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A REVIEW ARTICLE ON ORAL MUCOSITIS: THE CONCEALED VICIOUS OF CANCER THERAPY

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ABSTRACT

Chemo-radiotherapy patients almost always have an inflammatory response of the epithelial mucosa as a result of the cytotoxic effects, which causes mucositis. Mucositis develops in approximately 40% of chemotherapy patients and approximately 90% of head and neck cancer (HNC) patients treated with both chemo-radiotherapy. Patients with high-grade mucositis will be hospitalized around 19% of the time, lowering quality of life, resulting in a poor prognosis, and incurring ongoing treatment costs. Several therapies and prevention guidelines are currently available, but their effectiveness rates are unknown. This analysis shows mucositis completely, analyzing the effect of standard chemo-radiotherapy and tailored therapy on mucositis progression and pointing out the limitations and benefits of current mucositis treatment approaches and evaluation guidelines. Furthermore, an examination of the research to determine the existing biomarkers to predict patient risk of developing oral mucositis and their relevance in early diagnosis. Although the expression levels of some proteins involved in the inflammatory response, such as TNF- or IL-1, are associated with the mucositis process, their presence does not rule out other mucositis-free inflammation events. This strongly suggests the necessity to identify biomarkers that expressly incorporate mucositis as a measure of progression. Non-coding RNAs may have this capability.

Keywords: Oral mucositis, HNC, Biomarker, Cytokine, Non-coding RNA, Quality of life

INTRODUCTION:

Epidemiological data on mucositis are still underutilized and conflicting. This adverse event is frequently recorded only when individuals develop high-grade mucositis that necessitates clinical treatment. Furthermore, there is no common scale for scoring its severity, making disease staging and assessment difficult to compare. Unfortunately, no single scale exists to grade mucositis, and the World Health Organization (WHO) scale for oral mucositis (OM) evaluation takes into account objective criteria such as the appearance of erythema or ulceration. The Oral Mucositis Assessment Scales (OMAS) provide a quantitative scale to quantify ulceration dimension. In the common toxicity criteria guide, the Eastern Cooperative Oncology Group (ECOG) mucositis scale is described, in which mucositis severity is categorized differently dependent on the anatomic site of development. Similarly, the National Cancer Institute (NCI) provides a mucositis severity assessment scale depending on anatomic region of development and kind of treatment, either chemo or radiotherapy **[4]**, in the Common Terminology Criteria for Adverse Event (CTCAE).

Mucositis pathogenesis

Mucositis clinical signs are visible at the fourth stage of the inflammatory process, the ulceration phase. During this stage, mucosa and submucosal integrity are damaged, patients complain of pain, and they may require the assistance of caregivers. The presence of breaks in the submucosa allows several microorganisms, symbiotic residents of the healthy mucosa, to invade this tissue district, resulting in a mononuclear-infiltrating cell-mediated inflammatory response, promoting the release of new pro-inflammatory cytokines that amplify the expression of pro-apoptotic mediators and increase tissue damage **[14, 15]**.

Based on the duration and severity of neutropenia, patients may develop bacteremia or septicemia, which are primarily caused by streptococci and staphylococci in OM16. Mucositis is an acute condition that usually resolves itself once the anticancer treatment ends. The healing process is initiated at this point, and cues from the submucosa extracellular matrix and mesenchyme encourage tissue re-epithelialization **[5, 17]**.

Role of “old” and “new” anticancer agents in mucositis development

Mucositis incidence and severity are affected by the chemo-therapy regimen, dosage, and timing of treatment.

Antimetabolites such as platin-derived, taxanes, anthracyclines, irinotecan, and alkylating agents can cause mucositis, the severity of which varies depending on the medicine. Indeed, when compared to 5-FU treatment, the antimetabolite medicines S-1 and capecitabine are associated with a lower incidence of mucositis development **[18]**. When capecitabine is used with irinotecan (XELIRI regimen), a topoisomerase 1 inhibitor, it causes more gastro-intestinal mucositis (GIM) episodes than fluoruracil plus irinotecan (FOLFIRI) **[19]**.

