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Title: CANCER TREATMENT-INDUCED ORAL MUCOSITIS A CRITICAL REVIEW

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Abstract: Abstract:
Introduction.- Head and neck cancer represents actually one of the main oncological problems. In its treatment, radiotherapy and chemotherapy leads to mucositis, as well as other side effects.
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Material and methods.- A search of double blind randomised controlled clinical trials between 1985 and 2010 was performed in the Medline database. Oral mucositis, radiotherapy, chemotherapy, head and neck were used as keywords.
Results.- 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, anticholeric agents and homoeopathic agents.
Discussion.- To date no intervention has been able to prevent and treat oral mucositis on its own. Therefore, it is necessary to combine interventions that act on the different phases of mucositis.
Conclusions.- It is still unclear as to which strategies reduce oral mucositis, as there is not enough evidence that describes a treatment with a proven efficiency and better than the other treatments for this condition.

**Declaration Form**

Dear Sirs:

We remit the manuscript of the article "CANCER TREATMENT-INDUCED ORAL MUCOSITIS: A CRITICAL REVIEW" in order to be valued for their publication in International Journal of Oral and Maxillofacial Surgery.

We want to be grateful for all the comments of the reviewers, who have allowed a wide improvement of the manuscript.

In the same way, those signatories have revised the text of the article, we support their content and truthfulness, are willing to give the rights to *International Journal of Oral and Maxillofacial Surgery*, in case it is accepted.

Of equal it forms we affirm that:

a) The presented work is original

b) It has not been presented for their consideration in any other journal

c) It is a work free of interests and conflicts

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**Confirmation of Authorship form**

**Journal**: INTERNATIONAL JOURNAL OF ORAL & MAXILLOFACIAL SURGERY

**Title of Paper**:
CANCER TREATMENT-INDUCED ORAL MUCOSITIS A CRITICAL REVIEW

## Declarations

The following additional information is required for submission. Please note that failure to respond to these questions/statements will mean your submission will be returned to you. If you have nothing to declare in any of these categories then this should be stated.

**Please state any conflict of interests.** A conflict of interest exists when an author or the author's institution has financial or personal relationships with other people or organisations that inappropriately influence (bias) his or her actions. Financial relationships are easily identifiable, but conflicts can also occur because of personal relationships, academic competition, or intellectual passion. A conflict can be actual or potential, and full disclosure to The Editor is the safest course.

**Competing Interests**

None declared

**Please state any sources of funding for your research**

None

**Please state whether Ethical Approval was given, by whom and the relevant Judgement's reference number**

Not required

**This information must also be inserted into your manuscript under the acknowledgements section prior to the References. If you have no declaration to make please insert the following statements into your manuscript:**

Competing interests: None declared

Funding: None

Ethical approval: Not required

***Detailed Response to Reviewers**

Dear Editor:

We attach a copy with the new manuscript in two versions: clean and with the new data marked in red (we have marked in red the new paragraphs or those paragraphs which draft has been modified). The changes are deep, as the revisers were asking, but in general, they can be included in the following lines:

1. The structure of the article has been modified to contain the section of Introduction, Material and method, Results, Discussion and Conclusions

2. The authors we have returned to write the aims of the review, in sense of making them more realistic and fitted to the aim of the article. There have been modified the criteria of selection of articles (there have been made alone the articles centred on patients with cancer of head and neck), which have changed for point the results of the review and the conclusions.

3. The section of results has divided in two parts: The first one, an update of the basic aspects of the oral mucositis: concept, etiopatogenics, epidemiology, clinical manifestations, diagnosis and prognosis. The second part corresponds with a critical review of the different interventions published in the last 25 years in the prevention and treatment of the oral mucositis induced by radio and / or chemotherapy. In this second part, the classification of the results has been modified, trying to make one more valid (microbial, antiinflammatory agents, citoprotector agents, nutritional supplements, bioestimulant agents, natural and homeopathic agents, and others interventions).

4. We have included a section of (critical) discussion, in agreement to the title of the article. Also we have included a section of conclusions.

Later we include a response detailed to each of the reviewers:

Reviewer #1:

1. The revision do not present a critical discussion as the title suggests

   *The authors have incorporated a section of discussion, where a critical revision of the contributed evidence is done. There have been written the conclusions of the interventions that turned out to be beneficial in the treatment of the oral mucositis*.

2. Objectives were not in accordance with the text structure

   *The aim has returned to write, distinguishing two principal aims, in agreement to the rest of the text.*

3. The text presents no conclusions although Abstract do

   *We have added conclusions to the paper.*

4. Criteria applied to trials selection should be more detailed

*There have been detailed the criteria of selection of the selection of the bibliography*

6. Radio- and Chemo-induced mucositis should be more clearly distinguished

*In the section of Results and in the Table 1, we have distinguished clearly the interventions realized in patients with radiotherapy, chemotherapy, or combined therapy.*

Reviewer #2:

This is an interesting review article. I suggest that mention be made in the introduction paragraph 2 , to the role of HPV in the aetiology of oro-pharyngeal cancer. The authors have mentioned smoking and alcochol, HPV is now recognised for its role.

*The above mentioned paragraph has been added*

Reviewer #3:

This is a review article on the subject of treatment of mucositis which is of interest to IJOMS readers. The grammar and English needs some revision.

*The grammar and English has been checked.*

Unfortunately the "critical Review" part of the paper is really not apparrent and the discussion at the end is very short.

*The discussion has been extended and has focused of a more critical form.*

There is some confusion in this paper as to whether the authors are just reviewing the evidence for radiation induced mucositis, chemotherapy induced mucositis or chemo-radiation induced mucositis and it is not clear whether studies have been seperated out to distinguish these groups.

