Review

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Review

Oral Mucosa in The Cancer Patient; Putting the Pieces Together. A Narrative Review and New Perspectives

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Simple Summary: Oral mucosa, as part of human mucosa, is an essential part of the oral cavity. It is the first natural barrier against intrusion of newcomers and habitat for oral microbiome. As such, it is receiving an ever-increasing interest by clinical and translational research. However, it is in the field of cancer treatment and its toxicity where oral mucosa has a prominent role, as oral mucositis is one of the most debilitating cancer treatment complications, and a notorious source of worry for the oncologist and of poor quality of life for the cancer patient. This narrative review focuses on the entangled implications of human oral mucosa in cancer, and specifically in cancer-related oral mucositis support strategies development.

Abstract: Oral mucosa is a key player in the cancer patient and during cancer treatment. The increasing prevalence of cancer and cancer therapy associated side effects are behind the major role that oral mucosa plays in the oncological patient. Oral mucositis is a debilitating severe complication caused by early toxicity of chemo and/or radiotherapy that can restrict treatment outcome possibilities, even challenging patient's survival. It has been referred to as the most feared cancer treatment complication. Predictive variables as to who and to what extent will be affected are still unclear. Additionally, oral mucositis is one of the sources of the increasing economic burden of cancer, not only for patients and their families but also for institutions and governments. All efforts should be implemented in the search for new approaches to minimize the apparently ineluctable outburst of oral mucositis along the cancer treatment. New perspectives derived from different approaches in explaining the interrelation between oral mucositis and oral microbiome or the similarities with genitourinary mucosa may help elucidate the biomolecular pathways and mechanisms behind oral mucosa cancer-therapy related toxicity and what is more important its management in order to minimize treatment side effects and to provide enhanced cancer support.

Keywords: Oral mucositis; mucositis; oral mucosa; genitourinary mucosa; microbiome; dysbiosis; saliactive; cancer; PROMs; cancer toxicity; chemotherapy; radiotherapy; pain; olive oil; betaine; trimethylglycine; xylitol; breast cancer survivors; head and neck cancer; cancer support

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1. Introduction

The mucosa, also called mucous membrane, is one of the most extensive organs of the human body, found mainly in the oral cavity, gastro-intestinal tract, urogenital tract, respiratory tract, and to a lesser extent in organs such as the eyes. It behaves as a real defensive barrier, resists physical stimuli and friction and therefore has a high rate of cell turnover. It has also absorptive functions and carries a rich microbiota, which gives it unique properties in health and well-being.

The oral mucosa is the specialized part of the mucosa that covers the entire oral cavity up to the oropharynx. Histologically, it consists of a stratified squamous epithelium and an underlying connective tissue or lamina propria, which is keratinized in the sites of friction. In the area where it meets the teeth, it differentiates into a masticatory mucosa that is tightly adherent to the underlying bone, known as attached gingiva.

Furthermore, the function that has received most attention recently is the immunological role, in addition to serving as a preferential habitat for the oral microbiome, as mentioned previously [1].

2. Oral Mucosa and the Barrier Function

One of the main roles of the mucosa is the barrier function. An ample diversity of challenges can disrupt the epithelial barrier of the mucosa. Among them, end metabolites and allergens derived from food, alcohol, therapeutic agents, inadequate oral hygiene, bacteria, virus, and fungi. Dysregulation or unbalance of the epithelial barrier has been described as the origin of a leaky epithelium that generates dysbiosis through a double mechanism, first reducing commensal microbes and second enhancing opportunistic pathogens. Said damage to the mucosal barrier can be exerted at different levels of the epithelium, such as the zonula occludens 1, 2 and 3, claudins, E-cadherins, desmosomes and junctional adhesion molecules [2]. Breakage of the barrier is behind the crossing of species that penetrate the mucosa barrier and exert their different signals, inflammatory, carcinogenic, or infectious as well as immune system downregulation pathways. Species penetration have in the cancer patient a recently described double impact: initiation and progression of cancer and modulation on the treatment outcome [3].

The role of oral mucosa barrier in both the pathogenesis and resilience to COVID-19 infection is still under study. The preferential invasion of the virus through the oral mucosa is explained by the fact that it is a receptacle for a high number of ACE2 receptors throughout oral mucosal epithelium that are used as couplings by viral particles allowing the release of key parts of the virus into the cell cytoplasm for replication [4]. The elevated presence of ACE2 receptors in oral mucosal cells means that the oral mucosa should be considered an area of high risk for SARS-CoV-2 adhesion and penetration [5].

Lesions and manifestations of SARS-CoV-2 in the oral mucosa include dryness of the mucosa, mucosa irritation, inflammation and pain caused by the release of tumor necrosis factors and cytokines associated with the acute inflammatory episode characteristic of this viral infection [6].

Taste and smell reside primarily in the oral mucosa, in the taste receptors on the dorsum of the tongue (taste buds), in the tonsils and oropharynx, and in the olfactory receptors located in the nasopharynx. Both can be altered or markedly diminished in COVID-19. The loss of taste and smell (dysgeusia and anosmia) is often sudden and abrupt. Mucosal congestion or edema and mucosal dryness may explain the loss of smell [7], while the coincidence of most of the taste buds on the dorsum of the tongue, in particular in the area with the highest concentration of ACE2 receptors, and their involvement in the virus entry and local destruction mechanism and therefore heavily exposed to the cell damage caused by the virus, may be the origin of the loss of taste [8, 9]. Taste and smell are also claimed by patients to change during cancer treatment, as oral mucosa is especially susceptible to chemo and radiotherapy [10].