Irinotecan treatment has been widely explored in the development of GIM. Following that, patients experience late-onset diarrhea as a result of the irinotecan medication, which causes mucus hypersecretion, a decrease in goblet cell populations, and a general disaggregation of the gastrointestinal mucosa structure **[20]**.

Cisplatin has been shown to cause OM by inhibiting mucin secretion indirectly, while specifically damaging the ileal mucosa rather than the rest of the gastro intestinal tract **[21]**. Patients treated with cisplatin have a higher GIM severity than patients treated with other platinum-derived medications such as oxaliplatin and carboplatin **[22]**. Notably, when compared to paclitaxel, docetaxel treatment is associated with a greater incidence of mucositis development **[23]**. Patients with HNC who receive cisplatin plus RT develop oral mucositis **[24]**. Furthermore, patients getting traditional RT fractions develop mucositis more frequently than patients receiving high-dose single-fraction IMRT **[25]**. High-grade mucositis is more likely to be detected during an RT program in patients who are HPV/p16-negative **[26]** or have a higher salivary cytokine, IL-6 and IL-1, concentration **[27]**. Unfortunately, RT-associated lesions can last for up to six weeks after the last session **[28]**, reducing patients' quality of life severely.

Aside from normal chemo- and radiation, an increasing variety of targeted medicines are now employed in clinical practice to treat various forms of cancer. Macroscopically, it has a core necrotic region with an erythematous halo **[29-31]**. It usually appears within five days of the first cycle of treatment and either improves or resolves spontaneously even with mTOR inhibitor regimen therapy **[32]**; nonetheless, it is frequently the reason of therapy dosage re-modulation or, in the situation of severe mIAS, treatment termination. Indeed, in the BOLERO-2 study, the combination treatment of everolimus, a mTOR inhibitor, was limited by a significant frequency of all-

grade stomatitis (67% of all-grade stomatitis, 33% grade 2 and 8% grade 3) **[33]**.

Notably, patients on mTOR inhibitors are more likely to develop oral stomatitis and enteritis **[34]**. The occurrence of mIAS-toxicity varies according to cancer type. Individuals with renal cell carcinoma (RCC) have a reduced likelihood of developing mIAS than individuals with astrocytoma, gastric cancer, or breast cancer **[33]**. This is also due to the fact that the properties of the medicine connected with the mTOR-inhibitor varies between cancer kinds, according to therapeutic recommendations.

Table 1: List of therapies under investigation for mucositis development prevention grouped accordingly to their mechanism of action

Antioxidant agents	**Characteristics**	**Mechanism of action**
Amifostine	**Phosphorylated aminosulfhydryl compound**	**Promotes recruitment of ROS scavenger, reduces DNA strand breaks**
Glutamine	**Amino acid**	**Exerts antioxidant activities promoting glutathione synthesis**
Oral zinc supplement	**Essential mineral**	**Prevents lipids peroxidation, replaces redox reactive metals, induces metallothionein synthesis**
Vitamin E	**Lipid soluble α-tocopherol**	**Prevents tissue damages caused by the ROS release**
N-acetyl-cysteine amino acid L-cysteine	**N-acetyl derivative of the natural**	**Exerts antioxidant activities promoting glutathione synthesis, myeloperoxidase activity, xanthine dehydrogenase and oxidase activity.**
GC4419	**Synthetic manganese-based drug**	**Counteracts superoxide dismutase activity**
	Inhibitors of inflammation and cytokines production	
Turmeric	**Flowering plant belonging to Curcuma longa**	**Counteracts NF- κB activiy**
Clonidine lauriad mucoadhesive buccal tablets	**Tablets contain high concentrations of an anti-inflammatory active principle (clonidine)**	**Inhibits NF-κB activity and the downstream pro-inflammatory cytokines-mediated signal**
SMAD7 over expression	**Gene encoding the nuclear protein Smad7 that binds the E3 ubiquitin ligase SMURF2**	**Impairs TGF-β1 that NF-κB activities in mice model (K5.Smad7) irradiated**
Benzydamine hydrochloride rinses	**Indazole non-steroidal anti-inflammatory drug**	**Inhibits the activity and the production of pro-inflammatory cytokines, TNF-α and IL-1β**
Pentoxifylline	**Xanthine derivative**	**Impairs NF-κB activity and inhibits TNF-α and IL-1β action**
Dusquetide (SGX942)	**5-amino acid innate defence regulator (IDR) peptide**	**Modulates immune innate pro-inflammatory response**
Multi target natural agents	**Characteristics**	**Mechanism of action**
Honey	**Honey topical application**	**Attenuates burns and pressure wounds.**
Manuka and Kanuka essential oils	**Mix of essential oil from Leptospermum scoparium and Kunzea ericoides**	**Anti-inflammatory, analgesic and anti-micotic and -bacterial activities**

