*Int. J. Oral Maxillofac. Surg. 2012; 41: 225–238*
doi:10.1016/j.ijom.2011.10.011, available online at http://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Review Paper
Oral Medicine

# Cancer treatment-induced oral mucositis: a critical review

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*A. Rodríguez-Caballero, D. Torres-Lagares, M. Robles-García, J. Pachón-Ibáñez, D. González-Padilla, J. L. Gutiérrez-Pérez: Cancer treatment-induced oral mucositis: a critical review. Int. J. Oral Maxillofac. Surg. 2012; 41: 225–238.* 

*Abstract.* Head and neck cancer represents one of the main oncological problems. Its treatment, radiotherapy and chemotherapy leads to mucositis, and other side effects. The authors reviewed high-quality evidence published over the last 25 years on the treatment of cancer treatment-induced oral mucositis. A Medline search for double blind randomized controlled clinical trials between 1985 and 2010 was carried out. The keywords were oral mucositis, radiotherapy, chemotherapy, and head and neck. The different therapeutic approaches found for cancer treatment-induced oral mucositis included: intensive oral hygiene care; use of topical antiseptics and antimicrobial agents; use of anti-inflammatory agents; cytokines and growth factors; locally applied non-pharmacological methods; antioxidants; immune modulators; and homoeopathic agents. To date, no intervention has been able to prevent and treat oral mucositis on its own. It is necessary to combine interventions that act on the different phases of mucositis. It is still unclear which strategies reduce oral mucositis, as there is not enough evidence that describes a treatment with a proven efficiency and is superior to the other treatments for this condition.

Keywords: Oral mucositis; Oral cancer; Prevention; Treatment; Chemotherapy; Radiotherapy.

Accepted for publication 10 October 2011
Available online 8 November 2011

Head and neck cancer, principally squamous cell carcinoma, is one of the main oncological problems owing to its high mortality rate and the after-effects of the treatment. It makes up 4–5% of all cancers, is more common in men than in women (4:1), and is more common in those aged over 40 years[20,73].

Malnourished patients, or those who drink and/or smoke, are at greater risk. This is because the upper aerodigestive tract epithelium of consumers is changed predisposing them to develop many cancers. Recent studies demonstrate that although the principal risk factors for head and neck cancer remain tobacco and alcohol use, human papillomavirus (HPV) is aetiologically associated with 20–25% of upper aerodigestive tract cancer, mostly in the oropharynx[7,39,57]. The most common high risk-HPV associated with it is HPV-16[7,72].

Radiotherapy, whether on its own or in combination with other treatments, is an important option in the treatment of many of the lesions found in this part of the body. Radiation (and chemotherapy) affects malignant cells and is also absorbed by the buccal and peribuccal tissue, especially in rapidly dividing cells[158].

Gastrointestinal tract cells have the highest rate of cell proliferation and turnover in the human body. Even though antineoplastic treatment has become more effective, it continues to be associated with numerous short and long-term side effects[72].

Oral mucositis is one of the most common side effects of radiotherapy and/or chemotherapy. It is a debilitating condition that appears as a result of the cytotoxic effects of the chemotherapy drugs used and radiation to the oral mucosa[32,107].

This review aims to update knowledge about the concept, epidemiology, aetiopathogenesis, clinical manifestation, diagnosis and prognosis of oral mucositis induced by radiation or chemotherapeutic agents. It also aims to evaluate the effectiveness of interventions that have been used in the last 25 years to prevent and

 

treat it in patients with head and neck malignances.

## Material and methods

The authors performed two searches on the Medline database. In the first search they looked for metanalysis and systematic reviews related to concept, epidemiology, aetiopathogenesis, clinical manifestations, diagnosis and prognosis of oral mucositis induced by radiotherapy with or without chemotherapy, using the following keywords: induced oral mucositis cancer treatment.

In the second search, double-blind randomized controlled clinical trials in humans, from January 1985 to May 2011 were sought, using the following keywords: induced oral mucositis; stomatitis; head and neck cancer; radiotherapy; chemotherapy. 74 articles were found; of which only 62 complied with the objectives and criteria of the literature search. Inclusion criteria were: patients of both sexes; aged between 18 and 70 years; diagnosed with head and neck cancer undergoing radiotherapy and/or chemotherapy. The aims of the included studies were focused on the prevention and treatment of induced oral mucositis or stomatitis.

## Results

Oral mucositis is the result of a series of inflammatory changes in the epithelial and subepithelial cells of the oral mucosa caused by direct radiation or chemotherapy. Advanced head and neck cancer treatment is based on combined chemoradiotherapy sessions. It is often necessary to remove the tumour surgically before starting chemoradiotherapy therapy[71]. Establishing correct uninterrupted chemoradiotherapy treatment is often delayed or limited by the common complication of oral mucositis[111].

This is a serious issue which leads to problems in the progress of cancer treatment, which often has to be postponed or discontinued, compromising the patient's response to treatment. Many studies show that abandoning or interrupting treatment markedly increases the risk of residual tumour cell proliferation. This causes tumour recurrence and proliferation, worsening the patient's prognosis[15,111].

Mucositis is also related to debilitating side effects that seriously affect the patient's short and long-term quality of life, such as chronic airflow limitations, starvation or secondary infections. These infections can lead to bacteraemia causing severe pain. The patient may have to be hospitalized[50,59,107,117].

### Epidemiology

Approximately half of all head and neck cancers are treated with radiotherapy alone or in combination with chemotherapy and surgery[71,158]. The incidence of oral lesions varies depending on the pathogenesis, the type of treatment used, and the state of the mouth before the disease appeared[107,136].

When radiotherapy-induced oral mucositis develops in head and neck cancer, approximately 80% of patients treated suffer from ulcers or pseudomembranes. Of the patients who receive high doses of radiotherapy in the buccal cavity and pharyngeal region, 15% must be hospitalized due to complications from the treatment[107,117]. Younger patients seem to be at greater risk of chemotherapy-induced oral mucositis[62] because their epithelium has a higher mitotic rate and more epidermal growth factor receptors.

Current radiotherapy and chemotherapy protocols show that oral mucositis induced by these treatments has an 85–100% incidence and depends on three main modifying factors: the radiation dose received; the type of chemotherapy drug administered; and the administration plan (whether fractionated or not)[102].