*In the section of Results and in the Table 1, we have distinguished clearly the interventions realized in patients with radiotherapy, chemotherapy, or combined therapy.*

The authors have looked at all randomized prospective controlled trials and although they state there are no studies which show an effect they report results for significant improvement for the systemic groupd given GM-CSF or G-CSF (in chemotherapy patients?) also significant results for recombinant human keratinocyte growth factor, as well as low dose laser, honey, Traumseel S, and calciumphosphate/Fluoride rinses. It would seem to me that in the critical review in the discussion the authors should be able to define those therapies that had negative trials and have no evidence for use and then examine the trials of those therapies which did have significant results to assess whether there were enough patients, which populations were included ect to give us their conclusions from the available data which treatments should be used and when. Their current conclusion is short to the point of being non-existant.

*The authors have incorporated in the Table 1 the studies with positive results and with negative too, incorporating details of these studies. On the other hand, conclusions have joined in the sense at that the reviser aims.*

There are confusing contradictory statements e.g page 10 para 1 states mucositis starts with damage to the basal cells , then in para 2 it is stated that it is damage to the connective tissue and endothelium that is the initiator.

*The paragraphs to which the reviser refers are the following ones:*

*[gums. Radiotherapy-induced mucositis, however, affects the mobile mucosa as well as the fixed mucosa, even though the latter is less commonly involved (125).*

*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 (78, 122). The most frequently used criteria are the National Cancer Institute (NCI)-Common Toxicity Criteria (CTC) from the USA (120) and the criteria set out by the World Health Organisation in 1979 (124).*

*It is necessary to establish a correct differential diagnosis with other pathological conditions. This can sometimes be complicated as mucositis is an ideal place for bacterial, viral and fungal superinfection, as we have mentioned previously (88). ]*

*We could not have found the origin of the confusion to which it refers.*

Figure 1a and b has nothing to do with the article and should be deleted Figure 2 is surely not the best example of mucositis the authors possess. This is a review with a lot of work that could be salvaged to publish but needs major revision.

*The Figure 1 has been eliminated and the Figure 2 changed.*

# CANCER TREATMENT-INDUCED ORAL MUCOSITIS: A CRITICAL REVIEW.

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# CANCER TREATMENT-INDUCED ORAL MUCOSITIS: A CRITICAL REVIEW.

## INTRODUCTION

Head and neck cancer (H&NC), principally squamous cell carcinomas, is one of the main oncological problems due to its high mortality rate as well as 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 the over-40s (76, 21).

Malnourished patients, or those who drink and/or smoke, are at greater risk. This is due to the fact that it completely changes the upper aerodigestive tract epithelium and makes consumers predisposed to developing many cancers. Recent studies demonstrate that although the principal risk factors for H&NC remain tobacco and alcohol use, human papillomavirus (HPV) has been found to be etiologically associated with 20-25% of upper aerodigestive tract cancer, mostly in the oropharynx (7, 42, 60) . The most common high risk-HPV associated to it is HPV-16 (7, 75).

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. However, radiation (and chemotherapy) not only affects malignant cells, but it is also absorbed by the buccal and peribuccal tissue, especially the rapidly dividing cells (165).

Gastrointestinal tract cells have the highest rate of cell proliferation and turnover in the whole human body. Therefore, even though anti-neoplastic treatment has become even more effective, it continues to be associated with numerous short and long-term side effects (75).

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 the radiation to the region of the oral mucosa (111).

This review has a double aim: To update the knowledge about the concept, epidemiology, aetiophatogeny, clinical manifestation, diagnosis and prognosis of oral mucositis induced by radiation or chemotherapeutic agents, and to evaluate the effectiveness of interventions that have been used in the last 25 years in the prevention and treatment of this entity in patients with head and neck malignances.

## MATERIAL AND METHODS

**Comment [D1]:** In general terms, the draft of the article has been checked completely, there have been defined of more precise form the criteria of selection of articles for the present review, the aims have been modified, and there has been contributed a more critical vision of the included articles. And in last place, there have been revealed the conclusions obtained of the scientific literature published with regard to the prevention and treatment of the oral mucositis induced by oncologic treatment.

**Comment [D2]:** Paragraph introducing the etiological paper of the HPV in the oral cancer

**Comment [D3]:** The aim has returned to write, distinguishing two principal aims.

We performed two searches in the Medline database. In the first search we looked for metanalysis and systematic reviews related to concept, epidemiology, aetiopathogeny, 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, we looked for double-blind randomized controlled clinical trials in humans, from January 1985 to May 2011, using the following keywords: Induced Oral Mucositis, Stomatitis, Head and Neck Cancer, Radiotherapy, Chemotherapy. We found 74 articles, from which only 62 complied with the objectives and criteria of the literature search.

The criteria of inclusion were the following: The definition of case study was 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.

**Comment [D4]:** The search has been extended until May, 2011.

**Comment [D5]:** We have excluded those articles that were not centred on patients with cancer of head and neck, to try to obtain more precise conclusions.

**Comment [D6]:** There have been defined better the criteria of selection of articles.

## RESULTS

### *CONCEPT*

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.

At present, advanced head and neck cancer treatment is based on combined chemoradiotherapy (CRT) sessions. Further, it is often necessary to surgically remove the tumour before starting the therapy (74).

However, establishing a correct and uninterrupted CRT treatment is often delayed or limited by one of the most common complications: oral mucositis (116).

This is a very serious issue which leads to problems in the progress of cancer treatment for many types of tumor, especially for head and neck cancer as treatment often has to be temporarily postponed or discontinued permanently, either of which option compromises the patient's response to the treatment. Many studies show that abandoning or interrupting treatment markedly increases the risk of residual tumour cell

proliferation. This causes tumor recurrence and proliferation, worsening the patient's prognosis (116, 15).