Mucosal lesions associated with epidermal growth factor (EGFR) inhibitors occur in 15% of treated patients **[35]**. Clinically, they manifest as restricted lesions with mild erythema, which are sometimes comparable to aphthous lesions **[36]**. In the case of mIAS, the onset coincides with the first cycle of treatment, can affect the entire non-keratinized area, and can resolve on its own throughout treatment36. Less than 1% of patients treated with anti-EGFR antibodies, cetuximab or panitunumab, or EGFR-tyrosine kinase inhibitors (TKI), erlotinib or gefinitib, develop a high grade mucosal lesion, requiring treatment ri-modulation or suspension **[37-39]**. In patients treated with a multitargeted TKi, such as afatinib, lapatinib, or dacomitinib, the incidence and severity of the lesion increase **[40-42]**.

Indeed, when compared to other EGFR-TKi (40% vs. 15% of all-grade, 8.7 vs. 1% of grade 3) **[43]** or anti-EGFR monoclonal antibody therapy **[32]**, these cancer treatments are associated with a greater prevalence of all-grade mucositis. When cetuximab or panitunumab is combined with cisplatin, 5-FU, FOLFIRI, or FOLFOX32, the relative risk of developing high-grade mucosal lesions (3) increases dramatically. Furthermore, whereas adding cetuximab to RT had little effect on the likelihood of developing mucositis in HNC patients when compared to RT alone (approximately 60% of high grade 3), **[44, 45]** However, when paired with RT plus CT, it increases the probability of developing high grade mucositis when compared to RT plus CT treatment **[46, 47]**.

Mucositis caused by ado-trastuzumab emtansine (T-DM-1) is preferred to mucosal telangectasia **[48]**. T-DM-1 is now licensed for the treatment of HER2+, an EGF receptor that is abnormally expressed in some cancers, metastatic breast cancer. This medication promotes a mucosal vascular malformation, which results in epistaxis and GI or gynecological bleeding in 30% of patients **[48, 49]**. Oral mucositis, specifically stomatitis with aphthous ulcer, occurs in a very small number of patients receiving cyclin-dependent kinase 4/6 inhibitors (CDK4/6) **[50, 51]** as first- or second-line treatment for hormone positive/HER2 negative metastatic breast cancer. This regimen, however, promotes GIM rather than OM. Abemaciclib does, in fact, cause early-onset GIM in around 80% of patients during the first cycle of treatment **[51, 52]**. Notably, CDK4/6 inhibitors bind cyclin D3 in GI epithelial cells, limiting proliferation and, as a result, producing mucosal injury **[53]**. Asymptomatic hyperkeratotic lesions rise in both the keratinized and non-keratinized mucosa, including mucosal lesions with a verrucous or papillomatous appearance rising in the tongue, labial mucosa, and linea alba **[54-56]**. Non-specific stomatitis, defined by oral mucosal hypersensitivity and coupled with moderate erythema or severe inflammation, is a side effect of anti-angiogenetic medication treatment **[57]**. The likelihood of developing a stomatitis incident varies depending to the target medicine administered. Indeed, stomatitis is rarely caused by bevacizumab or ramucirumab, two monoclonal antibodies aimed