### Aetiopathogenesis

Mucositis is caused by the systemic effects of the chemotherapy cytotoxic agents and the local effects of radiation on the oral mucosa[102]. The biological complexity that lies beneath the damage in the oral mucosa has only been considered recently. It is thought that mucositis begins due to the direct damage of DNA in the cells of the epithelium that can cause cells to die. This damage to the genetic material of the cell could be induced by different mechanisms, some of them mediated by the generation of oxygen-reactive species[69,90,127,128].

Microvascular damage could play an important role in the development of radiation-induced damage[127–129]. Morphological evidence obtained through electron microscopy provides strong evidence that endothelial and connective tissue damage precedes the changes in the epithelium of the irradiated oral mucosa, following the current working model proposed by Sonis et al.[129]. The proposed aetiopathogenic model develops over five phases: initiation, message generation, signal amplification, ulceration, and healing.

Chemoradiation induces reactive oxygen species to be formed, causing cell damage in the epithelium and subepithelial mucosa (initiation phase). A series of transcription factors are activated and the production of proinflammatory cytokines, such as tumour necrosis factor-alpha, interleukin-1, interleukin-6, and C-reactive protein begins (message generation phase) causing a large increase in local vascularization.

The inflammatory modulators are activated and released into the interstitial space (signal amplification phase) and oedema is observed. In the following phase, the cytotoxic agents reduce the mitosis of dividing epithelial cells in the oral cavity causing atrophy and ulceration (ulceration phase), further causing severe pain and limiting how the patient functions[79,94,129].

Opportunistic microorganisms in the oral cavity quickly colonize these areas, increasing the risk of superinfection. In the final phase, the epithelial cells start to proliferate and differentiate, initiating mucosal tissue healing (healing phase)[129,131].

The earlier phases are characterized by marked neutropenia and leukopenia, although in the final phase, recovery of the white blood cell count can be observed[127,129]. Each of these phases can be potentially targeted by different therapeutic and preventive treatments.

### Clinical manifestations

Many complications can arise during conventional radiotherapy treatment as a result of the radiation. The first radiation dose (10–20 Gy) provokes hyperkeratosis of the oral mucosa, which manifests as a light decolouration that can often go unnoticed[129]. Once the patient has received more than 20 Gy of radiotherapy (Fig. 1), erythema, considered as the first clinical sign of mucositis, can be observed.

More severe stages are produced once the total accumulated dose is more than 30 Gy, which is usually after the third week of treatment. Ulceration appears which is sometimes covered by pseudomembranes that favour bacterial colonization[69,127–129]. Symptoms range from pain and discomfort to the inability to tolerate food or liquids. Marked xerostomia and dysgeusia can also occur. Once radiotherapy treatment has been completed, the mucositis will spontaneously subside over 2–6 weeks[129].

Chemotherapy-induced oral mucositis is usually more aggressive than that induced by radiotherapy. Erythema is observed on around the fifth to eighth day of treatment and in the following days oedema and ulceration are notable. At the end of chemotherapy treatment, the

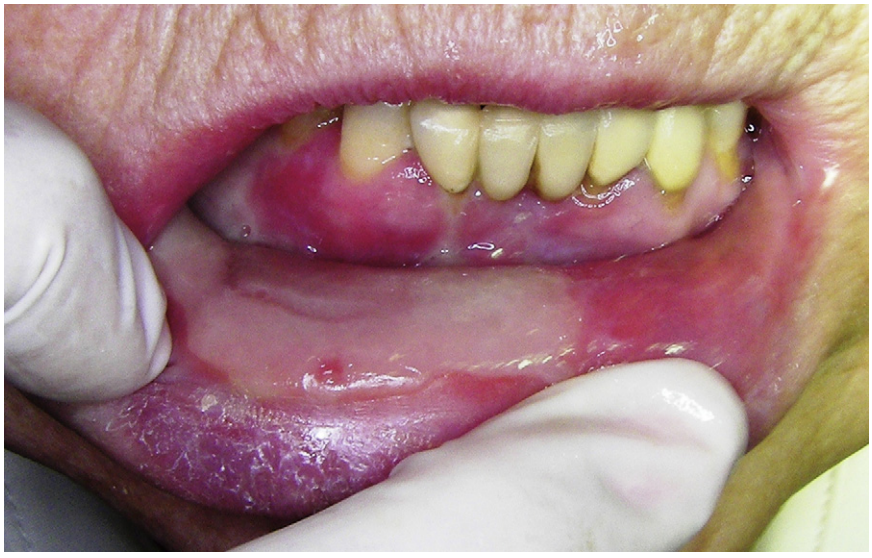

*Fig. 1.* Oral mucositis.

mucosa needs about 7–10 days to recover completely[79,94,129]. Lesions are especially visible with chemotherapy-induced mucositis. They are seen in the non-keratinized mucosa: buccal and labial mucosa, ventral and lateral surface of the tongue, floor of the mouth and soft palate. The hard palate and gums seem to be less susceptible to the effects of chemotherapy[121,122,127,131]. Chemotherapy-induced mucositis can affect the whole area exposed to radiation, including the keratinized regions of the oral cavity[79,121,122,128].

### Diagnosis

The diagnosis of mucositis is primarily based on clinical manifestations[120,132]. The administration of a stomatoxic treatment can be found in the patient's clinical history and the appearance, position and development of lesions in the mucosa can be seen in the oral examination. Chemotherapy-induced mucositis is often observed in the mobile mucosa and rarely affects the back of the tongue, the hard palate or the gums. Radiotherapy-induced mucositis affects the mobile mucosa as well as the fixed mucosa, even though the latter is less commonly involved[132].

The grade of severity of the mucositis is rated according to clinical assessment scales which include the different stages and evolution of the oral mucositis lesions[80]. The most frequently used criteria are the National Cancer Institute (NCI)-Common Toxicity Criteria (CTC) from the USA[23,137], the Toxicity criteria of the Radiation Therapy Oncology Group (RTOG), the European Organization for Research and Treatment of Cancer (EORTC)[29], and the criteria set out by the World Health Organization (WHO) in 1979[150].

It is necessary to establish a correct differential diagnosis with other pathological conditions. Sometimes this can be complicated by the fact that mucositis is an ideal site for bacterial, viral, and fungal superinfection[69,90,119].

