Management of mTOR inhibitors oral mucositis: current state of knowledge

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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.
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 (Nexavar®)
- 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 nonsteroidal 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].

**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 aphthoid 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...
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 aiphoid 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 | Clinical signs | Functionnal signs | WHO |
|-------|---------------|------------------|-----|
| 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 adequately aliment or hydrate orally | Oral ulcers, liquid diet only |
| 4     | Tissue necrosis, significant spontaneous bleeding, life threatening consequences | Symptoms associated with life threatening events | Oral alimentation impossible |
| 5     | Death         | Death            | Death |

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

| Duration | Recurrent Aphthoid Stomatitis (RAS) | mTOR inhibitor associated stomatitis |
|----------|--------------------------------------|-------------------------------------|
|          | 7-10 days                            | < 1 week up to ≥ 2 weeks            |
| Clinical phenotype | • Superficial ulcerations with erythema bordures | Idem RAS |
| | • Located in non keratinised mucosis |          |
| | • Pain                               | Idem RAS |
| Therapeutical response | Response to steroids administration, locally or systemically | Idem RAS |
| Pain management | Pain management can be completed by local anesthetics | Idem RAS |

Fig. 3. Comparison between clinical characteristics of recurrent aphthoid stomatitis and mammalian target of rapamycin-inhibitor-associated stomatitis.
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.
between 10 and 150 mW, with an energy of 2–3 J/cm² 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 cortico-steroid 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.

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