

Management of acute toxicities during radiotherapy of head and neck cancers

Gestion des toxicités aiguës lors de la radiothérapie des cancers de la tête et du cou

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ABSTRACT

Objective: Head and neck cancer management often involves multimodal treatment including radiotherapy. Despite the improvement of intensity-modulated radiation therapy, acute and late toxicities remain important. The goal of this work was to focus on optimal methods to prevent and manage acute skin and mucous reactions related to radiation through a systematic review of recently published literature.

Methods: The present review of literature focuses on data referenced in PubMed© and Google Scholar search engines from 1986 to 2021.

Results: Acute radiation mucositis and dermatitis remain the most commonly observed side effect during radiotherapy of head and neck cancers leading to complications such as infection, candidiasis and potentially treatment disruption. Management of these disease is still heterogenous. Currently, there is no general consensus about the prevention or about the treatment of choice. Various topical agents have been tried, however, their efficiency remains uncertain.

Conclusion: Present data from the literature highlight the need for further trials, in order to provide evidence-based treatments in order to harmonize clinical practice.

Key words: Head and neck cancer, Radiotherapy, Acute toxicity, Mucositis, Dermatitis.

RÉSUMÉ

Objectif: La prise en charge des cancers de la tête et du cou nécessite un traitement multimodal dont la radiothérapie qui en constitue une pierre angulaire. Malgré l'amélioration technique de la radiothérapie avec modulation d'intensité, les toxicités aiguës et tardives restent non négligeables. L'objectif de ce travail est de revoir les méthodes optimales de prévention et de gestion des réactions cutanéomuqueuses aiguës liées à la radiothérapie.

Méthodes: La présente revue de la littérature concerne les données référencées dans les moteurs de recherche PubMed © et Google Scholar entre 1986 et 2021.

Résultats: La radiomucite et la radiodermite aiguë restent les effets secondaires les plus observés lors de la radiothérapie des cancers de la tête et du cou entraînant des infections ou l'apparition de candidose pouvant conduire à l'interruption thérapeutique. La gestion de ces complications est assez hétérogène. Actuellement, il n'y a pas de consensus général sur la prévention et le traitement de choix. Divers agents topiques ont été étudiés, cependant, dans la majorité leur efficacité reste controversée.

Conclusion: Les données actuelles de la littérature soulignent la nécessité de poursuivre les essais, afin de fournir des traitements fondés sur des preuves pour harmoniser la pratique clinique.

Mots Clés: Cancer de la tête et du cou, Radiothérapie, Toxicité aiguë, Mucosites, Dermite.

INTRODUCTION:

Head and neck cancers are 6th cancer in incidence in the world [1]. Radiotherapy (RT) is one of the most important treatment modalities of these cancers. However, it is characterized by an acute toxicity mainly related to tissues with rapid renewal kinetics (high α/β ratio). RT should be carefully planned in order to

prevent the occurrence of side effects. Despite the improvement of intensity-modulated radiation therapy (IMRT), toxicities mucositis and dermatitis remain common during RT of head and neck cancers (HNC). Such side effects have a negative impact on patients' quality of life in addition to its economic and therapeutic impact due to extending the duration of hospitalizations and interruption of treatment [2]. The medical team

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should inform the patient about risks and toxicities by providing a personalized medical file with a complete information [3, 4].

In this article, we will describe the most common acute complications of HNC RT and therapeutic strategies of prevention and treatment.

METHODS:

The present review of literature focuses on data referenced in PubMed® and Google Scholar search engines from 1986 to 2021. In this search, more than 40 clinical studies have been selected and divided into the prophylactic or therapeutic uses of the evaluated treatment agents.

SUMMARY OF THE REVIEW:

1. The management of mucositis:

Oropharyngeal mucositis is a common complication of HNC RT (36 to 100% when combined with chemotherapy) [5,6]. Almost all patients receiving chemotherapy and cumulative radiation doses > 30 Gy to oral mucosal fields will develop mucositis [7]. The WHO and National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) scales are two of the most common utilized scales (Annex 1). The management of mucositis has three components: the patient's general care, the treatment of mucositis and its complications.

1.1. The patient's general care:

A psychological preparation of the patient is necessary. They should be informed about the progress of treatment, the side effects, the possible complications and the hygienic-dietary rules necessary to prevention. Weekly consultations are scheduled to assess and manage the various symptoms during RT.