Viral infections differ clinically from mucositis because of their location. They usually affect the keratinized mucosa of the hard palate, gums, and back of the tongue. The patient often has a fever at the same time. An exfoliative cytology and microbiological culture is necessary for definitive diagnosis[90,128].

### Prognosis

Chemotherapy-induced mucositis lasts for about 1 week and generally heals spontaneously 21 days after chemotherapy is administered. Radiotherapy-induced mucositis lasts for at least 2 weeks longer following radiotherapy (60–70 Gy)[79,90,94,128,131].

Severe ulcers that last for 5–7 weeks after the end of treatment are not uncommon in patients who have received concomitant chemo- and radiotherapy for head and neck cancer[79,131]. Chronic mucositis after radiation has also been described but in fewer cases[131].

The most common complication of mucositis, especially with neutropenia, is an increased predisposition to bacteraemia, septicaemia, and fungaemia. Sometimes this can put the patient's life at risk[79,131]. *Streptococcus mitis* and *Streptococcus oralis* are the most commonly isolated bacteria. *S. mitis* can cause respiratory distress syndrome in adults, more often when treated with high doses of cytarabine. Mucositis can also be the starting point for a mycotic infection, generally by *Candida albicans*, as well as other types of *Candida* such as *krusei*, *tropicalis*, *parapsilosis*, and *aspergillus*[131].

### Treatment

There are many treatments to choose from, but there is no summary bringing together the best evidence regarding them. Many studies have been carried out on mucositis owing to its importance and although there are various drugs to prevent and treat mucositis (Table 1), there is no gold-standard protocol that is prominently better than the rest. Despite all these treatment options[28,64,133,151] the strategies to reduce oral mucositis are still unclear. This is because there is not enough evidence describing a treatment with proven efficiency to surpass the other treatments. Some studies indicate that low-energy laser is showing encouraging results[28].

#### *Intensive oral care protocol*

Before starting cancer treatment, the patient who is to receive head and neck radiotherapy is assessed to anticipate any potential risk factors for oral complications. This is carried out by performing a thorough and complete oral and dental examination, including radiography[17,35,36]. Any infection must be eliminated before the oncological therapy.

*Table 1*. Summary of the treatments proposed for mucositis.

| Controlled clinical trial | Cancer treatment | Interventions | *n* | Results | Observations |
|---|---|---|---|---|---|
| Foote et al. [49] | R | Chlorhexidine | 52 | No E.S. | Nausea |
| Ferretti et al. [48] | Ch | | 70 | E.S. | |
| | R | | | No E.S | |
| Adamietz et al. [2] | ChR | Povidone iodine | 40 | E.S. | |
| Rahn et al. [109] | ChR | | 40 | E.S. | |
| Madan et al. [81] | R | Chlorhexidine vs povidone iodine vs salt | 80 | E.S. Povidone iodine | |
| Trotti et al. [138] | R | Isenagan HCl | 545 | No E.S. | |
| | ChR | | | | |
| Samaranayake et al. [114] | R | Benzydamine HCl vs chlorhexidine | 25 | No E.S. | CHX better tolerated |
| Stokman et al. [131] | R | Polimixina E | 65 | No E.S. | |
| Wijers et al. [149] | R | Tobramicin | 77 | No E.S. | |
| Okuno et al. [98] | R | Amfotericin B | 54 | No E.S. | |
| El-Sayed et al. [41] | R | Bacitracin Clotrimazol Gentamicin | 137 | No E.S. | |
| Kazemian et al. [66] | R | Benzydamine HCl | 100 | E.S. | |
| Epstein et al. [42] | R | | 82 | E.S. | |
| Kim et al. [68] | R | | 67 | E.S. | |
| Putwatana et al. [106] | R | Benzydamine HCl vs papayor | 60 | E.S. Papayor | |
| Hanson et al [58] | R | Prostaglandina E1 | 78 | No E.S. | |
| Veness et al. [145] | R | | 83 | No E.S. | |
| Veerasarn et al. [144] | R | Amifostine | 67 | E.S. | |
| Bourhis et al. [19] | R | | 26 | E.S. | Serious adverse effects |
| Rades et al. [108] | Ch | | 39 | No E.S. | |
| Vacha et al. [141] | ChR | | 56 | No E.S. | |
| Antonadou et al. [9] | ChR | | 50 | E.S. | |
| Peterson et al. [99] | Ch | Glutamine | 326 | E.S. | |
| Huang et al. [61] | R | | 17 | E.S. | |
| Etiz et al. [44] | R | Sucralfate | 44 | E.S. | |
| Cengiz et al. [24] | R | | 28 | E.S. | Moderate protective effect |
| Dodd et al. [37] | R | | 74 | No E.S. | Nausea |
| Lievens et al. [75] | R | | 102 | No E.S. | |
| Makkonen et al. [84] | R | | 40 | No E.S. | |
| Pfeiffer et al. [101] | Ch | | 40 | No E.S | |
| Saarilahti et al. [113] | R | Sucralfate vs GMCSF | 40 | E.S. GMCSF | Slight tendency |
| Barber et al. [12] | R | Gelclair | 20 | No E.S. | |
| Evensen et al. [46] | R | Na sucrose octasulfate | 52 | No E.S. | |
| Schneider et al. [118] | R | r-metHuG-CSF | 54 | E.S. | |
| Wu et al. [152] | R | RhEGF | 113 | E.S. | |
| | ChR | | | | |
| Ryu et al. [112] | R | GMCSF | 130 | No E.S. | |
| Sprinzl et al. [130] | ChR ChR R | | 35 | No E.S. | Subcutaneous administration |
| Makkonen et al. [85] | R | | 40 | No E.S. | |
| Masucci et al. [87] | R | | 92 | E.S. | |
| Simões et al. [125] | R | Low laser therapy | 39 | E.S. | |
| Maiya et al. [83] | R | | 50 | E.S. | |
| Bensadoun et al. [13] | R | | 30 | E.S. | |
| Wu et al. [153] | ChR | Extract of proteins | 156 | E.S. | |
| Dörr et al. [38] | R | Proteolytic enzymes | 69 | No E.S. | |
| Gujral et al. [56] | R | | 100 | E.S. | |
| Lin et al. [76] | R | Zinc supplement | 100 | E.S. | Significant differences in oral cancer |
| Ertekin et al. [43] | R | Zinc sulphate | 30 | E.S. | |
| Watanabe et al. [148] | ChR | Zn L-carnosine | 31 | E.S. | |
| Ferreira et al. [47] | R | Vitamin E | 54 | No E.S. | Less subjective symptoms |
| Khanal et al. [67] | R | Honey vs ligdocaine | 40 | E.S. Honey | |
| Rashad et al. [110] | ChR | Honey | 40 | E.S. | |