3. Oral Mucosa and the Toxicity of Cancer Treatment

Oral mucosa is a main actor in cancer. The toxicity of cancer treatment rapidly and preferentially affects oral mucosa causing oral mucositis.

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Oncological treatment-induced oro-gastro-intestinal mucositis, otherwise recognized as oral mucositis, or mucositis, is the most visible clinical complication of cancer therapy and one of the most feared by oncologists [11]. It has been described as the hidden side of cancer treatment [12]. Oral mucositis is highly prevalent in the treatment of head and neck cancer but also in the treatment of any type of cancer [13–15]. Mucositis can affect oral mucosa throughout the whole of the oral cavity, the throat, larynx, and also the digestive tract including the rectum and annus, the respiratory tract as well as vagina [16].

Oral mucositis lesions vary from erythema to ulceration of the mucosa coursing with different grades of pain, swallowing, eating, and speaking impairment, compromised nutrition, weight loss and dehydration with treatment delays, even interruptions and hospitalizations. Mucosa ulcerations and inflammation can be accompanied by bleeding and pain and may impair specific functions depending on the sites affected. Mucosa barrier disruption leads to pathogens penetration and potentially to systemic bacteriemia and sepsis that may be fatal. Oral mucositis has a significant impact on the patient's quality of life and may negatively impact survival of the cancer patient [17].

Thanks to the combination of metagenomics science and computational models the physio-pathologic understanding of oral mucositis has seen an evolution, from the classical 5 step model described by Sonis. The actual school of thinking hypothesizes that there is a gene pathway implication of an oral microbiome dysbiosis in the genesis of mucosa ulceration in oral mucositis and in delayed and/or impaired wound healing in oral mucositis [18,19]. In other words, the mucosa barrier breakage is in itself part of a mucosa dysbiosis.

Cancer treatment strategies are designed to target rapidly dividing cancerous cells. Subsequently, tissues characterized by a high cell turnover such as oral mucosa, gastrointestinal and vaginal mucosa are also subject to chemotherapeutic agents through cytotoxic effects from cancer therapy. The oro-gastro-intestinal mucosa is moist and elastic and exposed to friction (masticatory function and food transit) and therefore exhibits intense and constant cell turnover with high mitotic activity of cells and cell shedding every 14-21 days. This active cell turnover and metabolism is higher in the mobile mucosa and lower in the masticatory mucosa [20]. This particularity makes oral mucosa very sensitive to antineoplastic treatments meant to target cancer cells with a high proliferative capacity.

Oral microbiome that is attached to mucosa cells, as well the microbiome related host-defense and the crosstalk between the oral mucosa and the oral microbiome is also affected [3,21]. Whether it is the chicken or the egg, the dysbiosis a consequence of oral mucositis or the latter the consequence of the first, is yet unclear. What happens first in oral mucositis, the chemo-radiotherapy mediated cell death or the oral dysbiosis-related mucosa barrier disruption is today attracting the interest of researchers and clinicians [22,23].

4. Oral Mucositis and Oral Microbiome Dysbiosis

Dysbiosis has been reported to exist whenever disruption of the epithelial barrier occurs [24,25].

Patients immersed in cancer treatment suffer from a newly coined cancer dysbiosis [26]. Cancer therapy-induced dysbiosis has been found in different types of cancers [27]. Furthermore, it has been outlined that it could well be that an altered microbiota can enrich the list of predisposing risk factors for breast cancer [28].

Cancer treatment changes the oral microbiome. Now, the hypothesis that the microbiota exerts a fundamental part not only in cancer onset but also in the cancer treatment response is explained by the fact that certain species are behind delayed and reduced wound healing [29]. For instance, *P. gingivalis* can inhibit wound healing and is able to escape the host immunity [30].

Oral microbiome sampling displays specific signatures associated to different types of cancer. A reduction in Streptococcus and *Rothia* species in oral cancer for example [31], a reduced diversity and lower streptococcus in lung cancer [32] a reduced *neisseria* and reduced *streptococcus* as well in pancreatic cancer [33] and an enriched oral microbiota as an early marker of pancreatic cancer for example [34].

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It has been demonstrated that subjects with *P. gingivalis* and periodontitis are at higher risk of pancreatic cancer [35]. *P gingivalis* has been appointed as protagonist in oral dysbiosis in a manifold of papers. Its role in cancer and in oral mucositis is today thought to be more of a principal role than a passive kibitzer.

In oral mucositis, chemotherapy disrupted oral microbiota is shifted to Gram-negative bacteria such as *Fusobacterium nucleatum*, *Clostridia* and *Treponema* species typically found in periodontitis and inflammatory conditions while commensal subspecies like Streptococcus are diminished. Dysbiosis with high counts of *F. nucleatum* has been associated to severe mucositis by the aggravation of epithelial injury and enhanced inflammation and apoptosis [22,36].

Gram-negative species and the above-mentioned mucositis-associated-microbiome perpetuate themselves in the pro-inflammatory breeding ground, so all means to reverse or modulate oral dysbiosis could prove beneficial to the cancer patient.

In view of the current evidence showing the implications of certain microbiota hubs, such as the gut microbiota, in the response to radiotherapy-induced mucositis, it seems at least sensible if not wise to seek a reintegration of a balanced oral microbiome and an oral microbiome boost in order to try to modulate the host local response to the cancer therapy toxicity, namely a lesser degree of oral mucositis [37].