against the vascular endothelial growth factor receptor (VEGFR). In contrast, 25% of patients on multikinase inhibitors (MKIs) such as sunitinib, sorafenib, or cabozantinib get stomatitis during the first two months of treatment **[57]**. However, less than 10% require drug dosage re-modulation, and just 1% quit treatment **[57]**. Low grade stomatitis has been reported as an immunotherapy-related adverse event (irAE) in patients treated with the anti-programmed death 1 (PD1) drugs pembrolizumab and nivolumab, or the anti-programmed death ligand 1 (PDL1) drugs atezolizumab and durvalumab **[32]**. Patients on an immuno-checkpoint inhibitor experience varying degrees of diarrhea, which is frequently accompanied by stomach pain, dehydration, and constipation **[58, 59]**. Endoscopic examination revealed the existence of colic mucosa with moderate inflammation and/or ulceration in patients treated with PD1 or PDL1, but the same seemed ulcerated and friable in patients treated with a CTLA4 inhibitor **[35, 60]**. Indeed, GI problems are reported by 27-54% of patients treated with a CTLA4 inhibitor, leading to treatment re-modulation or discontinuation **[61]**.

Mucositis prevention

While there are a rising number of novel anti-cancer drugs in clinical trials, there are few therapeutic options for mucositis prevention or treatment. Their effectiveness remains low. Notably, Palifermin, a recombinant human keratinocyte growth factor 1 (KGF- 1), is the only medicine licensed by both the FDA and the European Medical Agency (EMA) for the prevention of OM in patients having high-dose CT combined total body RT prior to HSCT **[62]**. Palifermin promotes quicker tissue regeneration after chemo- and/or radiotherapy-induced injury by boosting epithelial cell proliferation and differentiation. This drug's efficacy in preventing OM was also investigated in HNC patients. Two separate investigations found that patients treated with Palifermin had a decreased incidence of high grade (3) OM **[63, 64]** but the high cost of this medicine, as well as worries about its ability to prolong cancer cell proliferation, make it inappropriate for OM therapy of HNC patients.

In the following sections, we will review clinical and pre-clinical information on the efficacy of some of the currently studied medications for mucositis development prevention, organized by mode of action.

Antioxidant agents

Mucositis development is a multistep process, therefore a viable therapeutic approach should act on multiple important pathways implicated in its pathobiology at the same time without compromising anti-neoplastic regimen efficacy. In this context, ROS, as early drivers of mucosa destruction, provide a possible target for mucositis inhibition. Antioxidants, such as amifostine, have been shown to help prevent mucositis during RT treatment by minimizing DNA strand breakage and preserving salivary gland, endothelial, and connective tissue integrity, **[65, 66]**. However, the associated

side effects and intravenous administration limit the use of amifostine in ordinary clinical practice. Other ROS-scavenger medicines, such as glutamine **[67-71]**, oral zinc supplement **[72-75, 77]**, vitamin E **[78-80]**, or N-acetyl-cysteine (NAC) **[81]**, have produced contradictory evidence of their efficacy in mucositis prevention. The MASCC/ ISOO expert group has recommended the oral administration of glutamine tablets for OM prophylaxis in HNC patients receiving CT-RT therapy. In contrast, given to the greater mortality risk associated with this medication, they have advised against parental administration of glutamine for OM prophylaxis in patients receiving HSCT108. Based on its capacity to decrease ROS production while counteracting superoxide dismutase (SOD) activity, GC4419 is now being studied in phase II research for mucositis prevention in HNC patients receiving cisplatin and RT **[33]**.

Inhibitors of inflammation and cytokines production

As previously stated, NF-B is the primary transcriptional mediator of the mucositis process, playing a role in the amplification of RT and CT-mediated damage signaling **[7, 8]**. NF-B has also been demonstrated to enhance drug resistance mechanisms **[109, 110]**; thus, impairing its function could affect both mucositis development and cancer progression. In this regard, turmeric, a flowering plant belonging to the ginger family Curcuma longa, has been demonstrated to attenuate and postpone OM severity in HNC patients by inhibiting NF-B activity following RT-mediated tissue injury **[84]**. Similarly, clonidine lauriad mucoadhesive buccal tablets (Clonidine Lauriad®) administration has been found to reduce the percentage of HNC patients developing high-grade mucositis (45.3% clonidine + CRT arm vs. 60% placebo + CRT arm), via direct inhibition of NF-B activity and the downstream pro-inflammatory cytokine-mediated signal **[85]**. Surprisingly, transgenic mice expressing high levels of Smad7 in oral epithelia were more resistant to radiation-induced oral mucositis development than wild type mice **[86]**. Indeed, high Smad7 levels have been demonstrated to block damage-mediated inflammation and promote rapid epithelia self-renewal, hence compromising OM development **[86]**.