Table 1 (*Continued*)

| Controlled clinical trial | Cancer treatment | Interventions | *n* | Results | Observations |
|---|---|---|---|---|---|
| Motallebnejad et al. [93] | R | | 40 | E.S. | |
| Biswal et al. [16] | R | | 40 | E.S. | |
| Su et al. [134] | R | Aloe vera | 58 | No E.S. | |
| Kaushal et al. [65] | R | Extract of human placenta | 60 | E.S. | |
| You et al. [156] | R | Indigowood root | 20 | E.S. | |
| Maddocks-Jennings et al. [82] | R | Essential oils | 19 | E.S. | |
| Scarantino et al. [116] | R | Pilocarpine | 245 | No E.S. | |
| Verdi et al. [146] | Ch | Pentoxifylline | 10 | No E.S. | |

R, radiotherapy; Ch, chemotherapy; E.S., statistically significant results.

*Antimicrobial agents*

Topical applications and systemic administrations of various drugs (e.g. chlorhexidine gluconate, povidone iodine, tobramycin, polymyxin E) were frequently used in the management of irradiation-induced mucositis as they were thought to be useful in maintaining acceptable standards of oral hygiene and reducing inflammation in compromised individuals. These agents have been tested in several studies over the past 25 years.

Chlorhexidine gluconate is an antimicrobial agent that appears to be effective in controlling early periodontal infection[18]. Chlorhexidine gluconate as a mouthwash, at concentrations below 0.12% and 0.2% has been assessed in several randomized clinical trials regarding its ability to prevent oral mucositis. The data available show that this agent does not have a great impact on preventing oral mucositis in patients undergoing radiotherapy with solid head and neck tumours[48,49,81,109,114]. In spite of there not being any demonstrable objective improvement in the incidence and severity of the mucositis, in comparison with the benzydamine mouthwash, it appears to be more readily accepted and tolerated by the patient, without significant adverse effects throughout radiotherapy treatment[114]. In contrast to the results with chlorhexidine gluconate used in irradiated patients, it seems that using chlorhexidine solution can significantly reduce the inflammation and oral ulceration associated with oral mucositis in patients undergoing intensive chemotherapy. The clinical trial carried out by Ferretti et al., demonstrates a potentially relevant clinical effect of chlorhexidine mouthwash as prophylaxis against oral mucositis and oral microbial pathogens in patients undergoing antineoplastic chemotherapy[114].

A recent study in irradiated patients who have been diagnosed with head and neck cancer compared the effectiveness of three mouthwashes versus placebo: chlorhexidine, povidone iodine and saline solution. The only one that showed a significant improvement in comparison with the control group was the povidone iodine mouthwash, which reduced the clinical severity of the mucositis from the third week of treatment and delayed the onset of oral ulcers[81]. Povidone iodine as a mouthwash could be useful in radio or chemotherapy-induced oral mucositis, resulting in a reduction of the severity and the onset of mucosal injuries[1,2,109,139].

Other studies have investigated the effects of applying a combination of antimicrobials topically or systemically, consisting of polymyxin E, tobramycin and amphotericin B (PTA), as a pill or toothpaste[131,149] and bacitracin, clotrimazole, and gentamicin (BCG)[41,98]. The results of these studies were contradictory, although ulceration was delayed. The colonization indexes of *Candida* species and Gram-negative bacilli were reduced in the PTA group and not in the placebo group. No significant connexion was found with these agents and mucositis prevention. It seems that selective oral flora elimination in head and neck irradiated patients does not prevent the development of severe mucositis[98].

The effects of iseganan hydrochloride on mucositis have also been studied. No significant preventive effects have been found, whether the mucositis is induced by radiotherapy, chemotherapy, or both[138].

### Anti-inflammatory agents

Benzydamine is a well-established mouth rinse solution with analgesic, anaesthetic, anti-inflammatory, and antimicrobial properties[42]. The ability of benzydamine as a preventive agent for radio-chemotherapy-induced oral mucositis has been studied in some double-blind randomized studies conducted in the last decades[42,66,68,106,114]. In three double-blind randomized clinical trials, benzydamine improved the ulcer rate, which reduced the incidence of ulceration and erythema. These studies also showed that benzydamine-treated patients needed less pain killers compared to patients treated with a placebo[66,68,106].

Payayor is the popular name of *Clinacanthus nutans* (Burm. f.) Lindau, it is a small herb, cultivated throughout Southeast Asia[27,135]. Benzydamine was compared with glycerin payayor in a double-blind randomized controlled clinical trial. Results showed that payayor was superior to benzydamine in preventing and relieving radiation-induced oral mucositis[106].

Prostaglandin E1 and E2 have been assessed in a small group of patients undergoing radiotherapy; results have been inconclusive. It seems not to have a significant effect towards improving oral mucositis, although there is a mild trend reducing the onset of oral ulcers[58,145].

### Cytoprotective agents

Sucralfate is an aluminium salt of sucrose sulphate that was used to treat gastric and duodenal ulcers. This drug is well-known and it needs an acid environment to be activated[145]. Since 1985, eight randomized clinical studies, in patients with head and neck malignances, have been recorded in which sucralfate was administered in oral suspension with different treatment protocols[12,24,37,46,75,84,101,113]. Only two of these[24,67] showed a reduction in the severity and duration of the radiotherapy-induced mucositis. Both of them were carried out in radiation-induced oral mucositis.

The ability of sodium sucrose octasulfate to relieve radiation-induced acute skin and mucosal reactions in patients with head and neck cancer was tested. No statistically significant difference was found between the results with sodium sucrose octasulfate and those with placebo for any of the variables[149].