5. The Example of Head and Neck Cancer

In 2020, global cancer statistics estimated 932,000 new cases of head and neck cancer (H&N) and 467,000 deaths globally [38]. The main risk factors have historically been alcohol and tobacco. However, in recent decades the incidence of tobacco-related cancer has decreased, while in recent years human papillomavirus (HPV) has become a major causative factor provoking more H&N cancers than cervical cancers [39]. In p16-positive oropharyngeal subjects, disease can occur at young ages creating a population of cancer survivors with potentially significant treatment-related morbidities for decades.

The current reality of the H&N patient is one of younger subjects with higher cure rates, increasing numbers of survivors, increasing number of years as a survivor, and a multimodality management including chemotherapy and/or radiotherapy and/or surgery.

The most prominent cancer-therapy related toxic effects according to the time of onset are the following:

1. Acute (during treatment): oral mucositis.
2. Chronic (after the end of treatment): xerostomia, dysphagia, pain, persistent/chronic oral mucositis.

Patients may experience pain, social and physical limitations, psychological effects related to these as well as self-appearance issues that altogether may lead to anxiety, depression and lack of motivation to enjoy life. Unfortunately, these complications may be present “per se” in an acute, chronic, and long-lasting manner [40]. Quality of life of the survivors has been described to be poor with more than one disability. A recent review coming from Japan alerts of the lack of protocols to improve long-term treatment outcomes and outlines a requisite for a paradigm shift from a disease oriented approach to a problem solving management [41]. This is also called better cancer support for the patients and their families.

6. The Financial Toxicity of Oral Mucositis

A patient facing a cancer diagnose will undergo numerous and important medical costs that will have an effect recently referred to as financial toxicity [42]. Household adaptation to the economic burden of cancer does not necessarily have a positive result for the cancer patient and his/her family. Furthermore, oral mucositis has been reported to be one of the most frequent and expensive secondary events induced by cancer treatment.

The costs derived from oral mucositis in the hematopoietic stem cell transplantation can range from 1124,47 US Dollars (USD) to 299214,14 USD per patient [43]. Hospitalization, and extended

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monitorization of patients with oral mucositis put pressure on the already high economic burden of cancer treatment also for institutions and governments.

Finding safe measures in oral mucositis looks like a necessity not only for the cancer patient but for the rest of the actors involved, including the Health Systems.

7. The Value of Patient Reported Outcome Measures (PROMs) in Mucositis

When it comes to oral mucositis, a divergence between a generally lesser severity picture perceived by the oncologist and what the patient experiences has been reported [44]. This discordant perspective has been noted in other fields of medicine where the mucosa is the main actor, such as gynecology and in particular in conditions such as breast cancer survivors and the genitourinary mucosa secondary effects of breast cancer therapy including adjuvant therapy that lead to a cancer-therapy related menopause [45–47]. PROMs are especially useful in the field of oncology where physicians and healthcare professionals tend to underestimate symptoms that affect patients' quality of life. The medical team focuses on survival and on the risk of recurrence of the cancer disease. This diverts attention from collateral symptoms that nevertheless severely affect the patient's quality of life or even lead to abandonment of treatment [48]. Therefore, questionnaires based on patient's reports, also called PROMs, have become increasingly important.

It is important that PROMs questionnaires implemented for the assessment of oncology patients include signs of the existence or not of the cohort of emotional and physical symptoms that are highly prevalent, namely sadness, anxiety, emotional distress, or social withdrawal. It is also advisable that the patient can report signs and symptoms such as the existence and degree of dysphagia, xerostomia, trismus, dysgeusia, appetite changes, sleep quality as well as difficulty in speaking and communicating [49–51]. However, a poor commitment to an extensive or numerous PROMs should be anticipated and maybe it is preferable to choose one with a smaller number of questions.

It has been reported that symptoms of cancer treatment toxicity subjectively perceived by the patient are at risk of being underestimated by the clinician, in the range of 40-70%. This occurs even in data collection during randomized studies, which is why the incorporation of ideally validated PROMs is emphasized in clinical studies [52].

Approaching patient needs and preferences from a shared patient-physician decision-making approach is now much promoted [53] and has been linked to greater independence, effectiveness and efficiency of treatment as well as increased adherence to treatment [54–56].

8. Measures to Improve Oral Mucosal Resilience in Cancer Treatment. New Perspectives and Future Directions

It has been reported that patients experiencing oral pain show a lower salivary flow when compared to controls [57]. Oral moisturizers and saliva stimulants for relieving long-term oral complications of cancer treatment, are the first line of treatment and have had a presence in guidelines and expert's recommendations. However, there is a concern on products based on acidic formulations regarding their erosive potential in already susceptible patients. In this respect, a non-acidic composition has been included in numerous guidelines and systematic reviews for the proven benefits in dry mouth patients [58–64].

A clinical trial performed in H&N cancer radiated patients with primary outcome being a decrease of symptoms after the use of the previously described composition, demonstrated a significant improvement in the long-term symptoms, physical, social, personal and pain, as well as in the quality-of-life parameters analyzed, limitation in eating, limitation in enjoying food, limitation in speaking, limitation due to dryness. Patients reported less interruptions during sleep [65]. No side effects nor adverse events were reported.

Although oral mucositis was not included as an outcome, patients experienced a statistically significant pain reduction even though only 40% of the patients showed an increased salivary flow, while 60% did not. Therefore, another mechanism for pain amelioration must be implicit.

