Research Article

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# Chemotherapy Induced Oral Mucositis: Causes and Treatments

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## ABSTRACT

**Introduction**: Oral mucositis is one of the most common complications of oncological treatments and is the consequence of the cytotoxic systemic effect of agents of chemotherapy and the local one of radiation. The frequency of oral mucositis in this population is between 30% and 40%. However, patients receiving high-dose chemotherapy (HDC) just in case of hematopoietic stem cell transplantation, even have a 76% chance of developing mucositis, and those treated with radiation, especially for head and neck cancers, have a 30-60% chance of having this complication. In this article, we want to describe its characteristics, causes, and some possible treatment strategies.

**Materials and Methods**: We conducted searches in PUBMED and GOOGLE SCHOLAR for papers and documents done on the pathogenesis, causes, and treatment of iatrogenic mucositis. We have selected research articles and reviews from 1990 to date, with no primary or secondary endpoint limitations.

**Discussion and Conclusion**: Oral mucositis can be very painful and can significantly influence nutritional intake and quality of life. For patients undergoing high chemotherapy doses can be the most complicated and severe and debilitating. In addition, in such patients, greater severity of the oral mucositis was found to be significantly associated with an increase in the number of days of hospitalization requiring nutrition and parenteral drug therapy, with an increase in hospital costs. Before starting chemotherapy it is important to have a general examination of the mouth by a specialist and carry out any dental treatment necessary to heal the teeth and gums. During chemotherapy, it is essential to regularly perform scrupulous and delicate oral hygiene, gargle and rinse with non-alcoholic disinfectant solutions (e.g. water and sodium bicarbonate), maintain good hydration, and promote saliva production, maintain proper nutrition and use topical anti-inflammatory and analgesic products.

**KEYWORDS:** Mucositis; Chemotherapy; Adverse drug reactions; Pharmacovigilance

**ABBREVIATIONS:** HDC: High Dose Chemotherapy; HSCT: Hematopoietic Stem Cell Transplantation; HSV: Herpes Simplex Virus; ROS: Reactive Oxygen Species; NF-kB: Nuclear Factor kappa B; TNF: Tumor Necrosis Factor; COX2: Cyclooxygenase 2; IL: Inter Leukin; VEGFR: Vascular Endothelial Growth Factor Receptor; PDGFR: Platelet Derived Growth Factor Receptor; EGFR: Endothelial Growth Factor Receptor; RET: Rearranged During Transfection; FGFR: Fibroblast Growth Factor Receptors

## INTRODUCTION

Oral mucositis, also called "stomatitis", is defined as inflammation of the mucous membranes lining the alimentary tract, causing mucosal injury. It can occur in response to systemic chemotherapy or other etiologies (e.g. infections or radiation) but is one of the most common complications of oncological treatments and is the consequence of the cytotoxic systemic effect of agents of chemotherapy and the local one of radiation [1]. The frequency of oral mucositis in this population is between 30% and 40%. However, patients receiving high-dose chemotherapy (HDC) just in case of hematopoietic stem cell transplantation (hematopoietic

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stem cell transplantation, HSCT), even have a 76% chance of developing mucositis, and those treated with radiation, especially for head and neck cancers, have a 30-60% chance of having this complication [2]. The increased incidence is not only related to drugs used, but also the number of chemotherapy cycles and the concomitant presence of mucositis. About 75-80% of patients receiving high-dose chemotherapy before haematopoietic cell transplantation can develop oral mucositis [3]. Patients treated with radiotherapy for cancer of the head and neck typically receive about 200 cGy of daily radiation dose, five days per week, for 5-7 weeks. Almost all of these patients will develop some degree of oral mucositis, as indeed observed in recent studies that have detected oral mucositis severe in a percentage between 29 and 66% of such patients. It can manifest as an erythematous lesion of the oral mucosa up to severe ulceration, with local superinfection and in some cases systemic (Figures 1,2). Oral mucositis lesions are often very painful, compromising nutrition [4,5]. The mucotoxicity produced by chemotherapy can be:

- Direct, a common effect of chemotherapeutic agents (Table 1).
- Indirect (resulting from immunosuppression caused by chemotherapy or related nutritional deficiencies)

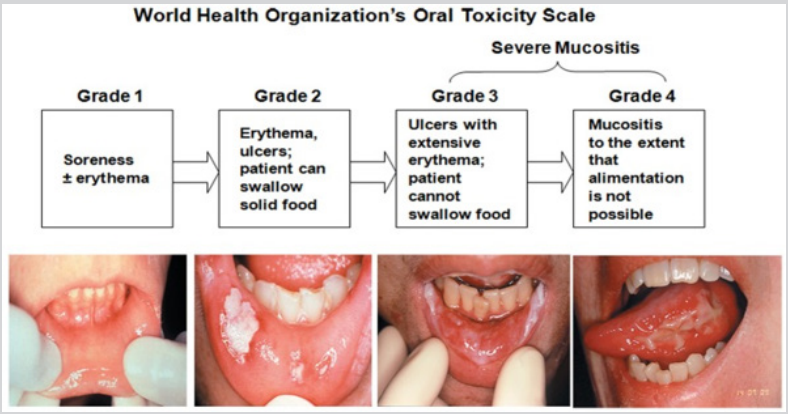


**Figure 1:** WHO classification of mucositis severity.

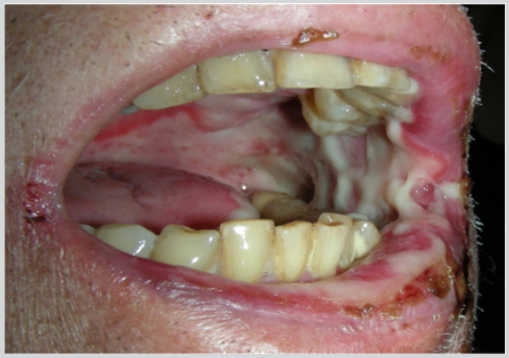

**Figure 2:** Example of severe mucositis extended to the entire oral cavity with superinfection.

**Table 1:** Risk factors influencing the frequency or severity of oral mucositis.

| | |
|---|---|
| **Patient Related** | Age, oral health (poor oral hygiene, periodontal diseases, dental caries), tumor type (hematological diseases), smoking or alcohol use, malnutrition |
| **Chemotherapy Agents** | Drugs that affect DNA synthesis like anthracyclines, antimetabolites, taxanes, topoisomerases inhibitors, purine analogues, antitumor antibiotics (bleomycin, mitomycin). |
| | Also important are doses and route of administration. Cyclophosphamide and etoposide have a 98% of risk of mucositis with grades 3-4, conditioning regimes of high dose melphalan or carmustine, etoposide and cytarabine hav a risk of 42-46% (grades 3-4). With fluorouracil-based regimens in colorectal cancer the risk is 70% of all grades and 20% of grades 3-4 |
| **Other Risk Factors** | Bone marrow transplantation, radiation to neck and head, xerostomia |

Oral mucositis occurs initially as a mild erythema of the oral mucosa. associated with burning and which then often progresses to erosion and ulceration, over the following 3 to 5 days. Ulcerations are typically covered with fibrin to form white pseudomembranes [6,7] with white desquamative patches advancing to shallow ulcerations and formation of large painful lesions. most frequently on the floor of mouth, tongue and soft palate. The lesions usually heal in about 2-4 weeks after the last dose of chemotherapy or radiotherapy. Patients receiving concurrent chemoradiotherapy regimens usually develop mucosal soreness by the end of the first week, with ulceration appearing at the end of the second week. The mucosal ulcerations consolidate to form larger ulcers by the end of the third week and persist for 2 to 4 weeks with most ulcers spontaneously resolving without scarring. In immunosuppressed