Amifostine (ethanethiol, 2[(3aminopropyl) dihydrogen phosphate] is an organic

thiophosphate that, in animal models, selectively protects normal tissue[89]. The ability of its thiol-containing components to protect normal tissue damage from radiation has been recognized for over 40 years. In 1999, amifostine was approved by the FDA for protection from xerostomia induced by postoperative radiotherapy for head and neck cancer. More than 100,000 patients have been treated with amifostine, but its role is still controversial, and it has not been clarified whether amifostine has a tumour protective effect[6,89].

Simplifying its action, amifostine is an active drug that acts as a protective agent against cytotoxic substances. It becomes an active metabolite when it is dephosphorylated by alkaline phosphatase. Normal cells take up this metabolite, more than neoplastic cells, due to the high activity of the alkaline phosphatase enzyme, which can be explained by the better vascularization and higher pH level of normal tissue[21,33,60].

Five randomized controlled clinical trials administered amifostine intravenously or subcutaneously to prevent mucositis in different treatment programmes[9,19,108,141,144]. Three studies showed significant differences. Two of them were in irradiated patients[9,19], although one of them had a very small sample size. The other significant result was in patients undergoing concurrent chemo-radiotherapy treatment[144]. The use of amifostine in preventing grade 3–4 mucositis in chemotherapy and radiotherapy shows no statistically significant effects in studies with a similar protocol but with a larger sample size[108,141].

The clinical trial carried out by Veerasarn et al.[144] showed that amifostine significantly decreased acute and chronic xerostomia. The benefit of the drug was not the same for everyone, but depended on the total radiation dose, the percentage of the salivary gland involved in the treatment field, and the baseline of the salivary gland function. They concluded that for head and neck cancer patients who have definite radiotherapy or postoperative radiotherapy, amifostine reduced the subjective mucositis and xerostomia but did not show an objective response in the acute phase[144]. The adverse effects and toxicity of this drug should be considered before its administration[108].

Recent studies have found that glutamine has an important effect in sick patients[96]. Glutamine is a conditionally essential amino acid that has multiple well-defined functions in human biological processes. Current evidence for the pathobiology of mucosal injury indicates that reactive oxygen species, generated from both chemotherapy and radiation therapy, play a critical role in the initiation of oral mucositis. Glutamine, a precursor for glutathione, plays a pivotal role in regulating the intracellular redox potential[96,147] and clinical investigations indicate that glutamine inhibits other mediators of mucosal barrier injury by reducing the production of proinflammatory cytokines and cytokine-related apoptosis[30,88]. Administering glutamine should have beneficial effects on patients undergoing radiotherapy and chemotherapy, as both therapies damage the mucosa, causing stomatitis, mucositis, or coloenteritis[29,45]. Oral glutamine was tested in two studies. Both showed significant differences in the use of glutamine to treat mucositis in radiotherapy-treated patients, with or without concomitant chemotherapy[61,99].

A multicentre, randomized, double-blind, placebo-controlled, crossover phase III trial was conducted by Peterson et al. in patients receiving chemotherapy, testing the efficacy of Saforis. Saforis (MGI Pharma, Inc., Bloomington, MN) is composed of glutamine in a novel, proprietary drug delivery system (UpTec) that is administered orally. Compared with other available forms of glutamine, Saforis has been shown to facilitate the uptake of $>100$ times more glutamine by epithelial oral mucosal cells[100]. The clinical trial showed that the incidence and severity of oral mucositis was significantly reduced for patients treated with Saforis. No treatment differences were observed with respect to intensity of oral pain or swallowing difficulty. Patient self-assessment of the ability to eat solid foods showed a statistically significant difference in the Saforis group[99].

In a pilot randomized trial conducted by Huang et al., oral glutamine significantly reduced the duration and severity of objective oral mucositis during radiotherapy. It also shortened the duration of subjective mucositis above grade 3. In spite of the small patient number, there were still statistically significant differences in the investigation[61].

Sodium hyaluronate gel is a new pharmaceutical concept, marketed as a class 1 medical device and solely dedicated to the treatment of oral mucositis. When diluted, it is applied to the surface of the oral mucosa in the form of a viscous gel that creates a protective adhesive barrier over the surface of the epithelium. A study suggests that sodium hyaluronate is no more effective than current therapy with sucralfate and mucaine in relieving the pain associated with radiotherapy-induced stomatitis[11].

*Nutritional supplements*

Using supplements such as proteins, vitamin E, and zinc sulphate, seems to show promising results, although more studies are needed. A protein-free extract obtained from filtered calf blood (Actovegin) was tested in the treatment of mucositis. It showed a positive effect on the treatment of various types of skin and mucosal ulcers[126]. According to the results of a recent clinical trial, intravenous Actovegin is potentially effective in the prevention and treatment of oral mucositis induced by chemoradiotherapy. Its administration reduces the severity of oral mucositis and decreases the incidence of severe pain. The efficacy of preventive application appears to work better than therapeutic application[153].

Proteolytic enzymes administered systemically, have been demonstrated to reduce the side effects of chemoradiotherapy-induced toxicity in breast cancer patients. Studies in patients with head and neck cancer who were irradiated showed contradictory results[38,56]. Dörr et al. found no significant differences in the administration of proteolytic enzymes in irradiation induced oral mucositis[38], whilst Gujral et al. gave evidence of a possible role of proteolytic enzymes in preventing and reducing the acute side effects of radiation therapy in this population[56].

Alpha-tocopherol, the main constituent of vitamin E, is the most important natural antioxidant present in human blood. Its main biological function is to scavenge peroxyl free radicals in the cell membrane. Vitamin E has been evaluated in clinical trials as a potentially mucosal protective drug because of its free radical inactivation capabilities[143]. Evaluating the effectiveness of vitamin E versus placebo, there were no statistical differences in the onset and the duration of symptomatic mucositis, but there was a trend in patients of the vitamin E group to have lower frequencies of symptomatic mucositis[47].

A number of studies have shown zinc to be the catalytic component of 300 enzymes, the structural constituent of many proteins, and the regulatory ion for the stability of proteins and the prevention of free radical formation. Zinc is a pivotal element in ensuring the functioning of various tissues and organs, including the immune response[5,91,104].