Partial unpublished data from an on-going interventional study, registered on the ClinicalTrials.gov under https://clinicaltrials.gov/ct2/show/NCT05635929 in 50 H&N cancer patients

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with mucositis severity outcome during the first 6 weeks of treatment and follow up after 6 months has pain as an outcome and oral mucositis severity. The use of PROMs in conjunction with a mucosa topical non-acidic lipophilic composition enriched with a potent natural antioxidant, under the name saliactive®, seems to be in line with the accumulating evidence of the reactive oxygen species (ROS) pathways and their mediation on the inflammatory cascade that may be behind a good part of the complex pathobiology of chemo/radiotherapy-induced oral mucositis [66]. Additional health benefits of naturally occurring antioxidants have been extensively documented [67]. In the acute phase, when measuring oral mucositis (OM), the percentage of patients that develop OM is 89.7% in line with previously reported data. However, the number of severe OM (grade 3-4) is 34.4% compared to the 66% severe OM by Elting et al [68], and 65% by Elad et al [69]. Only 3.4% patients have grade 4 OM while treatment interruptions have happened only in 13.3%. In the acute phase, already completed of the aforementioned interventional study, a convergence is detected between PROMs reported by the patient (subjective information) and mucositis grade observed by the clinician (objective information) independently of gender and age, reducing the gap oftentimes found between patients and clinicians' reports [70]. Data show a significant pain reduction after 1 month of use of the mucosa topical gel, along with significant improvement in recreation, appearance, saliva and mood analyzed 6 months after treatment.

In a previous study the association of severe OM with adverse clinical outcomes such as hospitalization and treatment interruptions were established. Furthermore, the authors concluded that the higher the grade of OM, the longer the interruptions [71].

The role of oral microbiome in the onset of an oral dysbiosis because of the cancer therapy and its relation to the cancer therapy response has been described before. The potential benefit to improve oral dysbiosis in this group of patients needs to be done with support measures as dental interventions are restricted during the duration of the cancer treatment. In this respect, a fresh from press controlled, double blind, and multicenter randomized clinical trial, declared at the ClinicalTrials.gov https://clinicaltrials.gov/ct2/show/NCT05463484 as part of the Stop Dysbiosis Project, has shown statistically significant superior clinical outcomes in oral clinical parameters in patients with oral dysbiosis, with the use of a microbiome boost toothpaste containing extra virgin olive oil (EVOO), xylitol, and betaine. While control and placebo groups resulted in a significantly decrease in pH level the tested group kept pH level in the physiologic value, contributing to oral eubiosis [72]. Low pH has been documented at dysbiotic sites with inflammation or cell destruction [73]. Furthermore, acidic pH has been associated to inflammasome and abundance of proinflammatory cytokines [74], while on the contrary physiological pH maintenance has been reported to inhibit the activation of proinflammatory pathways. A new body of thinking considers pH modulation a novel anti-inflammatory approach [74].

The results found in this RCT, as hypothesized by the authors, can be attributed to multiple mechanisms. Namely, the action of numerous phenolic compounds with strong anti-inflammatory and antioxidant capacities [75–79], a natural osmo-protecting amino-acid able to interfere with a wide range of inflammation-related circuits [80,81] and a prebiotic proinflammatory-cytokine inhibition [82]. Early detection and reversion of subclinical microbiome changes in human mucosa tissues may be of help if, as it seems, an imbalanced microbiome can influence the severity and course of OM [22]. Oral microbiota dysbiosis, in a recent review, is said to accelerate the development and onset of oral mucositis through factors influencing the oral mucosa microbiota shifts such as smoking, radiotherapy, stem cell transplants, inflammatory factors released into the oral cavity, genetic factors and epigenetic factors, oral mucosa barrier breakage and the combination of all or some of the mentioned [83].

Dysbiosis can be easily understood as a result of the cancer game-changing condition. However, a question has been posed regarding women with ovarian cancer and a dysbiosis of the vaginal mucosa. An imbalanced vaginal microbiota has been linked to an increased risk of ovarian cancer [84]. But, is the vaginal dysbiosis before or after the ovarian cancer? The unique lactobacillus predominant signature in a young and healthy woman is an opportunity for research to clarify the readiness of a disrupted microbiome to return to homeostasis as, a prerequisite in vagina is the

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existence of a low diversity and low pH (4-4,8). Interestingly it has been hypothesized that a vagina poor in lactobacillus species or otherwise a vagina dysbiosis.

that courses with inflammation and mucosa barrier breakage can facilitate papillomavirus penetration and tissue damage patterns associated to viral infection and eventually cervix cancer [85]. The finding that younger women with BRCA mutations were almost three times less likely to have a healthy vaginal microbiota than those without the mutation can only be explained if the changes in the microbiome are in some way dictated by the genetics of an individual. Not only that, but women with relatives diagnosed with ovarian cancer, were themselves more prone to vaginal dysbiosis.

An on-going randomized blind comparative experimental clinical trial, in patients with history of malignant breast cancer declared at the ClinicalTrials.gov https://clinicaltrials.gov/ct2/show/NCT05585476 will help to elucidate the potential of a synergistic and symbiotic interaction with the host at the genital mucosa level once it has lost the estrogen protection. All attempts to minimize cancer therapy related effects on genitourinary mucosa in breast cancer survivors should be promoted as therapeutic strategies are limited in this group of patients as application of estrogens and/or Selective estrogen receptor modulators are, either, non-indicated or highly restricted [86–88].