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. On many occasions the patient may have to be hospitalized (111, 62, 123, 53).

*EPIDEMIOLOGY*

Approximately half of all head and neck cancers are treated with radiotherapy alone or in combination with chemotherapy and surgery (165, 74). 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 (111, 142).

When, in head and neck cancer, radiotherapy-induced oral mucositis develops, 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 (111, 123). Younger patients seem to be at greater risk of chemotherapy-induced oral mucositis (65).

This is due to a higher mitotic rate of the epithelium and more epidermal growth factor receptors in the epithelium of young patients.

Current radio- and chemotherapy protocols show that oral mucositis induced by these treatments has an 85-100% incidence rate, and depends above all on three main modifying factors: the radiation dose received, the type of chemotherapy drug administered, and the administration plan (whether fractionated or not, etc.) (106).

*AETIOPATHOGENY*

Mucositis is caused by the systemic effects of the cytotoxic agents of chemotherapy and the local effects of radiation on the oral mucosa (106).

The biological complexity that lies beneath the damage in the oral mucosa has

only been considered recently. It is currently believed that mucositis first 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 (133, 134, 72, 94).

Furthermore, microvascular damage could play an important role in the development of radiation-induced damage (133, 134, 132). Morphological evidence obtained through electron microscopy gives 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. in 2004 (132).

The proposed aetiopathogenic model develops over five phases: initiation, message generation, signal amplification, ulceration, and healing.

First, chemo-radiation induces reactive oxygen species to be formed, causing cell damage in the epithelium and subepithelial mucosa (initiation phase). A series of transcription factors are then activated and the production of proinflammatory cytokines, such as tumor 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 are observed. In the following phase, the cytotoxic agents reduce the mitosis of dividing epithelial cells of the oral cavity causing atrophy and ulceration (ulceration phase), further causing severe pain and limiting how the patient functions (132, 82, 98).

Opportunistic microorganisms of 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) (132, 137).

The earlier phases are characterized by a marked neutropenia and leukopenia, although in the final phase, a recovery of the white blood cell count can be observed (132, 134). 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 itself as a light decoloration that can often go unnoticed (132).

Once the patient has received more than 20 Gy of radiotherapy (Figure 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. Ulcerations appear and are sometimes covered by pseudomembranes that favor bacterial colonization (133,134, 72, 132). Patients range from pain and discomfort to the inability to tolerate food or liquids. Marked xerostomia and dysgeusia can also appear. Once radiotherapy treatment has been completed, the mucositis will spontaneously subside over a period of 2 to 6 weeks (132).

Chemotherapy-induced oral mucositis is usually more aggressive than radiotherapy-induced.

Erythema is observed on around the 5th-8th day of treatment and in the following days edema and ulceration are already notable. After the end of chemotherapy treatment, the mucosa will need about 7-10 days to recover completely (132, 98, 82).

For chemotherapy-induced mucositis, lesions are especially visible, 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 (134, 137, 24, 127).

However, chemotherapy-induced mucositis can affect the whole area exposed to radiation, including the keratinized regions of the oral cavity (133, 82, 24, 127).

*DIAGNOSIS*

Mucositis diagnosis is primarily based on clinical manifestations (138, 126). 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, however, affects the mobile mucosa as well as the fixed mucosa, even though the latter is less commonly involved (138).

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 (83).

The most frequently used criteria are the National Cancer Institute (NCI)-Common Toxicity Criteria (CTC) from the USA (26, 143), the Toxicity criteria of the Radiation Therapy Oncology Group (RTOG), the European Organization for Research and Treatment of Cancer (EORTC) (33), and the criteria set out by the World Health Organization in 1979 (156).

It is necessary to establish a correct differential diagnosis with other pathological conditions.

Sometimes this objective can be complicated due to the fact that mucositis is an ideal site for bacterial, viral, and fungal superinfection, as mentioned previously (72, 94, 132).

Because of their location, viral infections differ clinically from mucositis. 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 would be necessary for a definitive diagnosis (133, 94).

*PROGNOSIS*

Chemotherapy-induced mucositis lasts about one week and generally heals spontaneously 21 days after chemotherapy is administered. Radiotherapy-induced mucositis lasts at least two weeks longer following radiotherapy (60-70 Gy) (133, 94, 98, 82, 137).

Severe ulcers that last for 5-7 weeks after the end of treatment are not uncommon in patients who have received concomitant treatment of chemo- and radiotherapy for head and neck cancer (82, 137). Chronic mucositis after radiation has also been described but in fewer cases (137).

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 (82, 137). *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* (137).

## *TREATMENT*

Comment [D7]: There have been distinguished clearer the interventions realized in patients with radiotherapy, chemotherapy, or combined therapy.

Presently, there is an alarming number of treatments that we can choose from, but there is no summary bringing together the best evidence with regard to them.

Many studies have been carried out on mucositis due 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 (139, 157, 67, 31) 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 for this condition. Nevertheless, some studies indicate that low-energy laser is showing encouraging results (31).

### - *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 thorough and complete oral and dental examination, including x-ray (38, 17, 40). Any infection must be eliminated before the oncological therapy.

### - *Antimicrobial agents*

Comment [D8]: The classification of the treatments has been changed in: antimicrobial agents, antiinflammatory agents, citoprotectors agents, nutritional supplements, bioestimulants agents, natural and homeopathic agents, and other interventions.

Topical applications and systemic administrations of various drugs (e.g. chlorhexidine gluconate, povidone-iodine, tobramycin, polymyxin E, etc.) were frequently used in the management of irradiation-induced mucositis as they are thought to be useful in maintaining acceptable standards of oral hygiene and reducing

inflammation in such compromised individuals. These agents have been tested in several studies over the past 25 years.