The compound *N*-(3-aminopropionyl)-L-histidinato zinc (Polaprezinc), a chelate of zinc and L-carnosine, is an anti-ulcer agent developed in Japan[140]. It is known that carnosine increases granulation tissue and accelerates gastric ulcer healing in rats. Zinc has been reported to have a protective

action against various experimental gastric lesions, and clinical studies have shown the anti-ulcer action of zinc in humans. Polaprezinc was originally designed to combine the beneficial effects of zinc and carnosine. The mechanisms of its anti-ulcer action could be partly explained by its stimulant effect on mucus secretion, membrane-stabilizing effect, and antioxidant properties, but they are not fully understood. Currently, there is a theoretical basis for the use of this agent as a novel type of anti-inflammatory drug to control gastric inflammatory responses[124]. The singular clinical trial using Polaprenzinc concluded that it is highly assumable that it is potentially useful for the prevention of oral mucositis and improving the quality of life without reducing the tumour response in patients receiving chemo-radiotherapy[148].

Recent findings indicate that zinc supplementation, formulated as a drug containing Pro-Z, is effective in improving mucositis in patients with oral cancer under either definite or adjuvant radiotherapy. Zinc supplementation was found to facilitate the smooth administration of radiotherapy. The benefits were not extensive in patients with nasopharyngeal carcinoma[76].

A study carried out by Ertekin et al. showed that zinc sulphate seems to be beneficial in decreasing the severity of radiation-induced oropharyngeal mucositis and oral discomfort[43]. These results warrant further evaluation in a randomized study with a larger number of patients.

### *Bio-stimulants*

Eight controlled clinical trials were found using growth factors against oral mucositis[85,87,112,113,130,152]; five by subcutaneous injection administration[26,31,85,87,112], and three topically applied[113,130,152]. Three of the five studies that used subcutaneous injection showed statistically significant differences in irradiated patients[31,87] and in those treated with chemotherapy[26]. One of the three clinical studies using topical application of the drug showed significant differences in irradiated patients[152]. Generally, growth factors seem to have more effectiveness when administered systemically.

Granulocyte-macrophage-colony stimulating factor (GM-CSF) is the most studied for this type of treatment. It is a glycoprotein that is produced by a variety of human cells, some of which include cells of the haematopoietic environment such as fibroblasts and endothelial cells and cells of the immune system (macrophages, stimulated T-cells)[105].

In the last 25 years, six studies have assessed the effectiveness of administering GM-CSF in radiotherapy and/or chemotherapy treated patients with head and neck cancer[26,85,87,112,113,130]. Two of which used topical application[113,130] and the other four used systemic administration. One of the studies in the former group showed improvement in the severity of the radiation-induced mucositis[113] and two in the latter group showed significant differences improving oral mucositis in irradiated patients[87] or in patients treated with chemotherapy[26].

Chi et al. performed a randomized cross-over study to prospectively evaluate the effects of subcutaneously applied GM-CSF in the reduction of chemotherapy-induced oral mucositis. The results exposed a significant decrease regarding the incidence, mean duration, and severity of oral mucositis following the application of chemotherapy[26].

Epidermal growth factor (EGF), first discovered in the submaxillary gland of a rat in 1962, comprises a single-chain polypeptide containing 53 amino acids[31,54,55,115]. EGF helps to maintain tissue homeostasis by regulating epithelial cell proliferation, growth, and migration. It also induces angiogenesis, which provides nutritional support for tissues. EGF plays an important role in wound healing and tissue generation and may be useful in the treatment of radiation-induced oral mucositis[52,97,105].

Masucci et al. came to the conclusion that recombinant human epidermal growth factor (rhEGF), used in spray form, is potentially beneficial in preventing and treating mucositis in radiotherapy patients[87].

In a double-blind, randomized controlled clinical trial carried out by Schneider et al., Filgastrim (r-met HuG-CSF) showed a potential benefit, improving the objective oral mucositis in patients receiving chemoradiotherapy[118]. More studies are needed in this regard.

### *Low-energy laser therapy*

The use of low-energy laser therapy to prevent and treat mucositis is the most up to date technique. It is used to accelerate tissue regeneration and heal wounds, reducing inflammation and pain[103].

The effect produced by phototherapy is based on the capacity to modulate various metabolic processes, by conversion of the laser light energy input through biochemical and photophysical processes, which transform the laser light into energy useful to the cell. Visible laser is absorbed by chromophores in the respiratory chain of the mitochondria, with increase in ATP production that results in increased cellular proliferation and protein synthesis, promoting tissue repair[63].Simões et al. found a reduction in the incidence and severity of radiation-induced mucositis with three different therapeutic laser protocols. Results showed that using low power laser alone or in association with high power laser when applied three times a week maintained oral mucositis grades at levels I and II. This fractioned laser phototherapy also prevents pain increase[125].

In two double-blind controlled studies, a significant reduction in the severity and duration of radiotherapy-induced oral mucositis was recorded in patients treated with low-energy helium-neon laser[10,13]. It was also observed that the patients in the control groups were given tube feeding due to the severity of mucositis, but the study group patients were able to take the liquid orally without pain. The laser application delayed the time of onset, attenuated the peak severity and shortened the duration of oral mucositis[10].

### *Natural and homoeopathic agents*

Honey has been used medically throughout history. More recently, it has been rediscovered by the medical profession for the treatment of burns, infected wounds and skin ulcers[92]. The rationale of using honey to manage radiation mucositis was derived from basic research and clinical observation of rapid epithelialization in tissue injuries[14].

Topical application of honey was assessed in four randomized clinical trials on patients receiving treatment in patients with head and neck malignances. Results showed that prophylactic use of pure natural honey was effective in reducing mucositis resulting from radiotherapy with or without concomitant chemotherapy[16,67,93,110]. Honey successfully eliminated potentially pathogenic microbial flora in treatment group patients, compared with controls[110].

Patients frequently use topical aloe vera gel to prevent radiation-related dermatitis and oral aloe vera to sooth esophagitis. Although the mechanism of action is not well established, one hypothesis is that aloe vera may have anti-inflammatory properties through the inhibition of cyclooxygenase[155]. In a double-blind, randomized trial to determine whether oral aloe vera can reduce the incidence, severity, and duration of radiation-induced mucositis in head-and-neck cancer patients at Stanford

University, no statistically significant benefits were found when adding aloe vera to the standard oral care in the management of radiation mucositis. Aloe vera did not reduce weight loss, the use of pain medications, the likelihood of treatment interruptions, or episodes of dehydration[134].