Moreover, complexity behind OM management is served as unexpected toxicity from usual oral hygiene ingredients or common oral antiseptics should not be mis-regarded in the cancer patient. In this sense, The Mucositis Oral Guidelines Leadership Group (MASCC/ISOO Mucositis Guidelines Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology) has updated its guidelines in 2021 by means of a systematic review through which they have been able to identify the interventions with the highest evidence of being the most effective [89].

Surprisingly, chewing gum is not recommended for oral mucositis in the above mucositis guidelines.

Several expert opinions complement these guidelines with the following recommendations: dental evaluation and professional treatment prior to cancer therapy with the desire to reduce the risks of local or systemic infections of odontogenic origin, patient education on the benefits of basic oral care to improve self-care and adherence to oral care protocol. Special attention should be implemented prior to and during treatment, including rinsing with saline and sodium bicarbonate, which, despite being inert, improve overall cleaning, helping to maintain oral hygiene and improve patient's wellbeing.

The implementation of oral care protocols is beneficial for the prevention of oral mucositis during QT, head and neck RT and hematopoietic stem cell transplantation (HSCT). Worth mentioning, it is suggested not to use chlorhexidine in patients treated with radiotherapy in the head and neck area. Furthermore, in a case-control study of risk factors regarding the onset of osteoradionecrosis of the jaw in radiated head and neck patients the use of chlorhexidine multiplied the risk by 1.28-fold and root scaling performed within the previous two weeks by 2.43-fold [90].

Careful timing of interventions is advisable as well as preferential use of natural ingredients such as honey, saliactive® composition, and glutamine, part of an emerging evidence of the potential of natural topical approaches for counteracting the toxicity in human mucosa [91–94]. Nevertheless an important consideration for honey in the management of oral mucositis is its diabetogenic side-effect.

Attention should be paid to the pro-metastatic evidence that some lipids, different to oleic or linoleic acid from extra virgin olive oil, such as palm or palmitic oil have shown. This is of special relevance in patients suffering from oral cancers, as the authors showed, that a short dietary exposure to palmitic acid from palm oil in mice with oral carcinomas led to a long-term stimulation of metastasis. A description of the pro-metastatic pathway of palm oil, when part of the diet even in small amounts, is a source of worry for the potentially negative complex interactions between palm oil low quality lipids present in the diet and H&N cancer patients [95].

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9. Conclusions

Oral mucositis is a complication that appears during chemo and/or radiotherapy treatment and involves the breakdown of the mucosal barrier, risk of systemic infection and substantial pain which can lead to premature termination or remodeling of treatment, interruption of treatment and eventually may affect patient's survival. Chronic side effects related to cancer and cancer therapy and chronic pain associated to oral mucosa also affect the quality of life of cancer survivors and challenge their health caretakers.

The increasing prevalence of cancer with more patients with access to cancer therapies, and more cancer survivors for more years, make it necessary to minimize the side effects of the cancer treatment toxicity on oral mucosa.

New approaches with synergistic efforts between basic science, clinicians from different disciplines and translational research are needed to limit the toxicity of cancer treatments to reduce the incidence and severity of oral mucositis and to provide better cancer support.

New topical antioxidant microbiome boost strategies to minimize cancer therapy adverse effects in oral mucosa seem to offer a window of opportunity for the patient during oncological treatment in the setting of oral mucositis.

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Conflicts of Interest: Dr. Debora R. Vilaboa and Dr. Beatriz R. Vilaboa are founding members of the company Mucosa Innovations S.L. Mucosa Innovations is the owner and developer of technology specifically focused on mucosa cancer-therapy related toxicities, microbiome modulation pathways and mucosa related women's health conditions. No known conflict of interests exists for the rest of the authors.

References

1. Groeger, S. and J. Meyle, *Oral Mucosal Epithelial Cells.* Front Immunol, 2019. **10**: p. 208.
2. Celebi Sozener, Z., et al., Epithelial barrier hypothesis: Effect of the external exposome on the microbiome and epithelial barriers in allergic disease. Allergy, 2022. **77**(5): p. 1418-1449.
3. Raza, M.H., et al., *Microbiota in cancer development and treatment.* J Cancer Res Clin Oncol, 2019. **145**(1): p. 49-63.
4. Jin, Y., et al., Virology, Epidemiology, Pathogenesis, and Control of COVID-19. Viruses, 2020. **12**(4).
5. Xu, H., et al., High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. International Journal of Oral Science, 2020. **12**(1): p. 8.
6. Atukorallaya, D.S. and R.K. Ratnayake, *Oral Mucosa, Saliva, and COVID-19 Infection in Oral Health Care.* Front Med (Lausanne), 2021. **8**: p. 656926.
7. Mullol, J., et al., *The sense of smell in chronic rhinosinusitis.* J Allergy Clin Immunol, 2020. **145**(3): p. 773-776.
8. Cooper, K.W., et al., COVID-19 and the Chemical Senses: Supporting Players Take Center Stage. Neuron, 2020. **107**(2): p. 219-233.
9. Glezer, I., et al., *Viral infection and smell loss: The case of COVID-19.* J Neurochem, 2021. **157**(4): p. 930-943.
10. Hovan, A.J., et al., *A systematic review of dysgeusia induced by cancer therapies.* Support Care Cancer, 2010. **18**(8): p. 1081-7.
11. Mosel, D.D., et al., Oral complications in the treatment of cancer patients. Oral Dis, 2011. **17**(6): p. 550-9.
12. Pulito, C., et al., *Oral mucositis: the hidden side of cancer therapy.* J Exp Clin Cancer Res, 2020. **39**(1): p. 210.
13. Al-Ansari, S., et al., *Oral Mucositis Induced By Anticancer Therapies.* Curr Oral Health Rep, 2015. **2**(4): p. 202-211.
14. Jham, B.C. and A.R. da Silva Freire, *Oral complications of radiotherapy in the head and neck.* Braz J Otorhinolaryngol, 2006. **72**(5): p. 704-8.
15. Lionel, D., et al., Oral mucositis induced by anticancer treatments: physiopathology and treatments. Ther Clin Risk Manag, 2006. **2**(2): p. 159-68.
16. Patel, J.M., et al., Vaginal mucositis related to immunotherapy in endometrial cancer. Gynecol Oncol Rep, 2021. **36**: p. 100742.

