

Updates on Nutritional Recommendations for Patients with Severe oral Mucositis Secondary to Chemotherapy and Radiation

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Abstract

Oral mucositis is one of the most devastating effects of cancer treatments and creates a significantly negative impact on quality of life for many patients with cancer. Oral mucositis is defined as inflammation of the mucous membranes lining the mouth, throat, and esophagus. Complications from oral mucositis include significant debilitating pain, xerostomia, impaired taste, and increased risk of oral infections. Patients undergoing chemotherapy for cancer treatment who experience oral mucositis are at greater risk of developing malnutrition, dehydration, and interruptions within their scheduled cancer treatments. Specifically, methotrexate, 5-fluorouracil, doxorubicin, bleomycin, vinblastine, paclitaxel, and docetaxel are specifically associated with oral mucositis. Additionally, in patients with head and neck cancer who receive radiation therapy, with or without chemotherapy, mucositis is the most common sequelae and often interferes with patients' nutrition, quality of life, and survival. Currently, clinical guidelines do not have specific endorsements for nutritional interventions. Through adequate hydration and nutritional recommendations, patients ensure success of adequate protein, glutamine, vitamins, honey, and caloric intake necessary for mucosal healing and decreased inflammation. This review particularly elaborates on the most up-to-date nutritional recommendations and interventions for oral mucositis management in adult patients undergoing chemotherapy, with or without concurrent radiation therapy. Additional research must be conducted to determine the safety and practicality of dietary and nutritional recommendations for increased oral mucositis management and mucosal healing.

Keywords: oral mucositis; mucous membranes; chemotherapy; malnutrition; dehydration

Introduction

Oral mucositis, a debilitating consequence of cancer treatments, stands as a critical concern in the field of oncology. This condition, characterized by inflammation affecting the mucous membranes of the mouth, throat, and esophagus, affects the lives of countless cancer patients. Its manifestations include severe pain, xerostomia (dry mouth), taste impairments, and heightened susceptibility to oral infections. Equally concerning are the secondary complications it results in, such as malnutrition, dehydration, and treatment disruptions, further compounding the challenges faced by those already burdened with cancer.

The pathophysiology of mucositis is a multifaceted process as suggested by Bell et al. and is initiated by tissue injury resulting from radiation, chemotherapy, targeted therapy, or their combination [1]. This injury primarily affects the basal epithelial layer, causing the release of reactive oxygen species. These reactive oxygen species further damage nearby tissues and activate the inflammatory pathway, including the

release of molecules like TNF alpha, leading to additional cellular death. Ultimately, this process culminates in the development of mucosal ulcerations, which manifest as significant physical exam findings and present challenges for patients in terms of eating and drinking.

When evaluating for oral mucositis there are several established scales that describe grades of severity based on clinical history and physical exam findings. Three different scales exist, two of which were developed by the National Cancer Institute that reports Grades 1-5 divided into a functional/symptoms-based exam and a clinical exam [1]. The third scale developed by the World Health Organization uses both subjective and objective measures of mucositis and Grades 0-4 [1]. Grade 3 and above mucositis is categorized as severe and holds significant implications for disease progression and mortality. At this stage, patients typically face challenges in maintaining sufficient nutrition and hydration, underscoring its clinical importance.

For individuals undergoing chemotherapy with certain agents, including methotrexate, 5-fluorouracil,

doxorubicin, bleomycin, vinblastine, paclitaxel, and docetaxel, development of oral mucositis is closely associated at approximately 20-40% [1]. However, the ordeal amplifies dramatically for patients coping with head and neck cancer, who often undergo radiation therapy, sometimes in conjunction with chemotherapy. In these scenarios, mucositis stands out as the predominant and disruptive complication, with some estimates indicating that over 80% of patients are affected, and 56% of them experiencing Grade 3 severity [2]. This, naturally, can have adverse effects on nutritional intake, quality of life, and even survival.

This literature review aims to explore the latest approaches for managing oral mucositis in adult cancer patients undergoing chemotherapy and/or radiation therapy. It examines a range of interventions, including honey, amino acids, proteins, glutamine, liquid diets, and adequate hydration, with the aim of mitigating the severity of symptoms and promoting mucosal healing. Additionally, it delves into emerging interventions like omega-3 supplementation, probiotics, photo biomodulation and others which hold potential for reducing mucositis severity and bolstering immune responses during cancer treatment. As we navigate the ever-evolving field of research regarding oral mucositis treatment and prevention, our review intends to consolidate and structure the emerging findings from the most current literature.