Chlorhexidine gluconate (CLX) is an antimicrobial agent that appears to be effective in controlling early periodontal infection (18). CLX as a mouthwash, at concentrations below 0.12% and 0.2% has been assessed in several randomized clinical trials with regards to its ability in preventing oral mucositis. The data available shows that this agent does not have a great impact on preventing oral mucositis in patients undergoing radiotherapy with solid head and neck tumors (51, 52, 113, 120, 84). In spite of there not being any demonstrable objective improvement in the incidence and severity of the mucositis, in comparison with the benzydamine mouthwash (BZD), it appears to be more readily accepted and tolerated by the patient, without significant adverse effects throughout radiotherapy treatment (120)

In contrast to the results of CLX used in irradiated patients, it seems that using chlorhexidine solution can reduce significantly the inflammation and oral ulceration associated with oral mucositis in patients undergoing intensive chemotherapy. The clinical trial carried out by Ferretti et al. in 1990, demonstrates a potentially relevant clinical effect of chlorhexidine mouthwash as prophylaxis against oral mucositis and oral microbial pathogens in patients undergoing antineoplastic chemotherapy (120).

A recent study in irradiated patients who have been diagnosed of H&N cancer compared the effectiveness of three mouthwashes versus placebo: chlorhexidina, povidone iodine and saline solution. The only one that showed a significant improvement in comparison with the control group was the povidona iodine mouthwash, which reduced the clinical severity of the mucositis from the third week of treatment and delayed the onset of oral ulcers (84).

Povidona iodine as a mouthwash could be useful in radiochemotherapy-induced oral mucositis, resulting in a reduction of the severity and the onset of mucosal injuries (1, 2, 114).

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 (136, 155) and bacitracine, clortimazole, and gentamicin (BCG) (44, 102). The results of these studies were contradictory, although ulceration was delayed to some extent. The colonization index of Candida species and Gram-negative bacilli were reduced in the PTA group and not in the placebo group. However, no significant connection 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 (102).

The effects of Iseganan hydrochloride on mucositis have also been studied.

However, no significant preventive effects have been found to date, whether the mucositis is induced by radiotherapy, chemotherapy, or both (144).

- *Anti-inflammatory Agents*

Benzydamine is a well-established mouth rinse solution with analgesic, anaesthetic, anti-inflammatory, and antimicrobial properties (45). The ability of benzidamine (BZD) as a preventive agent of radio-chemotherapy induced oral mucositis has already been studied in some double-blind randomized studies conducted in the last decades (45, 120, 69, 71, 110).

In three double-blind randomized clinical trials, BZD 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 (71, 110, 69).

Payayor is the popular name of Clinacanthus nutans (Burm. f.) Lindau, it is a small herb, cultivated throughout Southeast Asia (30, 141). 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 (110).

Prostaglandin E1 and E2 have been assessed in a small group of patients undergoing radiotherapy. However, results have been inconclusive. It seems not to have a significant effect toward improving oral mucositis, although there is a mild trend reducing the onset of oral ulcers (151, 61).

- *Cytoprotective Agents*

Sucralfate is an aluminium salt of sucrose sulphate that was used to treat gastric and duodenal ulcers in the past. This drug is well-known and it needs an acid environment to be activated (151).

From 1985 to date, 8 randomized clinical studies – in patients with head and neck malignances - have been recorded wherein sucralfate was administered in oral suspension form with different treatment protocols (11, 27, 39, 47, 78, 88, 105, 119).

Only two of these (70, 27) 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 Na sucrose octasulfate (Na SOS) 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 Na SOS and those with placebo for any of the variables (155).

Amifostine (ethanethiol, 2[(3aminopropyl) dihydrogen phosphate] is an organic thiophosphate that, in animal models, selectively protects normal tissue (93). 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 also approved by the FDA for protection from xerostomia induced by postoperative radiotherapy for head and neck cancer. Although more than 100,000 patients have already been treated with amifostine, its role is still a controversial matter, and it has still not been clarified whether amifostine has a tumor protective effect (93, 6).

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 uptake 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 (23, 36, 63).

Five randomized controlled clinical trials administered amifostine intravenously or subcutaneously to prevent mucositis in different treatment programs (150, 147, 112, 9, 20). Three studies showed significant differences. Two of them were in irradiated patients (9, 20), although one of them had a very small sample size. The other significant result was in patients undergoing concurrent chemoradiotherapy treatment (150). However, 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 (112, 147).

The clinical trial carried out by Veerasam et al. in 2006, 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 post-operative radiotherapy, Amifostine reduced the subjective mucositis and xerostomia but did not show an objective response in the acute phase (150). In addition, adverse effects and toxicity of this drug should be considered before its administration (112).

Recent studies have found that glutamine has an important effect in sick patients (100). Glutamine is a conditionally essential amino acid that has multiple well-defined functions in human biologic 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 (100, 154) and clinical investigations indicate that glutamine inhibits other mediators of mucosal barrier injury by reducing the production of proinflammatory cytokines and cytokine-related apoptosis (91, 32). Therefore, administering glutamine should have beneficial effects on patients undergoing radiotherapy and chemotherapy, as both therapies damage the mucosa, causing stomatitis, mucositis, or coloenteritis (33, 48).

Oral glutamina 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 (64, 103).

A multicenter, randomized, double-blind, placebo-controlled, crossover Phase III trial was conducted by Peterson et al. in 2007, 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 (104).

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. Nevertheless, patient self-assessment of the ability to eat solid foods showed a statistically significant difference in the Saforis group (103).

In a pilot randomized trial conducted by Huang and cols., oral glutamine could significantly reduce the duration and severity of objective oral mucositis during radiotherapy. It could also shorten the duration of > Grade 3 subjective mucositis. In spite of the small patient number, there were still statistically significant differences in our investigation (64).