patients (transplant patients; e.g., of hematopoietic cells), resolution of oral mucositis usually coincides with the recovery of granulocytes (In the case of HTC, the resolution coincides with the recovery of the white blood cell count, particularly when the absolute neutrophil count becomes greater than 500 cells / µL [8]. Patients with oral mucositis and neutropenia have a much higher relative risk of septicemia than patients with neutropenia alone, as mucositis can promote the entry of bacteria and fungi into the circulation). The ulcers typically present within two weeks of the onset of chemotherapy [9]. In radiation-induced oral mucositis, lesions are usually limited to irradiated tissues, with non-keratinized tissues affected more often. The clinical course of oral mucositis can sometimes be complicated by local infections, in particular in immunosuppressed patients, such as virus reactivation viral infections herpes simplex (herpes simplex virus, HSV), and fungal infections such as candidiasis. Although HSV infections do not cause oral mucositis, can complicate diagnosis and management [10]. In this article, we want to describe the pathological characteristics and some possible treatment strategies.

## MATERIALS AND METHODS

We conducted searches in PUBMED and GOOGLE SCHOLAR for papers and documents on the pathogenesis, causes, and treatment of iatrogenic mucositis. We have selected research articles and reviews from 1990 to date, with no primary or secondary endpoint limitations. We focused on research on articles on the pathogenesis and treatment of mucositis from cytotoxic chemotherapy. We have also finalized the data on the characteristics of chlorhexidine and benzydamine.

## DISCUSSION

The classic paradigm of the pathogenesis of oral mucositis was based on the toxic action of drugs on actively replicating cells, such as cancer, also causing damage to other cell lines such as the epithelium of the oral cavity. [11] In these cases, the non-specific DNA damage of normal cells such as gastrointestinal and del oral cavity would cause cell death with a deficit between cell loss and regeneration in a negative sense. Atrophy of the mucosa which it follows would result in ulceration, with the possibility of subsequent infection [12] This simple model (damage → ulceration → healing), however, cannot be considered complete. New evidence reveals the occurrence of a more complicated picture of events around mucositis, and consequently its treatment [13,14] The initiation phase of mucositis occurs when drugs damage DNA, causing breaks, and generating reactive oxygen species (ROS). This results in the activation of the nuclear factor kappa B (NF-kB). Over 200 genes are managed by NF-kB, including COX2 and proinflammatory cytokines such as TNF, IL-1b and IL-6. This signal amplification phase occurs when the proinflammatory cytokines accumulate and cause positive feedback loops that continuously activate NF-kB and amplify the response. Histology and electron microscopy show an evident early modification of the morphology of the submucosa, with damage initial here before clinical signs of erythema and ulceration: subepithelial damage with apoptosis of fibroblasts and endothelial cells of the microcirculation is earlier of epithelial death. And it must be said that the microscopic damage is very early and this evidence is not surprising since the damage is in fact in the submucosa rather than in the epithelium15; so during the early stage, we have an absence of clinical lesions. Ulceration of the epithelium occurs clinically a few days after treatment; the microscopic damage occurs more early in the submucosa in the endothelium rather than in the epithelium. The increase of pro-inflammatory cytokines is associated with the development of mucositis and plays a role important in the determinism of mucosal pathology. Levels of pro-inflammatory cytokines, like tumor necrosis factor (TNF), interleukin-6 (IL-6), and interleukin-1β (IL-1β) increase in an earlier stage [16]. The severity of oral mucositis is related to the intensity of platelet-activating factor and cytokine production [17]. It has been demonstrated that interventions that reduce aggregation platelet levels reduce the severity of mucositis. Much tissue damage is observed in mucositis as a consequence of apoptosis. It can start from the activation of a membrane receptor (signal transduction), by damage of the cell membrane or by direct mitochondrial and finally by irreparable DNA damage [18]. It is observed that this is a complex biological process that can be divided into five phases (Figure 3).