17. Rosenthal, D.I., Consequences of mucositis-induced treatment breaks and dose reductions on head and neck cancer treatment outcomes. J Support Oncol, 2007. **5**(9 Suppl 4): p. 23-31.
18. Liu, H., et al., *Integrating in silico resources to map a signaling network.* Methods Mol Biol, 2014. **1101**: p. 197-245.
19. Kirk, J., et al., Text mining-based in silico drug discovery in oral mucositis caused by high-dose cancer therapy. Support Care Cancer, 2018. **26**(8): p. 2695-2705.
20. Wang, S.S., et al., *The maintenance of an oral epithelial barrier.* Life Sci, 2019. **227**: p. 129-136.
21. Vasconcelos, R.M., et al., *Host-Microbiome Cross-talk in Oral Mucositis.* J Dent Res, 2016. **95**(7): p. 725-33.
22. Hong, B.Y., et al., Chemotherapy-induced oral mucositis is associated with detrimental bacterial dysbiosis. Microbiome, 2019. **7**(1): p. 66.
23. Sonis, S.T., The Chicken or the Egg? Changes in Oral Microbiota as Cause or Consequence of Mucositis During Radiation Therapy. EBioMedicine, 2017. **18**: p. 7-8.
24. Akdis, C.A., Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions? Nat Rev Immunol, 2021. **21**(11): p. 739-751.
25. Levy, M., et al., *Dysbiosis and the immune system.* Nat Rev Immunol, 2017. **17**(4): p. 219-232.
26. Sharma, V.R., et al., Microbiome dysbiosis in cancer: Exploring therapeutic strategies to counter the disease. Semin Cancer Biol, 2021. **70**: p. 61-70.
27. Stringer, A.M., et al., Chemotherapy-induced mucositis: the role of gastrointestinal microflora and mucins in the luminal environment. J Support Oncol, 2007. **5**(6): p. 259-67.
28. Alpuim Costa, D., et al., Human Microbiota and Breast Cancer-Is There Any Relevant Link?-A Literature Review and New Horizons Toward Personalised Medicine. Front Microbiol, 2021. **12**: p. 584332.
29. Kerr, A.R., *The oral microbiome and cancer.* J Dent Hyg, 2015. **89 Suppl 1**: p. 20-3.
30. Laheij, A.M., et al., The impact of virulence factors of Porphyromonas gingivalis on wound healing in vitro. J Oral Microbiol, 2015. **7**: p. 27543.
31. Schmidt, B.L., et al., Changes in abundance of oral microbiota associated with oral cancer. PLoS One, 2014. **9**(6): p. e98741.
32. Yang, J., et al., Dysbiosis of the Salivary Microbiome Is Associated With Non-smoking Female Lung Cancer and Correlated With Immunocytochemistry Markers. Front Oncol, 2018. **8**: p. 520.
33. Drew, K., et al., The Proteome Folding Project: proteome-scale prediction of structure and function. Genome Res, 2011. **21**(11): p. 1981-94.
34. Gaiser, R.A., et al., Enrichment of oral microbiota in early cystic precursors to invasive pancreatic cancer. Gut, 2019. **68**(12): p. 2186-2194.
35. Michaud, D.S., et al., Lifestyle, dietary factors, and antibody levels to oral bacteria in cancer-free participants of a European cohort study. Cancer Causes Control, 2013. **24**(11): p. 1901-9.
36. Lamont, R.J. and G. Hajishengallis, *Polymicrobial synergy and dysbiosis in inflammatory disease.* Trends Mol Med, 2015. **21**(3): p. 172-83.
37. Al-Qadami, G., et al., Gut microbiota: implications for radiotherapy response and radiotherapy-induced mucositis. Expert Rev Gastroenterol Hepatol, 2019. **13**(5): p. 485-496.
38. Sung, H., et al., Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin, 2021. **71**(3): p. 209-249.
39. Auperin, A., *Epidemiology of head and neck cancers: an update.* Curr Opin Oncol, 2020. **32**(3): p. 178-186.
40. Rathod, S., et al., A systematic review of quality of life in head and neck cancer treated with surgery with or without adjuvant treatment. Oral Oncol, 2015. **51**(10): p. 888-900.
41. Matsuda, Y., et al., Oral Health Management and Rehabilitation for Patients with Oral Cancer: A Narrative Review. Healthcare (Basel), 2022. **10**(5).
42. Carrera, P.M., H.M. Kantarjian, and V.S. Blinder, The financial burden and distress of patients with cancer: Understanding and stepping-up action on the financial toxicity of cancer treatment. CA Cancer J Clin, 2018. **68**(2): p. 153-165.
43. Rodrigues-Oliveira, L., et al., Direct costs associated with the management of mucositis: A systematic review. Oral Oncol, 2021. **118**: p. 105296.
44. Kanagalingam, J., et al., Patient and oncologist perceptions regarding symptoms and impact on quality-of-life of oral mucositis in cancer treatment: results from the Awareness Drives Oral Mucositis PercepTion (ADOPT) study. Support Care Cancer, 2018. **26**(7): p. 2191-2200.
45. Gabes, M., et al., Measurement properties of patient-reported outcome measures (PROMs) for women with genitourinary syndrome of menopause: a systematic review. Menopause, 2019. **26**(11): p. 1342-1353.
46. Huang, A.J., et al., Day-to-Day Impact of Vaginal Aging questionnaire: a multidimensional measure of the impact of vaginal symptoms on functioning and well-being in postmenopausal women. Menopause, 2015. **22**(2): p. 144-54.
47. Perez-Lopez, F.R., et al., Assessment of sexual function and related factors in mid-aged sexually active Spanish women with the six-item Female Sex Function Index. Menopause, 2012. **19**(11): p. 1224-30.