*Isatis indigotica* Fort (Indigowood root) is a medicinal plant belonging to the Brassicaceae family. It is different from *Isatis tinctoria* (European wood), which was used for production of the blue dye indigo. Its root is a commonly used Chinese herb to remove toxic heat, to reduce heat in blood, and to relieve convulsions. According to modern medical research, the major components of radix of *I. indigotica* include indirubin, indigotone, and indigo pigment contents, with antivirus, fever detoxification, and anti-inflammatory efficacy[51].

In a recent pilot study, Indigowood root was applied in patients with head and neck malignancy under radiotherapy treatment to evaluate whether radiation mucositis could be improved. Evidence showed that this medicinal plant effectively reduces the severity of maximal mucositis, and improved patients' quality of life such as anorexia and swallowing ability[156].

Manuka (*Leptospermum scoparium*) and kanuka (*Kunzea ericoides*) are indigenous to New Zealand and have a long history of medicinal use by Maori and early European colonists. Both of these essential oils are known to have antibacterial and antifungal activity and contain constituents, such as sesquiterpene hydrocarbons, which have anti-inflammatory and analgesic actions[77,78].Maddocks-Jennings et al. support the hypothesis that very small volumes of manuka and kanuka used in a gargle can provide a positive effect on the development of radiation induced mucositis. Owing to the small sample size in their study, it is recommended that the work be repeated in a large randomized clinical trial, which should include measuring anti-inflammatory markers such as salivary lactoferrin, oral microbial cultures and assessment of quality of life[82].

Placentrex is a formulation of fresh term human placenta and indicated for a number of skin conditions and inflammatory diseases[3,25]. Human placental extract appeared to be effective in the management of radiation-induced oral/oropharyngeal mucositis and especially in controlling subjective symptoms[65].

### *Other interventions*

Pentoxifylline is a synthetic derivative of dimethylxanthine, which is chemically paired with theophylline and caffeine, but in contrast to these drugs, pentoxifylline has haematological effects that are useful in the symptomatic treatment of complications of peripheral vascular diseases[154]. Pentoxifylline is a medicine that acts in different ways: it relaxes the blood vessel wall to make it easier for blood to pass through them; it increases the amount of blood that reaches the tissues; it stops platelet aggregation as it increases the formation of prostacyclin; and it reduces the viscosity of blood.

A randomized clinical trial assessed the effect of administering pentoxifylline orally to prevent chemotherapy-induced mucositis and did not show any benefits to the patient[146].

Oral administration of pilocarpine hydrochloride is indicated in some countries to treat radiotherapy-induced xerostomia. It has also been proved for oral mucositis in a double-blind controlled clinical trial and did not show significant differences in reducing the development of oral mucositis[116].

## Discussion

Oral mucositis is a very common, potentially severe side effect, caused by treatment with radiotherapy and chemotherapy for head and neck cancer. It can be a limiting factor in the cancer scheduled regimen, leading to suspension or interruption of the programmed treatment with the consequent decrease of its effectiveness.

This review provides an update of the following aspects related to oral mucositis: concept, epidemiology, aetiopathogenesis, clinical manifestations, diagnosis and prognosis. It evaluates the scientific evidence on the effectiveness of interventions that have been investigated during the past 25 years for the prevention and treatment of oral mucositis induced by cancer treatment in head and neck malignances.

The many interventions found in this review highlight the importance of this clinical entity, for which there are no well-defined protocols that have been shown to be clearly better than the rest. The mechanisms of action of the studied agents are diverse, including antimicrobial agents or antiseptics, anti-inflammatory agents, cytoprotective agents, biostimulant agents, nutritional supplements, vitamins and proteins, natural or homoeopathic agents, and other interventions as yet unclassified.

A clear understanding of the effect of radiation-induced mucositis on a patient's quality of life is lacking and poorly researched. The interaction of painful mucositis, xerostomia, loss of taste, weight loss and fatigue, often exacerbated by the addition of chemotherapy, continued smoking, and poor oral hygiene is complex. There are economic costs of inpatient care for patients becoming unwell during radiotherapy, but the cost implications of severe treatment-related mucositis are not well documented.

The use of structured abstracts and adherence to Consolidated Standards of Reporting Trials (CONSORT) guidelines would greatly improve the development and testing of randomized controlled trials, allowing the inclusion of a larger number in future meta-analysis.

Of the 30 interventions evaluated, 11 showed some benefit in the prevention and treatment of oral mucositis induced by cancer treatment, although the improvement was sometimes weak and some of these studies had limited sample size or design limitations in the clinical trials.

A complicating factor in comparing outcomes from different studies is the method of assessing mucositis. Several different scoring systems were used to assess the severity of mucositis and in some studies the scoring system was not defined. This variability may have led to disagreements between the studies. Accepting this caveat, there was consistency in the number of categories used, and in each case the lowest score indicated that there was no mucositis.

Use of antimicrobial agents is controversial. Prior to the current hypothesis made by Sonis et al.[129] on the pathogenesis of oral mucositis, it was thought that oral flora could be the aetiological factor, so interventions were focused on reducing the number of microorganisms in the oral cavity. It was thought that antiseptic or antimicrobial agents would decrease the incidence and severity of oral mucositis.

Selective elimination of oral flora did not result in a reduction of radiation-induced mucositis and therefore does not support the hypothesis of these bacteria playing a crucial role in the pathogenesis of mucositis. Currently, it is accepted that microorganisms are an aggravating factor of mucositis but they are not considered an aetiological factor.

The lack of effect of clorhexidine mouthwash in patients undergoing radiotherapy may be explained by the observation that the chlorhexidine molecule, a divalent cation, does not bind directly to epithelial tissues but to the negatively charged salivary mucins or glycoproteins. In vitro evidence supports the concept that salivary glycoproteins are necessary

cofactors for mucosal cell protection by chlorhexidine. Severe persistent xerostomia develops in patient receiving radiation therapy, thus depriving oral epithelial tissues of their usual coating of salivary fluids and diminishing the effect of chlorhexidine in these patients[34,48,53].