Some comorbidities such as malnutrition and diabetes increase the risk of mucositis and should be compensated [6]. Thus, a dietary consultation with a nutritional assessment is indicated before beginning RT. Smoking is also a predictor factor of mucositis and withdrawal should be advised to all HNC [8]. Most of this population have a poor oral health and need rehabilitation before starting RT.

Educating patients on oral hygiene is essential and the prescription of 14/1000 bicarbonate mouth washes after providing advice to the patient on their application is very important. A daily, lifetime application of fluoride gel should be instituted in patients dented by prophylaxis of dental caries [9-11]. Cryotherapy and keratinocyte growth factors have been shown to be effective in preventing mucositis [12]. Other treatments have a lower level of evidence regarding benefit such as aloe Vera, amifostine, intravenous glutamine supplementation, granulocyte growth factors, honey, laser and sucralfate [5].

1.2. Treatment of mucositis:

A variety of treatments are used for the management of oral mucositis. The choice depends on the clinical state, the available means, the patient's needs and the

practical recommendations:

- Povidone iodine: It is a broad-spectrum antiseptic non-irritating for the mucosal membrane. It seems efficient and should be used systematically. It has been shown in a randomized trial developed by Rhan et al. including 40 patients who underwent chemotherapy and RT that regular mouth washes could reduce the mucositis rate, mean grade and mean duration [13].

- Local antibiotics with reduced spectrum and antifungals: In a randomized study involving 275 patients and comparing local antibiotics to a placebo, authors found a lower rate of false membranes ($p=0.02$), dysphagia ($p=0.006$) and weight loss ($p=0.009$) [14]. Several authors have tested the use of antifungals with antibiotics in pellets in order to decontaminate the oral cavity. It has been demonstrated high curative rate when there is overt local infection [15].

- Corticosteroids: Local corticosteroids have been evaluated in small series and seem to have a benefit. but we must remain cautious because of the theoretical risk of infection that they can cause if used with the systemic form [15]. In a pilot study of 30 patients with oral or oropharyngeal cancer, it was found that the use of spacers, pilocarpine hydrochloride and topical corticosteroid therapy in addition to oral care dental professionals prevented severe radiation-induced oral mucositis [16]. Another multicentre, single-arm, phase 2 prevention study showed that the prophylactic use of oral dexamethasone solution substantially lowered the incidence and severity of mucositis in breast cancer patients receiving everolimus and exemestane and could lead to a new standard of oral care [17].

- Non-steroidal anti-inflammatory drugs: Some non-steroidal anti-inflammatory drugs acting by inhibition of prostaglandin have been tested in several studies such as: Indomethacin. A randomized study of 19 patients showed a reduction in the incidence of grade 3 mucositis with the use of indomethacin [18]. More recently, authors proved that indomethacin oral spray is an effective and safe preparation for pain relief and can be used as an alternative therapeutic option for oropharyngeal mucositis [19]. Benzylamine hydrochloride which has an analgesic, anesthetic, anti-inflammatory and antimicrobial effect, reduces incidence of ulceration and erythema [15].

- The low energy laser: This is the simple and atraumatic application of a monochromatic high density photons light. Its role in the preventive and curative treatment of radiation-induced oral mucositis has been demonstrated in several randomized studies [20-21]. In vitro and in vivo research has shown that it has three main photobiological properties: analgesic, anti-inflammatory and healing [22]. Recently, a prospective, double-blind, randomized and controlled study which was carried out in patients diagnosed with oral tumor and undergoing oncologic treatment showed that low-level laser therapy reduced the incidence and severity of mucositis in patients treated with RT with or without chemotherapy [20].

- Analgesics: The most common cause of pain in HNC is oral mucositis following chemo-radiotherapy (80% of patients). It can worsen their quality of life by preventing them from speaking, eating or drinking [23]. Its support is therefore a major element. An analgesic treatment adapted to stages of pain must be systematically prescribed. The morphine derivatives represent the treatment of choice. The use of topical anesthetics, like lidocaine gel, may be necessary in case of local pain but gives only a short relief [15].