Discussion

Literature Research (Methodology) and Study Selection

Our information search on oral mucositis was extensive, utilizing the PubMed and Google Scholar databases, and reputable medical journals. We employed a combination of keywords, including “oral mucositis,” “chemotherapy,” “radiation therapy,” “treatment,” “prevention,” “nutrition,” “honey,” “glutamine,” “amino acids,” “proteins,” and the “latest treatment guidelines.” We specifically targeted articles and reviews published no later than January 2020 up to the most recent months of 2023 to ensure the inclusion of the latest findings. Additionally, we enriched our research by referencing resources from the American Cancer Society and other esteemed journals specializing in cancer treatment and oral surgery. Furthermore, our focus extended to systematic reviews and meta-analyses, ensuring that

the information in this literature review was derived from the most robust evidence, thereby supporting the various treatment and prevention techniques for oral mucositis.

Summary of Current Studies

Oral mucositis is a common disabling early side effect of chemoradiotherapy. The available methods of treatment and prevention are lacking, especially given the extent to which this disease affects patients' quality of life. Herein we summarize current clinical studies that evaluated different types of nutrition therapy and supplements as both treatment, primary and adjunctive, and preventative measures of oral mucositis.

Honey

Honey, a naturally occurring substance with a millennia-long history of medicinal utilization, continues to yield substantial benefits in the contemporary era, likely attributable to its pronounced antioxidant and anti-inflammatory effects. The anti-inflammatory properties are due to its ability to inhibit the cyclooxygenase pathway, achieved through B and T lymphocyte proliferation [3]. Furthermore, honey exhibits notable antibacterial qualities, likely because of its concentration of flavonoids and phenolic acids [3]. In the context of managing oral mucositis, it is most beneficial for mitigating severity of disease, likely through pain reduction via decreasing inflammation [4]. Hunter et al. included thirteen studies in their paper that demonstrated topical honey application in patients undergoing chemoradiotherapy reduced the severity or duration of disease in comparison to control groups with a statistically significant result [5]. This study also determined that manuka honey specifically was associated with adverse effects, which is interesting to contemplate given the unique types of honey and how differences can affect response to treatment [5].

According to the most recent guidelines as of 2020, the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology's (MASCC/ISOO) suggests topical or systemic honey to prevent oral mucositis in patients who receive chemotherapy and/or radiation therapy for the treatment of head and neck cancer [2]. However, it is important to note that these recommendations are based on existing available data with certain limitations which necessitate cautious interpretation. Therefore, only a suggestion was deemed possible

until more supportive data becomes available. Yarom et al. reviewed four studies for honey in the management of mucositis for patients receiving head and neck chemoradiotherapy and concluded insufficient data existed to make firm recommendations [6]. Because honey production is highly dependent on source and can vary by location and processing methods, it becomes even more difficult to reach a conclusion which can be used as a standardized treatment recommendation, although it remains important to consider it as adjunctive symptomatic therapy when treating these patients. Larger studies need to be completed to better determine the full effects of honey when treating patients with oral mucositis. Nevertheless, the use of honey is relatively without side effects and worthwhile to suggest to patients.

In a meta-analysis of 28 randomized trials totaling 1861 patients, Ya Ying-Yu et al. evaluated multiple agents for use in prevention and treatment of oral mucositis and compared them [7]. In addition to honey, they also researched curcumin which is another natural agent also known as Chinese herbs. The results supported that chlorhexidine, benzylamine, honey, and curcumin were all more effective than placebo, and that honey and curcumin were more effective than povidone-iodine [7].

Zhang et al. conducted a systematic review and meta-analysis of pediatric patients specifically and whether honey is effective at treating radiation or chemotherapy induced oral mucositis⁸. They evaluated five studies totaling 316 patients and concluded that honey significantly reduced both the recovery time and the occurrence of oral mucositis. The authors also described that one of the studies they included evaluated weight change of patients after the intervention and showed that the honey group had a higher body weight. This is yet another added benefit of complementary honey administration when treating oral mucositis, as many of these patients become malnourished and lose weight from their cancer treatments and the side effects associated with them, leading to less favorable outcomes [8].