However, the data acquired from the aforementioned investigations are extremely preliminary; further research is required to offer substantial evidences of turmeric and clonidine usefulness in mucositis prevention, as well as to comprehend the impact of Smad7 over-expression on tumor behavior. In contrast, significant evidence supports the use of benzydamine hydrochloride rinses for OM prophylaxis in HNC patients undergoing RT, but not in

those undergoing CT or CT-RT. It was discovered to suppress the activity and synthesis of many pro-inflammatory cytokines, lowering the frequency of severe mucositis development (43.6% in the benzydamine arm vs. 78.6% in the placebo arm) and the proportion of patients having mucosa erythema or ulceration **[87, 88]**. Based on these findings, the European Medicines Agency (EMA), the Multinational Association of Supportive Care in Cancer, and the International Society of Oral Oncology (MASCC/ ISOO) guidelines recommend the use of benzydamine rinses in HNC patients undergoing moderate-dose RT (50 Gy), as well as for OM prevention in HNC patients receiving RT-CT **[108]**. More research is being conducted to investigate the efficacy of benzydamine in individuals receiving high-dose RT. It has been shown to reduce OM formation in mice subjected to irradiation **[89]** and, in conjunction with vitamin E, to reduce RT-induced OM severity in a small cohort of HNC patients **[90]**.

According to a randomized phase II research, intravenous duquetide administration in HNC patients treated with CDDP and RT significantly reduced OM duration and infection rate compared to individuals in the placebo arm **[91]**. Phase III studies with large patient cohorts will firmly demonstrate the efficacy of pentoxifylline and duquetide in OM prophylaxis.

Natural agents

Natural chemicals, in contrast to the majority of the medications mentioned above, can be used as dietary supplements, are frequently well accepted by patients, and do not cause significant adverse reactions. Furthermore, due to their chemical structure, they can simultaneously impinge on various cellular signaling pathways, altering mucositis pathogenesis at multiple levels and negatively impacting cancer cell tumorigenic activities **[109, 111, 112]**.

Several natural products have already been evaluated, while others are being investigated in active clinical trials. Among the natural medicines investigated thus far, glutamine, vitamin E, and oral zinc supplementation have received the most attention. However, as previously stated, the findings presented are conflicting and do not support their use in mucositis prevention **[17, 81, 113]**. Furthermore, promising data are sometimes hampered by the small number of patients involved and/or the lack of an established methodological methodology for compound manufacture. This is the case with manuka essential oils, which appear to be useful in OM prevention as well as the administration of Chinese herbal medications (Indigo-wood root or R. algida), chamomile, or aloe vera **[113]**. In contrast, systemic topical honey treatment is recommended in HNC patients receiving either

RT or CT- RT to prevent the development of OM **[108]**.

Physical intervention

In animal models **[114, 115]**, low level monochromatic laser and low-level laser therapy (LLLT), also known as photobiomodulation, have been demonstrated to stimulate repair of damaged tissue and decrease inflammation. Several clinical studies have further established the efficacy of LLLT in lowering mucositis severity via tissue regeneration, both in patients undergoing chemo-radiotherapy prior to HSCT **[73]** and in HNC patients treated with only RT **[83]**. For these reasons, the MASCC/ISOO guidelines suggest the use of LLLT in the setting of an HSCT regimen for OM prophylaxis **[108]**.

As a result, more research is needed to provide a precise guideline for the proper use of LLLT in patients with solid tumors. In general, it is advised that low-level laser impulses not be applied directly to cancer tissue, as well as strict patient vigilance **[83]**. The usage of ice chips, cubes, or lollipops is related with a decrease in 5-FU-mediated OM incidence and severity **[73, 81]**. Cryotherapy treatment causes local vasoconstriction, which reduces mucosal exposure to 5-FU **[104]**.

Oral care and probiotics

Although there is no significant evidence of its usefulness for OM prevention, the MASCC / ISOO guidelines **[108]** recommend standardizing oral care. Healthy oral hygiene does, in fact, have a good impact, reducing infections or sepsis episodes after mucosa ulceration. Furthermore, frequent oral cavity examinations by oral care experts before and during anticancer therapy may lower infection risk and aid to detect earlier mucositis development **[105]**.