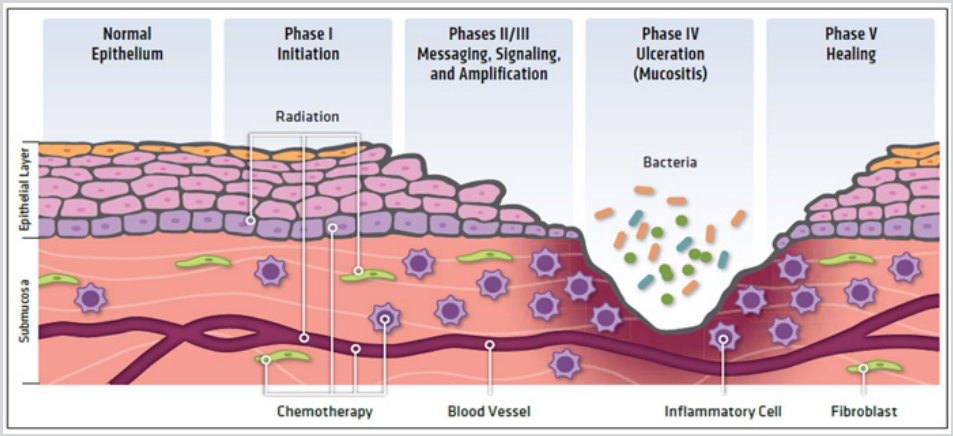


**Figure 3:** Phases of mucositis tissue damage.

During stage 3 of transmission and amplification, i.e. already from the first therapeutic cycles, both the epithelium and the submucosa are also damaged whether they can appear normal and the patient has few symptoms [19,20]. The stage of ulceration and inflammation, on the other hand, is the one which causes the worsening of the symptomatological picture. The loss of integrity of the mucosa causes extremely painful lesions that can also become infected [21]. Bacterial proteins stimulate the release of inflammatory cytokines and as a result, an elevated risk of bacteremia and sepsis represents an unfavorable prognostic factor [22].

### Stomatitis and Targeted Therapy

Stomatitis is a common adverse effect reported with almost all targeted therapies. All grade stomatitis in angiogenesis inhibitors ranges from 7 to 30%, with a higher incidence reported with sunitinib and other multi-TKIs. They are often multikinase inhibitors like VEGFR, PDGFR, EGFR, RET and FGFR. They include sorafenib, sunitinib, ponatinib, cabozatinib and others. Sorafenib and sunitinib are the most known for causing mucositis. EGF promotes cell growth and turnover and plays a major role in the maintenance of mucosal integrity by acting as a mitogen and by inducing mucus and prostaglandin synthesis. Inhibition of squamous epithelium maturation promotes ulcer formation.