Protein

Sustaining a sufficient protein intake is paramount during the recuperative phase of pathological conditions to prevent malnutrition and cachexia, conditions frequently observed as consequences of radiation therapy or chemoradiotherapy. This is especially significant for patients receiving radiotherapy or chemoradiotherapy to head and neck

cancers as they can develop dysphagia, dry mouth, dysgeusia, and oral mucositis which can make them averse to eating appropriately. Radiation therapy as a risk factor for these side effects is compounded by modifiable risk factors such as smoking, drinking, or even psychological stress.

Studies have shown that diminished protein intake and subsequent levels in the body during these therapeutic regimens can impede healing in oral mucositis [8]. Maintaining an adequate intake of proteins is imperative for sufficient production of albumin, which is used for energy, tissue synthesis, and as a source of nitrogen for the body's essential metabolic processes [8]. In current practice, nutritional intervention is typically only implemented when oral mucositis has already developed, or severe gastrointestinal reactions cause insufficient intake. Zheng et al. conducted a review to better ascertain the effects of nutritional intervention at different periods of oral mucositis with the purpose to provide a point of reference for the utility of early nutritional intervention strategies in clinical practice [9].

Glutamine

Similar to protein, glutamine is a non-essential amino acid found in abundance within the human body and from food sources high in protein and works as both fuel and nitrogen donor for tissues damaged by chemotherapy and radiation. Glutamine specifically is used for energy for leukocytes to assist with fortifying the mucosa to perform as a barrier against infection and inflammation, in addition to helping with the healing process [10]. Oral supplementation of glutamine in cancer patients to modulate the side effects of chemotherapy and radiation treatment has been studied in many trials. Glutamine demand is increased in catabolic states [4,11]. In addition to possibly reducing the severity of oral mucositis, it may lessen diarrhea and intestinal absorption of nutrients [11]. The plasma level of glutamine may be evaluated in patients via the lab but may significantly vary in cancer patients due to the metabolic effects of cancer cells [11]. Anderson et al. determined that topical oral swish and swallow glutamine and a disaccharide have the potential to ameliorate oral mucositis, as disaccharides have the ability to increase mucosal glutamine absorption and decrease the extent of damage [10].

In a randomized placebo-controlled trial by Widjaja, et al. it was found that the supplementation of oral glutamine at 400 mg/kg body weight once daily in pediatric patients with acute lymphoblastic leukemia

(ALL) being treated with high dose Methotrexate therapy significantly reduced the development of oral mucositis and was directly associated with its prevention [12]. Limitations of this study include a small sample size of patients and the concentration on ALL [12]. However, in a narrative review by Garcia-Gozalbo and Cabanas-Alite completed in adults between the ages of 19-70 years old, results were varied on the effectiveness of glutamine supplementation when clinical trials were evaluated [4]. Of note in this narrative review, two supplemental formulations that are enriched with glutamine were evaluated and showed a decrease in oral mucositis severity [4]. These studies demonstrate the possible effectiveness of glutamine in the prevention and severity reduction of oral mucositis.

The Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) completed a new systematic review in 2020 to update clinicians on the current guidelines of the management of oral mucositis and, in respect to glutamine, recommends 10-30 mg daily of oral glutamine supplementation in the management of oral mucositis due to chemotherapy or radiation therapy². There is also strong caution against the use of parenteral glutamine in the management of these patients, as a higher mortality rate is seen². In conclusion, oral glutamine supplementation in pediatric and adult patients undergoing chemotherapy or radiotherapy can be recommended at the doses aforementioned to prevent and mitigate oral mucositis.

Liquid Diets

Whether induced by chemotherapy or radiation, patients experiencing mucositis must adjust their diet to minimize further irritation and trauma to the mucosa. This involves avoiding acidic, spicy, sharp, or rough-textured foods. The primary goal is to maintain oral feeding, as the use of enteral nutrition and parenteral venous nutrition is not the optimal choice initially. The preferred first-line approach involves applying local anesthetics like 2% viscous lidocaine in a swish-and-spit manner prior to eating [13]. Additionally, opting for liquid or semi-solid foods that are rich in calories and protein is essential, as protein has demonstrated the ability to uphold mucosal integrity and facilitate the repair of mucosal lesions [14]. In cases where sustaining oral intake cannot be maintained, enteral nutrition is preferred over parenteral nutrition.

