Cancer/Radiothérapie xxx (2017) xxx–xxx

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Review article

Pharmacological modulation of radiation-induced oral mucosal complications

Modulation pharmacologique des complications muqueuses orales secondaires à la radiothérapie

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ARTICLE INFO

Article history:
Received 18 July 2017
Received in revised form 9 November 2017
Accepted 15 November 2017

Keywords:
Oral mucositis
Radiotherapy
Supportive care
Clinical management

ABSTRACT

Radiation-induced mucositis is a common toxicity, especially in patients with head and neck cancers. Despite recent technological advances in radiation therapy, such as intensity-modulated radiotherapy, radiation-induced mucositis is still causing treatment disruptions, negatively affecting patients' long and short term quality of life, and impacting medical resources use with economic consequences. The objective of this article was to review the latest updates in the management of radiation-induced mucositis, with a focus on pharmaceutical strategies for the prevention or treatment of mucositis. Although numerous studies analysing the prevention and management of oral radiation-induced mucositis have been conducted, there are still few reliable data to guide daily clinical practice. Furthermore, most of the tested drugs have shown no (anti-inflammatory cytokine, growth factors) or limited (palifermin) effect. Therapies for acute oral mucositis are predominantly focused on improving oral hygiene and providing symptoms control. Although low-level laser therapy proved efficient in preventing radiation-induced oral mucositis in patients with head and neck cancer, this intervention requires equipment and trained medical staff, and is therefore insufficiently developed in clinical routine. New effective pharmacological agents able to prevent or reverse radio-induced mucositis are required.

Mots clés :
Mucite orale
Radiothérapie
Soins de support
Traitement médical

RÉSUMÉ

La radiomucite est une toxicité fréquemment rencontrée chez les patients pris en charge par radiothérapie pour un cancer de la tête et du cou. Malgré l'avènement de la radiothérapie avec modulation d'intensité (RCMI), la radiomucite reste un effet secondaire fréquent, qui altère la qualité de vie des patients à court et long termes, et nécessite parfois des interruptions de traitement. L'objectif de ce travail était d'effectuer une synthèse de la littérature portant sur la prévention non dosimétrique et la RCMI. Même si

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https://doi.org/10.1016/j.canrad.2017.11.006
1278-3218/

nombreuses études ont étudié la prise en charge de la radiomucite orale, peu de données sont transférables aux patients. Par ailleurs, la plupart des molécules testées ont montré soit une efficacité limitée (palifermine), soit une absence d'efficacité (cytokines anti-inflammatoires, facteurs de croissance). Finalement, le traitement de la radiomucite orale repose principalement sur l'amélioration de l'hygiène buccodentaire et sur la prise en charge symptomatique. Le laser de basse énergie a démontré une efficacité dans des stratégies préventives, mais son coût et l'expertise nécessaire expliquent probablement sa faible disponibilité en routine. Le développement d'agents pharmacologiques pouvant prévenir ou traiter la radiomucite demeure une priorité.

1. Introduction

Because of an important turnover, mucosa cells are highly sensitive to ionizing radiation, and cell deaths occur in a few days following the first course of radiotherapy. Radiation-induced mucositis in the oral cavity and pharynx interferes with comfort, nutrition, communication and general well-being. It may lead to treatment disruption, identified as a factor of local recurrence in various primary tumours, including head and neck cancers [1]. The management of radiation-induced mucositis is a major challenge, because it occurs in most of patients with head and neck cancer treated with external beam radiotherapy or brachytherapy [2–4]. Although intensity-modulated radiotherapy (IMRT) showed superiority over three-dimensional conformal radiotherapy regarding salivary preservation [5], radiation-induced mucositis requiring supportive care remains frequent and potentially even more frequent with IMRT due to the use of alternate beam paths [6]. Mucosa sparing techniques (based on the correlation between acute mucositis grade and percentage of volume of oral cavity receiving a certain amount of dose) are promising strategies [7–10], but difficult to achieve given the proximity of the target volume, and given the uncertainties of definition/delineation [11]. In this context, the pharmacological modulation of radiation-induced oral mucosal complications is a real necessity.