With regard to antiseptics agents, povidone iodine showed the best results in improving oral mucositis. Similar results were obtained by other authors. Rahn et al. and Madan et al. found that rinsing with povidone iodine, in addition to a standard prophylaxis regimen, reduced the incidence, severity and duration of radiation-induced oral mucositis[81,109]. In contrast to other antiseptic agents, povidone iodine does not lead to any irritation or damage to the oral mucosa, even when rinsing is performed over a period of 8 or 10 weeks[144,157]. When it is absorbed, iodine can cause serious metabolic complications. In the studies in this review, the resorption of iodine by the oral mucosa did not lead to any disturbances in thyroid function in patients who did not suffer from thyroid disease. Rinsing with povidone iodine should be done very carefully to avoid swallowing any iodine.

Papayor could be beneficial in the prevention and treatment of oral mucositis in patients undergoing cancer treatment, although further studies are needed. The only clinical trial found was conducted in one setting in Thailand. Generalization of this finding should be tested in different locations. Distribution of the product is limited to Thailand, and it has a short life of only 1 year[142].

According to the clinical trials evaluated, the intravenous application of amifostine in patients irradiated for head and neck cancer could be beneficial in oral mucositis, but it is also associated with a high rate of serious adverse effects resulting in discontinuation of amifostine, especially amongst patients undergoing concurrent chemotherapy[123]. Brizel et al. did not mention the reason for discontinuation in 13/35 patients[21]. Discontinuation may have occurred due to other adverse effects reported in that study such as weakness, drowsiness, erythema, or fever. Regarding these methodical problems, discontinuation of amifostine appears to be a more reliable endpoint for evaluation than severe adverse effects alone. In the series of McDonald et al.[89] and Bourhis et al.[19] discontinuation of amifostine was strictly correlated with amifostine related toxicity, which was the only reason for discontinuation. Subcutaneous application of amifostine was reported to be associated with less toxicity than intravenous application, but the rate of severe adverse effects was still 10%[8,70]. Despite the potential benefit of amifostine in improving oral mucositis, clinicians must be prudent in its administration.

The advantages of using low power laser therapy in patients undergoing antineoplasic treatment for controlling signs and symptoms of oral mucositis are clear[22,40,83,95,119]. The possible mechanism could be due to the anti-inflammatory and analgesic effect of the laser irradiation on the local tissue, which in turn increases the vascularity, and re-epithelization of injured tissue. In oral tissues, laser applications could stimulate DNA synthesis in myofibroblasts, without degenerative changes, and could transform fibroblasts into myofibroblasts, which may promote and activate the epithelial healing of mucosa. Another mechanism that has been proposed for pain relief is the modulation of pain perception by modification of nerve conduction via release of endorphins and encephalins[74]. The mechanisms underlying the effects of laser in these patients are still not known.

In vitro and in vivo evidence shows that it can act on cell proliferation, cytokine production, and mast cell degranulation[4,86]. These are physiological steps related to inflammation and wound healing processes, which in turn could participate in the positive effects of low laser therapy in the patients under radiation. It is important to emphasize the use of wavelength-specific goggles during laser application for patients and the physiotherapist to prevent retinal damage by laser.

In patients undergoing radiotherapy for head and neck cancers, it is possible to demonstrate a beneficial effect for a fractioned therapy (three times a week) using low power laser alone or associated with high power laser. New studies are required to find more accurate parameters for controlling the undesired side effects of radio- and chemotherapy.

Properly designed clinical trials and interventions to prevent mucositis induced by chemotherapy and radiotherapy are needed. These studies should be reported according to the CONSORT guidelines and include a sufficient number of participants to allow subgroup analysis by type of disease and chemotherapeutic agent or radiotherapy schedule. To facilitate the comparison between interventions for the prevention and treatment of mucositis it would be useful to use a simple mucositis index on a scale of 0–4. The most recommended criteria are those of WHO, RTOG and NCI-CTC as part of its assessment of oral mucositis.

This review has updated the relevant aspects of oral mucositis and has highlighted several interventions (povidone iodine, benzidamine, glutamine, zinc supplementation, growth factor, low power laser therapy, honey) with evidence of effectiveness in reducing the onset and duration of oral mucositis.

In conclusion, to date, no intervention has been able to prevent and treat oral mucositis on its own. It seems necessary to combine interventions that act on the different phases of mucositis[112]. There are currently an alarming number of treatments, but there is no gold-standard protocol that is prominently better than the rest.

In the authors' search of randomized and controlled clinical trials in the prevention and treatment of oral mucositis induced by cancer treatment carried out in the last 25 years, they found the following interventions to have a benefit for the patient. Before starting cancer treatment, there is evidence of the effectiveness of an intensive oral care protocol based on oral exploration, radiographic analysis, and elimination of potential sources of infection. Regarding antiseptics and antimicrobials agents, selective elimination of oral flora using topical and systemic antimicrobial agents does not prevent or improve the development of severe oral mucositis. Povidone iodine mouthwash is the most effective intervention in irradiated patients. Chlorhexidine could be beneficial in patients undergoing chemotherapy.

Regarding anti-inflammatory agents, benzydamine mouthwash is potentially beneficial in patients receiving chemotherapy regimens. Papayor is effective in reducing oral mucositis in patients undergoing cancer treatment. Regarding cytoprotective agents, oral glutamine improves subjective and objective oral mucositis in irradiated patients or those undergoing chemotherapy. Intravenous amifostine shows a tendency to reduce the severity and duration of oral mucositis induced by radiotherapy and chemoradiotherapy, but it has several side effects, the most common are nausea and vomiting.

Regarding nutritional supplements, intravenously administered Actovegin improves oral mucositis in patients undergoing chemoradiotherapy. Systemic administration of zinc supplements is beneficial for oral mucositis in irradiated patients diagnosed with oral carcinoma. Polaprenzinc is potentially useful for prevention and treatment of oral mucositis in patients receiving radiochemotherapy.

Regarding biostimulant agents, the results for growth factors, despite having been evaluated in several clinical trials,

are controversial. They seem to be more effective when administered systemically. The use of low power laser delays the onset of ulcers and attenuates the severity and duration of oral mucositis in irradiated patients.

Regarding natural and homoeopathic agents, topical application of honey is effective in reducing oral mucositis resulting from radiotherapy with or without chemotherapy. Indigowood root seems to be useful in reducing the severity of oral mucositis in patients undergoing radiotherapy. Essential oils extracted from plants are an alternative treatment for oral mucositis, but there are few studies on them.

## Competing interests

None declared.

## Funding

None.

## Ethical approval

Not required.

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