1.3. The treatment of complications of mucositis:

-Oral candidiasis:

Mucositis destroys the oral epithelium and inhibits its renewal, resulting in epithelial atrophy that facilitates adhesion and invasion of *Candida Albicans* and thus leads to oral candidiasis [24]. The management of oropharyngeal candidiasis should be as rapid as possible to avoid any risk of oesophageal extension or systemic spread. Specific treatments should be associated with rules of oral hygiene and multi-day mouthwash with sodium bicarbonate. It is recommended to use the antifungals with local action, to choose topicals without drug interactions, the least possible resistance and a spectrum extended if possible to all *Candida*. Thus, the systemic antifungals forms are reserved to invasive and/or severe candidiasis [25,26].

Amphotericin B (Fungizone®) is the most well-known molecule of this class and has long been the reference topic in oropharyngeal candidiasis. A pure suspension of amphotericin B is used. The antifungal is left in contact with the mucosa for at least two minutes and then swallowing the suspension. Applications should be repeated at least four times a day [27]. Several galenic forms exist for miconazole such as oral gel or gingival mucoadhesive tablet (Loramyc®). According to the recommendations of Saint-Paul-de-Vence 2009 on oropharyngeal candidiasis, this treatment is of interest in the first-line treatment [27].

Oral candidiasis can be linked to decreased salivary flow or xerostomia, hence the benefit of maximum lasting salivary preservation allowing to reduce the occurrence of oropharyngeal candidiasis and to improve quality of life of patients. The increasing use in recent years of Intensity modulated irradiation (IMRT) has made it possible to preserve salivary flow compared to standard techniques [28].

-Malnutrition:

Malnutrition is a problem frequently encountered during irradiation of head and neck cancers [29,30]. This malnutrition is multifactorial; it is mainly related to oral pharyngeal pain, loss of appetite, dysgeusia and fatigue [31].

The detection of malnutrition must be early from the first diagnostic consultation. A nutritional status assessment should be repeated regularly at each visit. Weight, BMI and assessment of oral intake should be measured [32].

The management of this complication requires supportive care combining analgesics and appropriate

nutritional support [33]. Several studies have evaluated the benefit of oral nutritional supplementation in irradiated patients for tumors of the upper aerodigestive tract, most of which have been shown to significantly reduce weight loss as well and improves the quality of life of patients [34, 35].

Feeding is provided either by a nasogastric tube, by an endoscopic, radiological or surgical gastrostomy or by a jejunostomy. Enteral feeding is used to provide nutrients to patients when oral feeding is not sufficient [36]. A randomized trial comparing the different gastrostomy pathways showed that the rate of serious complications and death was lower with endoscopic gastrostomy [37].

2. The management of radiodermatitis:

Acute radiodermatitis is the most common side effect of RT. Up to 85% of patients treated with RT develop moderate-to-severe skin reactions [38-40].

The Radiation Therapy Oncology Group (RTOG) has developed a standardized grading system to evaluate acute radiation-induced skin toxicity. It ranges from mild erythema to desquamation and ulceration (Annex 2).

It has been reported that the IMRT technique can cause more acute dermatitis because more beams are used than with 3DRT, resulting in a larger volume of irradiated skin to receive an intermediate dose. On the other hand, the study by Gupta et al. found no difference in acute dermatitis between IMRT and 3DRT [41,42].

The management of the side effects of RT requires preventive and curative measures taken during the pre therapeutic weekly consultation. There is currently no consensus on how to manage them [43-44].

2.1. The preventive treatment of radiodermatitis:

Prevention involves motivating patients to take care of their skin. Care givers should advise them to apply a mild, overgrown, non-detergent soap with a neutral pH, to avoid excess moisture, friction and even minimal trauma on the treated area, avoid sun exposure on the irradiated area and any use of irritative substance (perfume, deodorant...). Any self-medication should be prohibited, because if at best it proved to be ineffective, in the worst scenarios it can be deleterious. Screening and management of other contributing factors especially diabetes, smoking and malnutrition is an important step [45,46,39].

2.2. The curative treatment of radiodermatitis:

Cutaneous application of topical agents must be applied few hours after the radiotherapy session: an interval of four hours before and after must be observed in order to mitigate a bolus effect which represents an artificial increase in the dose of radiation perceived by the epidermis aggravating skin toxicity [39]. A variety of treatment is proposed:

- Trolamine: Initially developed for the management of thermal burns, trolamine has antioedematous properties that promote the repair of radiodermatitis. There is no evidence in the literature showing a benefit of trolamine [47].