As for prevention, these patients should be assessed prior to treatment initiation by a dental professional to identify potential dental treatment requirements such as infection prevention, caries treatment and tooth extractions. When mucositis is manifested, THE CONTROL OF INFLAMMATION AND PAIN is a priority in all cases. Mouthwashes with a saline base and sodium bicarbonate have been studied with conflicting results, also like chlorhexidine, but they are frequently used, also in combination with pieces of ice and rinses that contain an anesthetic, such as 2% lidocaine [23]. It can be mixed with equal volumes of diphenhydramine and a soothing coating agent such as a combination of magnesium hydroxide/aluminum hydroxide or bismuth subsalicylate in equal volumes. [24] Topical anesthetic agents can provide medium-term relief. Also, some bio-adherent mucosal topical agents are not anesthetic is not available but give immediate relief because they quickly reduce pain by forming a protective coating on the ulcerated mucosa. "Magic mouthwash" is a galenic option, but without a standard formula. These formulations contain analgesic or oral anesthetics, antifungals or antibiotics, steroids and antacids (to allow for mouth coating). The MASCC / ISOO guidelines advise against the use of sucralfate in mucositis induced by radiation due to lack of effectiveness [25]. In addition to the use of topical agents, most patients with severe mucositis require systemic analgesics; often, to relieve pain, opiates should be used. The guidelines of the MASCC / ISOO also advise using a protocol of oral hygiene through the use of a soft toothbrush combined with the use of non-medicated rinses (eg. with physiological solution or sodium bicarbonate). [26] Patients should be educated about the importance of effective oral hygiene. Chlorhexidine-based mouthwashes containing alcohol can be irritating and painful in the presence of oral ulcerations [27]. Multiple studies have examined the role of chlorhexidine mouthwash in oral mucositis but have not shown significant efficacy in reducing the severity of mucositis. Therefore, the guidelines advise against the use of chlorhexidine mouthwash for the prevention or treatment of mucositis oral; some Centers prefer to use mouthwashes with antibacterial enzymatic formulation and alcohol-free [28]. The use of nystatin in mycotic mucositis from chemotherapy was not found to be effective in reducing the severity of induced mucositis chemotherapy. On the other hand, a recent study indicated that systemic fluconazole significantly reduces the incidence of severe mucositis induced by Candida after radiotherapy (15% vs. 45%) in patients with head or neck cancer. Furthermore, the MASCC / ISOO guidelines advise against the routine use of antimicrobials or acyclovir, to avoid oral mucositis. However, drugs such as acyclovir and valacyclovir have a well-established role in prophylaxis and the treatment of injuries caused by HSV in this patient population [29]. Finally, it should be mentioned bioadhesive and topical anti-inflammatory agents: Benzydamine hydrochloride (Figure 4) is a topical anti-inflammatory drug that inhibits the pro-inflammatory cytokines including TNF-α. The MASCC / ISOO guidelines recommend the use of benzydamine in patients treated with moderate doses of radiation. However, this drug has not received approval for use in mucositis by the FDA of the United States [30].

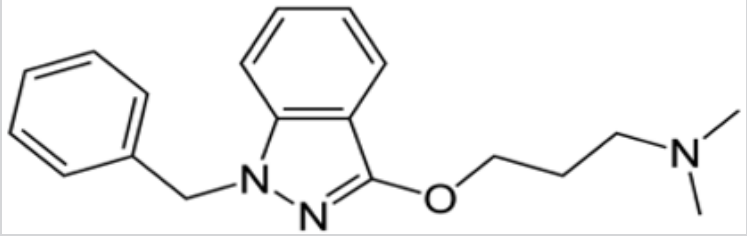


**Figure 4:** Chemical structure of benzydamine.

In Italy, benzydamine hydrochloride is available as a mouthwash, either alone or in combination with cetylpyridinium. It is an NSAID available exclusively for topical treatment, with an indication for the symptomatic treatment of inflammatory vegetative states associated with pain in the oral cavity. It has no particular contraindications to the exclusion of patients with allergies to NSAIDs; However, burning and dry mouth reactions have been described in up to one in 1000 people. It should also be noted that it contains 96% ethanol among the excipients [31].

## CONCLUSION

Oral mucositis can be very painful and can significantly influence nutritional intake and quality of life. For patients undergoing high chemotherapy doses can be the most complicated and severe and debilitating [32]. In addition, in such patients, greater severity of the oral mucositis was found to be significantly associated with an increase in the number of days of hospitalization requiring nutrition and parenteral drug therapy, with an increase in hospital costs. Before starting chemotherapy, it's important to have a general examination of the mouth with a specialist and carry out any dental treatment necessary to heal the teeth and gums [33]. During chemotherapy, is essential to regularly perform scrupulous and delicate oral hygiene, gargle and rinse with non-alcoholic disinfectant solutions (e.g. water and sodium bicarbonate), maintain good hydration, promote saliva production, maintain proper nutrition and use topical anti-inflammatory and analgesic products. In severe cases, the use of analgesics including systemic opioids and temporary feeding assistance may be necessary. It should be remembered that iatrogenic mucositis is often self-limiting by suspending or reducing treatment in a few weeks but can themselves lead to the early and sometimes definitive administration of cytotoxics, acting as factors limiting adherence to therapies [34,35].

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