The current physiopathology of radiation-induced mucositis is reviewed in the present article and available data on its pharmacological prevention/treatment are discussed.

2. Pathogenesis, clinical presentation and risk factors of oral mucositis

2.1. Pathogenesis

Oral mucositis is the consequence of complex biological events and does not only result from an indiscriminate destruction of rapidly dividing basal epithelial stem cells. This process involves multiple phases and biological interactions [12–18], and has been summarized in five steps (Fig. 1).

2.1.1. Initiation phase

At initiation phase, lethal DNA damages lead to clonogenic death of basal epithelial cells. DNA damages are both direct and indirect, with the generation of reactive oxygen species induced by radiation.

2.1.2. Message generation phase

The message generation phase is the activation of various transcription factors (p. 53, nuclear factor-kappa B [NF-kB], Wnt), through a cascade effect induced by reactive oxygen species [16]. Activation of NF-kB pathway produces cytokines with key roles in the pathogenesis of mucositis (tumour necrosis factor-α, interleukin [IL]-1, IL-6, C-reactive protein), as well as enzymes involved in the oxidative stress (superoxide dismutase, cycloxygenase-2, inducible NO-synthase), and cell adhesion molecules [13–15]. Endothelial cell apoptosis is also promoted by the asmase/ceramide pathway activated by high radiation doses [19]. The damages caused to connective tissues result in fibrinolysis, which stimulates macrophages to produce matrix metalloproteinases [17].

2.1.3. Signal amplification phase

In the signal amplification phase, pro-inflammatory cytokines activate downstream signalling pathways, further amplifying the inflammatory cascade, increasing permeability. Other pro-inflammatory cytokines are recruited, amplifying the biological cascade and resulting in clinical erythema and oedema [20].

2.1.4. Ulceration phase

Ulcers appear, since detaching mucosal cells are not replaced by differentiating basal cells, because of their radio-induced cell death. At this phase of mucositis, severe pain can occur. Mucosal ulcers are colonized by bacteria, actively contributing to the mucositis process: bacterial products, such as lipopolysaccharide penetrate into the submucosa, and stimulate the secretion of pro-inflammatory cytokines by macrophages. There is also a risk of sepsis [21–23].

2.1.5. Healing phase

Last step is the healing phase, as the consequence of an active biological process in which the submucosal extracelllular matrix drives proliferation, migration and differentiation of the epithelium bordering the ulcer. Disruption of the submucosal extracelllular matrix can delay the healing process or even prevent it [20–23].

2.2. Clinical manifestation

After a normo-fractionated radiation dose below 20 Gy, hyperkeratosis of the mucosa can be observed, with a slight discoloration [20–22]. At doses above 20 Gy, erythema and oedema can be seen. At doses above 30 Gy, ulcerations appear, often coalescing and covered by pseudomembranes. Ulcerations may last for up to three or four weeks following treatment completion.

Xerostomia is also an important radiation side effect that frequently firstly occurs during the radiotherapy course and can then turn into a permanent symptom. However, clear "cut off" doses cannot be provided. Indeed, xerostomia is partly caused by hyposalivation (that is typically reported at 15 to 20 Gy, due to a reduction of saliva production of at least 40%) but also partly by changes in saliva composition [24]. Salivary glands produce approximately 1 L of saliva per 24 h, mainly containing serous and mucous secretions. The serous secretion includes salivary amylase that is crucial for nutrition. Mucous secretion includes mucin, which gives saliva its lubricating and mucosa-protecting nature [25]. Major salivary glands (parotid, submandibular and sublingual glands) produce 90% of saliva but only a slight part

Please cite this article in press as: Bockel S, et al. Pharmacological modulation of radiation-induced oral mucosal complications. Cancer Radiother (2017), https://doi.org/10.1016/j.canrad.2017.11.006