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.

The study carried out by Barber and col. suggests that sodium hyaluronate is no

more effective than current therapy with sucralfate and mucaine in relieving the pain associated with radiotherapy-induced stomatitis (12).

- Nutritional Supplements

Using supplements such as different kinds of proteins, vitamin E, and zinc sulfate, seems to show promising results, although a greater number of studies with regard to this matter are still needed.

A protein-free extract obtained from filtered calf blood (Actovegin) was tested in the treatment of mucositis. It showed to have a positive effect on the treatment of various types of skin and mucosal ulcers (131, 163).

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 (159).

Proteolytic enzymes administered systemically, have been demonstrated to reduce the side effects in first clinical studies of chemoradiotherapy-induced toxicity in breast cancer patients. However, studies in patients with head and neck cancer who were irradiated showed contradictory results (41, 59). Dörr et al. found no significant differences in the administration of proteolytic enzymes in irradiation induced oral mucositis (41), while Gujiral and col. gave evidence of a possible role of proteolytic enzymes in preventing and reducing the acute side effects of radiation therapy in this population (110).

Alpha-tocopherol, the main constituent of vitamin E, is the most important natural antioxidant present in human blood. Its main biologic function is to scavenge peroxyl free radicals in the cell membrane. Because of its free radical inactivation capabilities, vitamin E has been evaluated in clinical trials as a potentially mucosal protective drug (149). Evaluating the effectiveness of vitamin E versus placebo, there were not found 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 (50).

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. Therefore, zinc is a

pivotal element in ensuring the functioning of various tissues and organs, including the immune response (95, 108, 5)

The compound *N*-(3-aminopropionyl)-L-histidinato zinc (Polaprezinc), a chelate of zinc and L-carnosine, is an anti-ulcer agent developed in Japan (146). 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. Although the mechanisms of its anti-ulcer action could be partly explained by its stimulant effect on mucus secretion, membrane-stabilizing effect, and antioxidant properties, 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 (129).

The singular clinical trial using Polaprenzinc that we found in our search, concluded that it is highly assumable that it is potentially useful for prevention of oral mucositis and improvement of quality of life without reducing the tumor response in patients receiving chemoradiotherapy (153).

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. However, the benefits were not found extensive to patients with nasopharyngeal carcinoma (79).

The study carried out by Ertekin et al. showed that Zinc sulfate seems to be beneficial in decreasing the severity of radiation-induced oropharyngeal mucositis and oral discomfort (47). These results warrant further evaluation in a randomized study with a larger number of patients.

*- Bio-stimulants*

*Growth Factors*

In our search, we found 8 controlled clinical trials using growth factors against oral mucositis (87, 90, 117, 118, 158, 135); 5 by subcutaneous injection administration (117, 34, 29, 90, 87), and 3 topically applied (118, 158, 135). 3 Out of the 5 studies that used subcutaneous injection showed statistically significant differences in irradiated patients (90, 34) and in those treated with chemotherapy (29). Just 1 out of the 3 clinical

studies with topical application of the drug showed significant differences in irradiated patients (158). Generally, the growth factors seem to have more effectiveness when administered systemically.

Granulocyte-macrophage-colony stimulating factor (GM-CSF) has been studied the most for this type of treatment. This 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) (109).

In the last 25 years, 6 studies have assessed the effectiveness of administering GM-CSF in radiotherapy and/or chemotherapy treated patients with head and neck cancer (117, 90, 118, 135, 87, 29). Two of which used topical application (118, 135) and the other 4 used systemic administration. One of the studies in the former group showed improvement in the severity of the radiation-induced mucositis (118) and two in the latter group showed significant differences improving oral mucositis in irradiated patients (90) or in patients treated with chemotherapy (29).

Chi and colleagues, 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 (29).

Epidermal growth factor (EGF), first discovered in the submaxillary gland of a rat in 1962, comprises a single-chain polypeptide containing 53 amino acids (34, 121, 57, 58). EGF helps maintain tissue homeostasis by regulating epithelial cell proliferation, growth, and migration. It also induces angiogenesis, which provides nutritional support for tissues. Thus, EGF plays an important role in wound healing and tissue generation and may be useful in the treatment of radiation-induced oral mucositis (109, 101, 55).

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 (90).

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 (124). 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 updated technique. It is used to accelerate tissue regeneration and the healing of the wounds, reducing inflammation and pain (107).

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 (66).

Simoes 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 associated with high power laser when applied three times a week maintains the oral mucositis grades in levels I and II. Furthermore, this fractioned laser phototherapy also prevents pain increase (130).

In other 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 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 (96). The rationale of using honey to manage radiation mucositis was derived from basic research and clinical observation of rapid epithelialisation in tissue injuries (14).

Topical application of honey was assessed in 4 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 (97, 70, 115, 16). In addition, honey successfully eliminated potentially pathogenic microbial flora in treatment group patients, compared with controls (115).

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 (161).

However, 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, there were found no statistically significant benefit to adding Aloe vera to the standard oral care in the management of radiation mucositis. Furthermore, Aloe vera did not reduce weight loss, the use of pain medications, the likelihood of treatment interruptions, or episodes of dehydration (140).

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 Isatis indigotica Fort include indirubin, indigotone, and indigo pigment contents, with antivirus, fever detoxification, and anti-inflammatory efficacy (54).

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 (162).

Manuka (Leptospermum scoparium) and kanuka (Kunzea ericoides) are indigenous to New Zealand and have a long history of being used medicinally by both Maori and early European colonists. Both of these essential oils are known to have antibacterial and antifungal activity and contain constituents, such as sesquiterpenes hydrocarbons, which have anti-inflammatory and analgesic actions (80, 81).