Preclinical evidence suggests that probiotic treatment protects mucosal gut architecture, limiting disaggregation in the event of damage **[107]**. As a result, an ongoing experiment will investigate the function of Lactobacillus in avoiding irinotecan-induced diarrhea **[106]**. The use of Lactobacillus probiotics to prevent diarrhea in patients with pelvic cancer treated with RT or RT with CT has recently been recommended by MASCC / ISOO recommendations **[108]**.

Mucositis-related symptoms treatment

Mucositis-related pain has a negative impact on the patient's quality of life. High-grade mucositis frequently results in insufficient food intake; as a result, patients can develop major nutritional deficiencies and require parenteral feeding. Furthermore, approximately 15% of them have premature therapy cessation or dosage re-modulation, affecting survival. As a result, treating discomfort associated with mucositis is critical for cancer patients' clinical management. Analgesics are the most

commonly used medications to treat OM-related pain. Morphine is, in fact, recommended by MASCC/ISOO recommendations for OM-related discomfort produced by CT and RT treatment in patients undergoing hematopoietic stem cell transplantation **[119]**. In HNC patients with high degree OM, mouth rinses or washes containing morphine are also administered. Furthermore, various "magic" mouthwashes for pain reduction in patients have been developed. They typically include anesthetics, antacids, and diphenhydramine, as well as steroids and anti-micotics **[83]**. A pilot study of 26 HNC patients undergoing RT plus CT revealed that patients who managed OM-associated pain with mouthwashes containing 0.2% morphine reported less severe pain and required less systemic analgesic administration than patients who used the magic formulation (lidocaine, magnesium aluminum hydroxide, diphenhydramine oral rinses) **[120]**. MASCC/ISOO recommendations recommend topical 0.2% morphine mouthwashes for HNC patients with OM induced by concurrent radiotherapy and chemotherapy **[108]**.

The MASCC/ISOO mucositis study group assessed the effectiveness of other drugs, but the provided data did not allow their use for OM-related pain management **[108, 119]**. for example, MuGard, whose qualities were investigated in a multicenter experiment that reported primarily palliative effects **[121**.

Sucralfate enemas, which operate as a protective barrier, are indicated for rectal bleeding caused by RT-induced proctitis; loperamide therapy, which failed, is recommended for diarrhea control in patients undergoing RT plus CT before HSCT **[119]**.

Biomarker feasibility for oral mucositis development risk assessment and early diagnosis

The ability to stratify cancer patients based on their likelihood of developing mucositis, as well as identify mucositis development and severity in an early stage, represents an unmet need for researchers and doctors. The discovery of a standardized biomarker for mucositis assessment and/or early diagnosis may allow for precision patient care, decreasing hospitalization, drug discontinuation, and dosage re-modulation, and thereby lowering patient management costs. Cytokines generated following chemo- and/or radio-mediated tissue initial injury operate as signal transducers, causing damage response amplification. Several writers have studied the potential of correlating their levels with mucositis severity and/or early detection based on their roles and features. However, the data presented thus far is contentious. TNF- levels, for example, have been shown to be either high **[123, 124]** or low **[125, 126]**

during RT in various trials, with only one study demonstrating a significant association between TNF- levels and OM severity **[124]**. Studies that connected IL-10 and IL-1 levels and OM in HNC patients having CT or/and RT **[123, 125, 126]** produced the same contentious results. More data is needed to prove the link between high-grade mucositis development and IL-6 or IL-1 levels in RT patients **[123-125]**.

TGF- was discovered in high concentrations in the plasma of patients suffering from RT-induced severe toxicity **[127, 128]**. TGF- concentrations increased in response to RT, but they did not correlate with the likelihood of mucositis development **[127, 128]**. In contrast, plasma levels of the epidermal growth factor (EGF) were found to be adversely associated to the likelihood of developing OM. Indeed, HNC patients with low EGF levels prior to therapy were at a high risk of developing OM during RT **[129-131]**.