- Calendula officinalis: It is a substance marketed in the management of superficial burns and irritative



dermatitis. Despite its antioxidant activity [44], there are no preclinical data on its use during irradiation [48].

-Dermocorticoids: Several studies have shown a benefit in terms of functional symptoms of radiodermatitis, but without a decrease in lesion incidence and severity [49, 50]. Potera et al. reported no significant difference in the duration or intensity of dermatitis with prophylactic use of 0.2% hydrocortisone cream and placebo in patients with various cancer diagnoses [51].

- 1-2% aqueous eosin: This product is routinely used for its drying power in oozing dermatitis grade 2 or higher. Its use with radiotherapy has never been truly evaluated. On the other hand, its intense red color makes skin examination difficult and could promote photosensitization [52].

- Dressings with hydrocolloids and hydrogel: Facilitates skin healing by favoring a humid environment [43].

- Hyaluronic acid: Hyaluronic acid is one of the main components of the cutaneous extracellular matrix. A randomized, open-label, monocentric, phase III trial including 200 breast cancer patients with grade 1 to 2 radiation-induced dermatitis during postoperative radiotherapy was designed to demonstrate the superiority of hyaluronic acid. They were randomized to receive either hyaluronic acid (A) or a simple emollient (B). No significant difference between hyaluronic acid and the simple emollient in the treatment of acute radiation-induced dermatitis has been shown. There was, however, a trend towards improvement in both pain level and skin colorimetry[52].

- Analgesic: Prescribed in order to reduce the pain.

- Treatment of infection: Skin infection without any general repercussion can be dealt with by using a local antibiotherapy targeting cutaneous flora, such as fucidic acid.

Other products have been described in the literature without proof of their effectiveness such as Aloe Vera-based gel, sucralfate cream, vegetable oils.

CONCLUSION: _____

The management of radiomucite is a daily issue based on a good preparation of HNC patient (educating patients on oral hygiene, encouraging smoking cessation, oral rehabilitation before the start daily treatment and mouth washes...). In a curative intent, the application of antiseptic treatment, antibiotics, corticosteroids, antiinflammatories, low-energy laser and especially analgesic are useful according to the clinical presentation. The management of induced complications (candidiasis, denuitrition) is a fundamental step to ensure better therapeutic results. The management of radiodermatitis includes a preventive and a curative aspect. The patient's awareness of the importance of dietary and lifestyle measures and the rapid and adequate dermatological therapeutic management from the onset of skin damage are the two pillars of good management of this acute toxicity. Present data from the literature highlight the need for further trials, in order to provide evidence-based treatments in order to harmonize clinical practice. Compliance with ethical standards

Compliance with ethical standards

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Annex1: WHO and CTCAE scales for oral mucositis.

WHO scale for oral mucositis

Grade 0 = No oral mucositis

Grade 1 = Erythema and soreness

Grade 2 = Ulcers, able to eat solids

Grade 3 = Ulcers, requires liquid diet (due to mucositis)

Grade 4 = Ulcers, alimentation not possible (due to mucositis)

NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

Grade 1 = Asymptomatic or mild symptoms; intervention not indicated.

Grade 2 = Moderate pain; not interfering with oral intake; modified diet indicated

Grade 3 = Severe pain; interfering with oral intake

Grade 4 = Life-threatening consequences; urgent intervention indicated

Grade 5 = Death

Annex 2: Radiation Therapy Oncology Group classification for acute radiation dermatitis.

Grade 0 = Normal skin; no visible changes to the skin

Grade 1 = Follicular, faint, or dull erythema; epilation; dry desquamation; decreased sweating. Mild tightness of skin and itching may occur. In darker skin types, the affected area may appear slightly darker

Grade 2a = Tender or bright red erythema; dry desquamation; skin may feel tight, sore and itchy. In darker skin types, the area will appear darker

Grade 2b = Patchy, moist desquamation. Yellow, pale, or green exudates may be visible on the surface. Soreness and edema are present

Grade 3 = Confluent, moist desquamation other than skin folds. Yellow, pale, or green exudates will be visible on the surface. Pitting edema. Bleeding may occur

Grade 4 = Ulceration and necrosis