 at D15
If improvment: visit at D21. If no improvment: visit at D19

D-21: second tratment by LLLT Laser if no clinical improvment

Fig. 6. Procedure for treating patients who are being treated with mTOR inhibitors.

between 10 and 150 mW, with an energy of 2–3 J/cm^2 on the surface to be treated. These effects were observed especially in young patients as part of a hematopoietic stem cells treatment for hematological malignancies, or in patients treated with radiotherapy/chemotherapy for UADT cancers [20]. Experimentally, it has been proposed that LLLT may decrease the expression of inflammatory cytokines, including the tumor necrosis factor α (TNF α) and interleukin 1 (IL 1) [21]. Some also propose to use LLLT alone or in combination with corticoid mouthwashes to treat mIAS. However, there is no clinical trial to scientifically validate its use to date in this indication. Therefore, recommendations can be proposed and summarized in a summary table [10] based on a modified NCI-CTCAE 4.0. Algorithm (Fig. 5).

Conclusion

The course of treatment with mTOR inhibitors may need to be discontinued by the onset of severe mucositis. Therefore, the management of these manifestations represents a major challenge in the overall patient treatment. Recent studies support a good response of aphthoid ulcerations to corticosteroid treatments and dexamethasone preventive mouthwashes seem to provide an appropriate response to this problem by allowing a net reduction in the incidence of these lesions. Therefore, a standardized management process, taking preventive mucositis induced by mTOR inhibitors into account, is required. This involves close collaboration between oral cavity experts and oncologists, making it possible to create a course of care where the patient, after a dental checkup and oral rehabilitation, is educated on the rules of hygiene, informed about these lesions, and treated for them (Fig. 6).

Conflicts of interest: The authors declare that they have no conflicts of interest in relation to this article.

References

1. Sibaud V, Vigarios E. Toxicités orales des thérapies ciblées anticancéreuses. Med Buccale Chir Buccale 2015;21:149–155.
2. Sonis ST, Elting LS, Keefe D, Peterson DE, Schubert M, Hauer-Jensen M, et al. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. Cancer 2004;100(9 Suppl):1995–2025.
3. Stepkowski SM, Tian L, Napoli KL, Ghobrial R, Wang ME, Chou TC, et al. Synergistic mechanisms by which sirolimus and cyclosporin inhibit rat heart and kidney allograft rejection. Clin Exp Immunol 1997;108:63–68.
4. Martins F, de Oliveira MA, Wang Q, Sonis S, Gallotini M, George S, et al. A review of oral toxicity associated with mTOR inhibitor therapy in cancer patients. Oral Oncol 2013;49:293–298.
5. Rugo HS, Pritchard KI, Gnant M, Noguchi S, Piccart M, Hortobagyi G, et al. Incidence and time course of everolimus-related adverse events in postmenopausal women with hormone receptor-positive advanced breast cancer: insights from BOLERO-2. Ann Oncol 2014;25:808–815.
6. Agbo-Godeau SN, Scotté F. Gestion des effets secondaires des thérapies ciblées dans le cancer du rein: effets secondaires stomatologiques (mucites, épistaxis). Bull Cancer 2011;98:117–126.

7. Vigarios E, Epstein JB, Sibaud V. Oral mucosal changes induced by anticancer targeted therapies and immune checkpoint inhibitors. Support Care Cancer 2017;25(5):1713–1739.
8. 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(1):210–215.
9. Boers-Doets CB, Epstein JB, Raber-Durlacher JE, Ouwerkerk J, Logan RM, Brakenhoff JA, et al. Oral adverse events associated with tyrosine kinase and mammalian target of rapamycin inhibitors in renal cell carcinoma: a structured literature review. Oncologist 2012;17(1):135–144.
10. Martins F, de Oliveira MA, Wang Q, Sonis S, Gallottini M, George S, Treister N. A review of oral toxicity associated with mTOR inhibitor therapy in cancer patients. Oral Oncol 2013;49(4):293–298.
11. Peterson DE, O'Shaughnessy JA, Rugo HS, Elad S, Schubert MM, Viet CT, et al. Oral mucosal injury caused by mammalian target of rapamycin inhibitors: emerging perspectives on pathobiology and impact on clinical practice. Cancer Med 2016;5(8):1897–1907.
12. Bankvall M, Sjoberg F, Gale G, Wold A, Jontell M, Ostman S. The oral microbiota of patients with recurrent aphthous stomatitis. J Oral Microbiol 2014;6:25739.
13. Sonis S, Andreotta PW, Lyng G. On the pathogenesis of mTOR inhibitor-associated stomatitis (mIAS)—studies using an organotypic model ofthe oral mucosa. Oral Dis 2017;23(3):347–352.
14. Divers J, O'Shaughnessy J. Stomatitis associated with use of mTOR inhibitors: implications for patients with invasive breast cancer. Clin J Oncol Nurs 2015;19:468–474.
15. Porta C, Ostanto S, Ravaud A, Climent MA, Vaishampayan U, White DA, et al. Management of adverse events associated with the use of évérolimus in patients with advanced renal cell carcinoma. Eur J Cancer 2011;47:1287–1298.
16. Pilotte AP, Hohos MB, Polson KM, Huftalen TM, Treister M. Managing stomatitis in patients treated with mammalian target of rapamycin inhibitors. Clin J Oncol Nurs 2011;15:E83–E89.
17. Cardona A, Balouch A, Abdul MM, Sedghizadeh PP, Enciso R. Efficacy of chlorhexidine for the prevention and treatment of oral mucositis in cancer patients: a systematic review with meta-analyses. J Oral Pathol Med 2017;46(9):680–688.
18. de Oliveira MA, Martins Q, Wang S, Sonis S, Demetri S, George S, et al. Clinical presentation and management of mTOR inhibitor-associated stomatitis. Oral Oncol 2011;47:998–1003.
19. Rugo HS, Seneviratne L, Beck JT, Glaspy JA, Peguero JA, Pluard TJ, et al. Prevention of évérolimus-related stomatitis in women with hormone receptor-positive, HER2-negative metastatic breast cancer using dexamethasone mouthwash (SWISH): a single-arm, phase 2 trial. Lancet Oncol 2017;18(5):654–662.
20. Lescaille G, Lang P, Ernenwein D, Javelot MJ, Descroix V. Intérêt de la photothérapie au laser pour le traitement des mucites de la cavité buccale. Présentation d'un cas et revue de la littérature. Med Buccale Chir Buccale 2010;16:171–176.
21. Bensadoun RJ, Franquin JC, Ciais G, Darcourt V, Schubert MM, Viot M, et al. Low-energy He/Ne laser in the prevention of radiation-induced mucositis. A multicenter phase III randomized study in patients with head and neck cancer. Support Care Cancer 1999;7 (4):244–252.