48. Vistad, I., et al., Postradiotherapy morbidity in long-term survivors after locally advanced cervical cancer: how well do physicians' assessments agree with those of their patients? Int J Radiat Oncol Biol Phys, 2008. **71**(5): p. 1335-42.
49. Bjordal, K., et al., A 12 country field study of the EORTC QLQ-C30 (version 3.0) and the head and neck cancer specific module (EORTC QLQ-H&N35) in head and neck patients. EORTC Quality of Life Group. Eur J Cancer, 2000. **36**(14): p. 1796-807.
50. de Oliveira Faria, S., et al., Identifying Patient-Reported Outcome Measures (PROMs) for Routine Surveillance of Physical and Emotional Symptoms in Head and Neck Cancer Populations: A Systematic Review. J Clin Med, 2021. **10**(18).
51. Kushner, J.A., et al., Development and validation of a Patient-Reported Oral Mucositis Symptom (PROMS) scale. J Can Dent Assoc, 2008. **74**(1): p. 59.
52. Di Maio, M., et al., Symptomatic toxicities experienced during anticancer treatment: agreement between patient and physician reporting in three randomized trials. J Clin Oncol, 2015. **33**(8): p. 910-5.
53. Charles, C., A. Gafni, and T. Whelan, Shared decision-making in the medical encounter: what does it mean? (or it takes at least two to tango). Soc Sci Med, 1997. **44**(5): p. 681-92.
54. Griffin, S.J., et al., Effect on health-related outcomes of interventions to alter the interaction between patients and practitioners: a systematic review of trials. Ann Fam Med, 2004. **2**(6): p. 595-608.
55. Bauman, A.E., H.J. Fardy, and P.G. Harris, *Getting it right: why bother with patient-centred care?* Med J Aust, 2003. **179**(5): p. 253-6.
56. Upton, J., et al., Shared decision making or paternalism in nursing consultations? A qualitative study of primary care asthma nurses' views on sharing decisions with patients regarding inhaler device selection. Health Expect, 2011. **14**(4): p. 374-82.
57. da Silva, L.A., et al., Xerostomia and salivary flow in patients with orofacial pain compared with controls. Arch Oral Biol, 2011. **56**(10): p. 1142-7.
58. Gil-Montoya, J.A., et al., *Treatment of xerostomia and hyposalivation in the elderly: A systematic review.* Med Oral Patol Oral Cir Bucal, 2016. **21**(3): p. e355-66.
59. Lopez-Lopez, J., E. Jane Salas, and E. Chimenos Kustner, *[Prognosis and treatment of dry mouth. Systematic review].* Med Clin (Barc), 2014. **142**(3): p. 119-24.
60. Lopez-Pintor, R.M., et al., Effects of Xerostom((R)) products on xerostomia in primary Sjogren's syndrome: A randomized clinical trial. Oral Dis, 2019. **25**(3): p. 772-780.
61. Ship, J.A., et al., Safety and effectiveness of topical dry mouth products containing olive oil, betaine, and xylitol in reducing xerostomia for polypharmacy-induced dry mouth. J Oral Rehabil, 2007. **34**(10): p. 724-32.
62. Villa, A., et al., World Workshop on Oral Medicine VI: a systematic review of medication-induced salivary gland dysfunction: prevalence, diagnosis, and treatment. Clin Oral Investig, 2015. **19**(7): p. 1563-80.
63. Villa, A., C.L. Connell, and S. Abati, *Diagnosis and management of xerostomia and hyposalivation.* Ther Clin Risk Manag, 2015. **11**: p. 45-51.
64. Wiegand, A., M. Gutsche, and T. Attin, Effect of olive oil and an olive-oil-containing fluoridated mouthrinse on enamel and dentin erosion in vitro. Acta Odontol Scand, 2007. **65**(6): p. 357-61.
65. Martin, M., et al., Products based on olive oil, betaine, and xylitol in the post-radiotherapy xerostomia. Rep Pract Oncol Radiother, 2017. **22**(1): p. 71-76.
66. Iglesias-Bartolome, R., et al., mTOR inhibition prevents epithelial stem cell senescence and protects from radiation-induced mucositis. Cell Stem Cell, 2012. **11**(3): p. 401-14.
67. Karković Marković, A., et al., Hydroxytyrosol, Tyrosol and Derivatives and Their Potential Effects on Human Health. Molecules, 2019. **24**(10).
68. Elting, L.S., et al., Risk, outcomes, and costs of radiation-induced oral mucositis among patients with head-and-neck malignancies. Int J Radiat Oncol Biol Phys, 2007. **68**(4): p. 1110-20.
69. Elad, S., et al., The broadening scope of oral mucositis and oral ulcerative mucosal toxicities of anticancer therapies. CA Cancer J Clin, 2022. **72**(1): p. 57-77.
70. Leimola-Virtanen, R., et al., Expression of estrogen receptor (ER) in oral mucosa and salivary glands. Maturitas, 2000. **36**(2): p. 131-7.
71. Vera-Llonch, M., et al., Oral mucositis in patients undergoing radiation treatment for head and neck carcinoma. Cancer, 2006. **106**(2): p. 329-36.
72. Rodriguez-Agurto, A., et al., Randomized clinical trial on the clinical effects of a toothpaste containing extra virgin olive oil, xylitol, and betaine in gingivitis. Sci Rep, 2023. **13**(1): p. 6294.
73. Menkin, V., Biology of inflammation; chemical mediators and cellular injury. Science, 1956. **123**(3196): p. 527-34.
74. Rajamaki, K., et al., Extracellular acidosis is a novel danger signal alerting innate immunity via the NLRP3 inflammasome. J Biol Chem, 2013. **288**(19): p. 13410-9.
75. Beauchamp, G.K., et al., Phytochemistry: ibuprofen-like activity in extra-virgin olive oil. Nature, 2005. **437**(7055): p. 45-6.