Maddock 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. However due to the small sample size in their study, it is recommended that the work be repeated in a large randomized clinical trial and should include measuring anti-inflammatory markers such as salivary lactoferrin, oral microbial cultures and assessment of quality of life (85).

Placentrex is a formulation of fresh term human placenta and indicated for a number of skin conditions and inflammatory diseases (3, 28). Human placental extract appeared to be effective in the management of radiation-induced oral/oropharyngeal mucositis and especially in controlling subjective symptoms (68).

*- 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 (160). Pentoxifylline is a medicine that acts in different ways: it relaxes the blood vessels' 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 (152).

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 (122).

## DISCUSION

**Comment [D9]:** The discussion has been extended

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

A clear understanding on 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. However, the cost implications of severe treatment-related mucositis are not well documented.

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

It was found that of the thirty different interventions evaluated, eleven 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 of the clinical trial.

A complicating factor in comparing outcomes from different studies is the assessment method of mucositis. It was used several different scoring systems to assess the severity of mucositis and in some studies were not defined scoring systems. This variability may have led to disagreements between the studies. Accepting this caveat, there was consistency in the number of categories used 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. on the pathogenesis of oral mucositis, it was thought that oral flora could be the etiological factor of this clinical entity, so the interventions were focused on reducing the number of microorganisms in the oral cavity, expecting a decrease in the incidence and severity of oral mucositis, either with antiseptic or antimicrobial agents.

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. Therefore, currently, it is accepted that microorganisms are an aggravating factor of mucositis but they are not considered as an aetiological factor.

The lack 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 rather binds to the negatively charged salivary mucins or glicoproteins. In vitro evidence further 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 (51, 37, 56).

With regard to antiseptics agents, Povidone iodine showed the best results 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 (84, 113). 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 (164, 150). When it is absorbed, iodine can cause serious metabolic complications. In the included studies in this review, the resorption of iodine by the oral mucosa did not lead to any disturbances in thyroid function in patients who do not suffer from thyroid disease. However, rinsing with povidone-iodine should be done very carefully to avoid swallowing any iodine.

Papayor, Clinacanthus nutans (Burm. f.) Lindau, could be beneficial in the prevention and treatment of oral mucositis in patients undergoing cancer treatment, although further studies are needed in this regard. The only one clinical trial found in our search, was conducted in one setting in Thailand. Generalization of this finding should be further tested in different locations. In addition, distribution of the product is limited to Thailand, and the product has a short life of only one year (148).

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 among patients undergoing concurrent chemotherapy. It is remarkable that Brizel et al. did not mention the reason for discontinuation in 13/35 patients (22). Discontinuation may have occurred due to other adverse effects reported in that study such as weakness, drowsiness, erythematic, or fever. Regarding these methodical problems, discontinuation of amifostine appears to be a more reliable endpoint for our evaluation than severe adverse effects alone. Furthermore, in the series of McDonald et al. (92) 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. However, the rate of severe adverse effects was still 10% (8, 73). So despite the potential benefit

of amifostine improving oral mucositis, we 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 (86, 99, 25, 125, 43). 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 the 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 eukephalins (77). Nevertheless, the mechanisms underlying the effects of laser in these patients are still not totally known.

In vitro and in vivo evidence show that it can act on cell proliferation, cytokines production, as well as in mast cell degranulation (4, 89). 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. Nevertheless, it is important to emphasize the use of wavelength specific goggles during the laser application for patients as well as treating physiotherapist for preventing retinal damage by laser.

In patients under RT for treating head and neck cancers, it is possible to demonstarte a beneficial effect of a fractioned therapy (three times a week) using low power laser alone or associated to high power laser. However, new studies must be done for searching more accurate parameters for controlling the undesired side effects of radio as well as chemotherapy.

Clinical trials properly designed and interventions to prevent mucositis induced by chemotherapy and radiotherapy are needed. These studies should be reported according to guidelines Consolidated Standard of Reporting Trials (CONSORT) and include a sufficient number of participants that will perform 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 would be useful to use a simple mucositis index on a scale of 0-4. The most recommended criteria are World Health Organization (WHO), Radiation Therapy Oncology Group (RTOG) and National Cancer Institute - Common Toxicity Criteria (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 (povidona-iodine, benzidamine, glutamine, zinc supplementation, growth factor, low power laser therapy, honey and other interventions) with evidence of effectiveness in reducing the onset and duration of oral mucositis.

## CONCLUSION

Comment [D10]: There have been written the conclusions of the interventions that turned out to be beneficial in the treatment of the oral mucositis.

To date, no intervention has been able to prevent and treat oral mucositis on its own.

Therefore, it seems necessary to combine interventions that act on the different phases of mucositis (117).

There are currently an alarming number of treatments, however there is no gold-standard protocol that is prominently better than the rest.

In our 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, we 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 to antiseptics and antimicrobials agents, selective oral flora elimination through topic and systemic antimicrobial agents do 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-inflamatory agents, Benzydamine mouthwash is potentially beneficial in patients receiving chemotherapy regimens. Papayor, Clinacanthus nutans (Burm. f.) Lindau, is effective in reducing oral mucositis in patients undergoing cancer treatment.

Regarding to 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 to nutritional supplements, Actovegin intravenously administered improves the oral mucositis in patients undergoing concomitant chemoradiotherapy treatment. Systemic administration of Zn 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 growth factors, despite having been evaluated in several clinical trials, the results are still controversial. In general terms, it seems to be more effective when they are 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.

With regard to the natural and homeopathic agents, topical application of honey is effective in reducing oral mucositis resulting from radiotherapy with or without chemotherapy. Indigowood root seems to be useful 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 very few studies in this regard to make a statement.