The feasibility of using "inflammatory acute phase" indicators as mucositis biomarkers has also been investigated. The C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR) are two significant markers that are frequently assessed in blood tests to determine the existence of an inflammation process. At the end of RT **[132-135]**, their levels were found to be high in the blood of patients. Notably, Ki *et al*. discovered a link between increased CRP levels, but not ESR levels, and mucositis progression **[132]**, whilst Chethana *et al*. discovered a link between OM and CRP levels only in the initial weeks of treatment **[135]**. A few studies have looked at a possible link between OM development and/or severity and the amounts of several proteins involved in processes including apoptosis, ROS scavengers, adhesion, and structural proteins. In the context of high-grade mucositis, elevated levels of p53 **[124]**, BPI Fold Containing Family a Member 1 (BPIFA-1) **[130]**, Intercellular Adhesion Molecule 1 (ICAM-1), E-selectin, Lymphocyte function-associated antigen 1 (LFA-1) and macrophage integrin (Mac-1) have been found **[131]**. Low amounts of pro-apoptotic proteins, such as B-cell lymphoma 2 (BCL-2) and induced myeloid leukemia cell differentiation protein **[124]**, have been described, as have low levels of antioxidant glutathione GSH **[126]**. The variability of the evaluated research, as well as the small number of included patients, preclude their use for mucositis prediction **[132]**. The specificity of these proteins for OM evaluation should be studied further.

As previously stated, radiation directly injures the mucosa, causing double strand breaks (DSBs) of DNA. As a result, a decrease in the activity of essential proteins involved in DNA repair may be related to the occurrence and/or severity of mucositis. Among these, the histone protein -H2AX

levels were linked to radiotherapy-induced toxicities like oral mucositis **[128, 129]**. The presence of particular SNPs does, in fact, affect the actions of the corresponding translated protein **[133]**. Some SNPs are found in genes such as XRCC1, XRCC3, and RAD51, whose activities are crucial during DNA repair. Their presence has been linked to a higher risk of developing radiotherapy-related toxicities **[134-136]**. However, the link with OM is weak **[132]**; more research is needed to confirm their assessment for OM development.

Gutierrez-Camino and colleagues discovered a link between the presence of SNP rs10505168 in the sequence of miR-2053 and an increased risk of developing OM in children undergoing methotrexate treatment for pediatric acute lymphoblastic leukemia (ALL) **[134]**.

Laheji and colleagues recently examined oral microbioma from patients undergoing CT plus RT treatment prior to autologous hematopoietic stem cell transplantation and discovered that patients who did not develop ulcerative OM had more resilient microbioma than those who did **[135]**.

As previously stated, the majority of the biomarkers studied thus far require additional research to be confirmed for either mucositis diagnosis or mucositis severity prediction. To clinically confirm their usage as biomarkers, a consistent technique for their measurement, as well as strict patient enrollment criteria, are required. However, these factors may not be sufficient; the fundamental limitation is that none of them is a specific marker that characterizes the mucositis process. They are, in fact, formed as a result of several stresses. This could jeopardize their utility as mucositis indicators. During antineoplastic treatment, the entire organism is subjected to a number of stimuli that can either conceal or mimic the mucositis process. Finding a marker that particularly recognizes mucositis process progression could be beneficial. Non-coding RNAs have been discovered to be more lineage-specific than protein coding genes, revealing how differences in expression may particularly influence cell phenotype. As a result, RNAs that are uniquely implicated in the mucositis process, and their evaluation could be employed as a mucositis biomarker.

CONCLUSION:

The advancement of cancer medicines has considerably improved patient survival. However, as medicines become more effective, there are only a few viable choices for antineoplastic therapy-induced oral mucositis treatment or prophylaxis, which frequently results in treatment discontinuation or re-modulation. This also increases hospitalization, resulting in a rise in public health costs and a decrease in patient quality of life. The ability to determine patient susceptibility to develop

OM using an accessible and non-invasive test assessing the expression of OM-related particular biomarkers may allow for the formulation of a personalized targeted treatment. This may also allow new drugs' preventive activity to be tested in a high-risk subpopulation, increasing the therapeutic importance of the outcome.

Oral mucositis is still an underappreciated side effect of cancer treatment today. The collaborative efforts of basic, translational, and clinical scientists are critical for improving cancer patients' quality of life and, as a result, lowering their management costs.

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