76. Bertelli, M., et al., Hydroxytyrosol: A natural compound with promising pharmacological activities. J Biotechnol, 2020. **309**: p. 29-33.
77. Lozano-Castellon, J., et al., Health-promoting properties of oleocanthal and oleacein: Two secoiridoids from extra-virgin olive oil. Crit Rev Food Sci Nutr, 2020. **60**(15): p. 2532-2548.
78. Romani, A., et al., Health Effects of Phenolic Compounds Found in Extra-Virgin Olive Oil, By-Products, and Leaf of Olea europaea L. Nutrients, 2019. **11**(8).
79. Scotece, M., et al., Further evidence for the anti-inflammatory activity of oleocanthal: inhibition of MIP-1α and IL-6 in J774 macrophages and in ATDC5 chondrocytes. Life Sci, 2012. **91**(23-24): p. 1229-35.
80. Go, E.K., et al., Betaine suppresses proinflammatory signaling during aging: the involvement of nuclear factor-kappaB via nuclear factor-inducing kinase/IkappaB kinase and mitogen-activated protein kinases. J Gerontol A Biol Sci Med Sci, 2005. **60**(10): p. 1252-64.
81. Lee, E.K., et al., Betaine attenuates lysophosphatidylcholine-mediated adhesion molecules in aged rat aorta: modulation of the nuclear factor-kappaB pathway. Exp Gerontol, 2013. **48**(5): p. 517-24.
82. Han, S.J., et al., Xylitol inhibits inflammatory cytokine expression induced by lipopolysaccharide from Porphyromonas gingivalis. Clin Diagn Lab Immunol, 2005. **12**(11): p. 1285-91.
83. Min, Z., et al., Oral microbiota dysbiosis accelerates the development and onset of mucositis and oral ulcers. Front Microbiol, 2023. **14**: p. 1061032.
84. Nené, N.R., et al., Association between the cervicovaginal microbiome, BRCA1 mutation status, and risk of ovarian cancer: a case-control study. The Lancet Oncology, 2019. **20**(8): p. 1171-1182.
85. Łaniewski, P., Z.E. Ilhan, and M.M. Herbst-Kralovetz, *The microbiome and gynaecological cancer development, prevention and therapy.* Nat Rev Urol, 2020. **17**(4): p. 232-250.
86. ; Available from: https://cima.aemps.es/cima/dochtml/p/72726/Prospecto_72726.html.
87. ACOG Committee Opinion No. 659: The Use of Vaginal Estrogen in Women With a History of Estrogen-Dependent Breast Cancer. Obstet Gynecol, 2016. **127**(3): p. e93-e96.
88. Santen, R.J., et al., *Managing Menopausal Symptoms and Associated Clinical Issues in Breast Cancer Survivors.* The Journal of Clinical Endocrinology & Metabolism, 2017. **102**(10): p. 3647-3661.
89. Elad, S., et al., MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer, 2020. **126**(19): p. 4423-4431.
90. Chang, C.T., et al., Dental Prophylaxis and Osteoradionecrosis: A Population-Based Study. J Dent Res, 2017. **96**(5): p. 531-538.
91. Alkhouli, M., M. Laflouf, and J.C. Comisi, Assessing the topical application efficiency of two biological agents in managing chemotherapy-induced oral mucositis in children: A randomized clinical trial. J Oral Biol Craniofac Res, 2021. **11**(3): p. 373-378.
92. Sayles, C., et al., Oral Glutamine in Preventing Treatment-Related Mucositis in Adult Patients With Cancer: A Systematic Review. Nutr Clin Pract, 2016. **31**(2): p. 171-9.
93. Triarico, S., et al., Oral Microbiota during Childhood and Its Role in Chemotherapy-Induced Oral Mucositis in Children with Cancer. Pathogens, 2022. **11**(4).
94. An, W., S. Li, and L. Qin, Role of honey in preventing radiation-induced oral mucositis: a meta-analysis of randomized controlled trials. Food Funct, 2021. **12**(8): p. 3352-3365.
95. Pascual, G., et al., Dietary palmitic acid promotes a prometastatic memory via Schwann cells. Nature, 2021. **599**(7885): p. 485-490.