## DECLARATIONS

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| Controlled Clinical Trial | Cancer Treatment | Interventions for O.M. | (n) | Results | Observations |
|---|---|---|---|---|---|
| Foote et al. 1994 | R | Chlorhexidine | 52 | No E.S. | Nausea |
| Ferretti et al. 1990 | Ch | | 70 | E.S. | |
| | R | | | No E.S | |
| Adamietz et al. 1998 | ChR | Povidone Iodine | 40 | E.S. | |
| Rahn et al. 1997 | ChR | | 40 | E.S. | |
| Madan et al. 2008 | R | Chlorhexidina Vs Povidone iodine Vs Salt | 80 | E.S. Povidone iodine | |
| Trotti et al. 2004 | R | Isenagan HCl | 545 | No E.S. | |
| | ChR | | | | |
| Samaranayake et al. 1988 | R | Benzydamine HCl Vs Chlorhexidine | 25 | No E.S. | CHX better tolerated |
| Stokman et al. 2003 | R | Polimixina E | 65 | No E.S. | |
| Wijers et al. 2001 | R | Tobramicina | 77 | No E.S. | |
| Okuno et al. 1997 | R | Amfotericina B | 54 | No E.S. | |
| El-Sayed et al. 2002 | R | Bacitracina | 137 | No E.S. | |
| | | Clotrimazol | | | |
| | | Gentamicina | | | |
| Kazemian et al. 2009 | R | Benzydamine HCl | 100 | E.S. | |
| Epstein et al. 2001 | R | | 82 | E.S. | |
| Kim et al. 1985 | R | | 67 | E.S. | |
| Putwatana et al. 2009 | R | Benzydamine HCl Vs Papayor | 60 | E.S. Papayor | |
| Hanson et al. 1997 | R | Prostaglandina E1 | 78 | No E.S. | |
| Veness et al. 2006 | R | | 83 | No E.S. | |
| Veerasarn et al. 2006 | R | Amifostine | 67 | E.S. | |

| | | | | | |
|---|---|---|---|---|---|
| Bourhis et al. 2000 | R | | 26 | E.S. | |
| Rades et al. 2004 | Ch | | 39 | No E.S. | Serious adverse effects |
| Vacha et al. 2003 | ChR | | 56 | No E.S. | |
| Antonadou et al. 2002 | ChR | | 50 | E.S. | |
| Peterson et al. 2007 | Ch | Glutamine | 326 | E.S. | |
| Huang et al. 2000 | R | | 17 | E.S. | |
| Etiz et al. 2000 | R | Sucralfato | 44 | E.S. | |
| Cengiz et al. 1999 | R | | 28 | E.S. | |
| Dodd et al. 2003 | R | | 74 | No E.S. | |
| Lievens et al. 1998 | R | | 102 | No E.S. | |
| Makkonen et al. 1994 | R | | 40 | No E.S. | Moderate protective effect |
| Pffeifer et al. 1990 | Ch | | 40 | No E.S | Nausea |
| Saarilahti et al. 2002 | R | Sucralfato Vs GMCSF | 40 | E.S. GMCSF | Slight tendency |
| Barber et al. 2007 | R | Gelclair | 20 | No E.S. | |
| Evensen et al. 2001 | R | Na Sucrosa Octasulfate | 52 | No E.S. | |
| Schneider et al. 1999 | R | r-metHuG-CSF | 54 | E.S. | |
| Wu et al. | R<br>ChR | RhEGF | 113 | E.S. | |
| Ryu et al. 2007 | R | GMCSF | 130 | No E.S. | |
| Sprinzl et al. 2001 | ChR ChR<br>R | | 35 | No E.S. | |
| Makkonen et al. 2000 | R | | 40 | No E.S. | |
| Massucci et al. 2005 | R | | 92 | E.S. | Subcutaneous administration |
| Simões et al. 2009 | R | Low laser therapy | 39 | E.S. | |
| Maiya et al. 2006 | R | | 50 | E.S. | |

| | | | | | |
|---|---|---|---|---|---|
| Bensadoun et al. 1999 | R | | 30 | E.S. | |
| Wu et al. 2010 | ChR | Extract of Proteins | 156 | E.S. | |
| Dörr e t al. 2007 | R | Proteolytic enzymes | 69 | No E.S. | |
| Gujral et al. 2001 | R | | 100 | E.S. | |
| Lin et al. 2010 | R | Zn Supplement | 100 | E.S. | Significant differences in oral cancer |
| Ertekin et al. 2004 | R | Zn Sulfate | 30 | E.S. | |
| Watanabe et al. 2010 | ChR | Zn L-Carnosine | 31 | E.S. | |
| Ferreira et al. 2007 | R | Vitamin E | 54 | No E.S. | Less subjective symptoms |
| Khanal et al. 2010 | R | Honey Vs Ligdocaine | 40 | E.S. Honey | |
| Rashad et al. 2009 | ChR | Honey | 40 | E.S. | |
| Motallebnejad et al. 2008 | R | | 40 | E.S. | |
| Biswa et al. 2003 | R | | 40 | E.S. | |
| Su et al. 2004 | R | Aloe vera | 58 | No E.S. | |
| Kaushal et al. 2001 | R | Extract of human placent | 60 | E.S. | |
| You et al. 2009 | R | Indigowood root | 20 | E.S. | |
| Maddocks et al. 2009 | R | Essencal oils | 19 | E.S. | |
| Scarantino et al. 2006 | R | Pilocarpine | 245 | No E.S. | |
| Verdi et al. 1995 | Ch | Pentoxifylline | 10 | No E.S. | |

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

(R – Radiotherapy ; Ch – Chemotherapy; E.S. - Statistical significance in results)

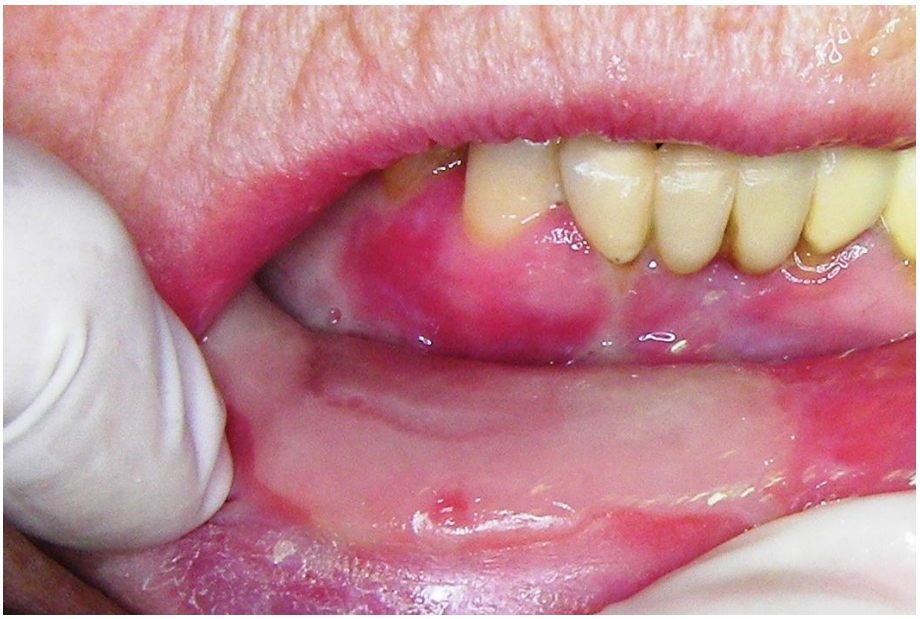

Figure 1.- Oral mucositis

**Figure 1**

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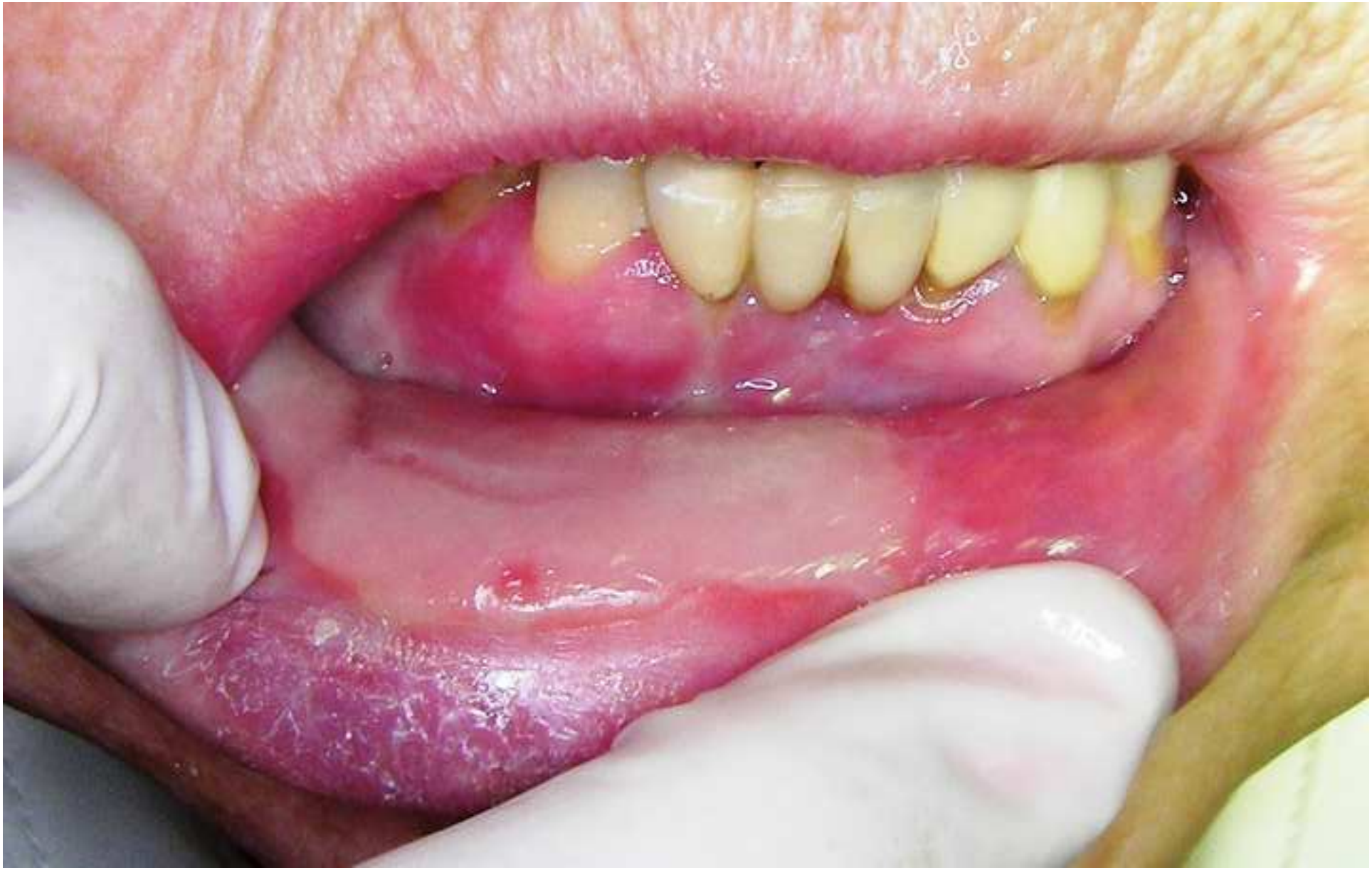

**Supplementary data - Manuscrit with comments**

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