The preference for enteral nutrition as a second-line dietary recommendation for mucositis patients is rooted in its physiological compatibility, as it preserves gastrointestinal integrity. Enteral nutrition can be administered through various methods, including nasogastric tubes, nasojejunal tubes, gastrostomy, and jejunostomy. Each method has its own set of advantages and disadvantages, and the choice is typically based on factors such as the estimated duration of use, patient preference, and contraindications. Regarding specific nutritional parameters, a personalized approach and dietary assessment by nutrition specialists are crucial for ensuring an adequate supply of both macro and micronutrients. Prophylactic administration of enteral nutrition, in particular, has shown promising results in reducing or preventing weight loss, sarcopenia, and dehydration, thus lowering hospital admissions and enhancing overall quality of life [15]. If enteral nutrition is compromised in any way, or if the patient lacks an intact gastrointestinal tract, then, as a last resort to urgently maintain feeding, parenteral nutrition can be employed. However, due to the higher risk of infection, increased cost, and greater fluctuation in essential solutes like potassium, phosphorus, and magnesium in the patient's blood, parenteral nutrition is typically reserved for situations where no other option is available. Consequently, as soon as hindrances to enteral or oral feeding are resolved, patients are often transitioned away from parenteral nutrition quite promptly. Until this transition is feasible, various studies recommend a gradual introduction, starting with 15–20 calories per kg of body weight per day, with a maximum of 1000 calories a day, up to 25 kcal/kg of ideal body weight, to achieve optimal parenteral nutrition parameters [15].

Adequate Hydration

Oral hydration plays a crucial role in preventing and alleviating pain associated with oral mucositis. Recent studies have highlighted a positive connection between dehydration and the severity of oral mucositis [16]. When patients experience severe pain, they often respond by reducing their fluid intake, leading to dehydration. Consequently, patients may develop symptoms like orthostasis and reduced renal function, often necessitating hospitalization for intravenous fluid rehydration. Emerging literature now suggests that intervening with intravenous hydration before patients exhibit late-stage symptoms, as described above, can even alleviate initial oral

mucositis pain, thereby reducing the need for hospitalization or the administration of feeding tubes. This underscores the importance of adequate hydration, not only for its well-known benefits in lubrication and reducing inflammation, but also as a pain reliever that enables patients to maintain oral hydration and calorie intake. Additional hydration methods, like using ice chips for lubrication and a numbing effect, as well as artificial saliva to prevent dry mouth and subsequent cracking, can also provide relief from discomfort in cases of mucositis.

Others

The realm of preventing and treating oral mucositis remains dynamic, with ongoing studies exploring novel remedies. Zinc is another mineral supplement that has been implicated for the use of oral mucositis prevention. According to a meta-analysis conducted by Liu et al, they evaluated patients undergoing chemotherapy and/or radiation therapy for head and neck cancer [17]. Zinc is naturally present in saliva, dental plaque, and hard tissues and zinc deficiency is associated with poor oral and periodontal health. It is also known to participate in wound healing as a necessary cofactor and has anti-inflammatory properties. According to this meta-analysis study, the overall incidence of oral mucositis was 30.5% in the zinc intervention group and 51.3% in the control group; however, when stratified by type of treatment there was no significant difference. When they are grouped for all types of cancer therapy, a beneficial effect was observed with relative risk 0.67 and a p-value of 0.03 [17].

Omega-3, recognized for its anti-inflammatory properties, antioxidant functions, and early wound healing capabilities attributed to EPA and DHA, works at the cellular level to maintain epithelial integrity and cell barrier function. This is achieved by averting disruptions in tight junction structure and reducing cell necrosis [18]. A recent randomized controlled trial demonstrated that when omega-3 was formulated into a nanoemulgel and applied topically to patients, it led to a notable reduction in both the incidence and severity of oral mucositis [19]. Additionally, the omega-3 nanoemulgel exhibited a

capacity to manage oral bacterial dysbiosis, specifically influencing the abundance and diversity of microbes, a topic of increasing interest due to its potential link with oral mucositis.

The microbiome is a subject of extensive research, showing promise not only in improving the tolerance of cancer treatment side effects but also in enhancing the effectiveness of chemotherapy, immunotherapy, or radiation therapy in reducing tumor burden. Recent findings emphasize the potential of probiotics in bolstering immune responses during cancer treatment, notably in reducing the severity of oral mucositis (OM) [20]. The evidence points to specific probiotic combinations, including *L. plantarum*, *B. animalis*, *Lactis LPL-RH*, *L. rhamnosus*, and *L. acidophilus*, as promising interventions for mitigating cancer treatment-related side effects, particularly in patients with oral mucositis and nasopharyngeal carcinoma (NPC) [21]. These insights underscore the growing importance of probiotics in supporting patients' immune systems during cancer therapy and in modulating toxic side effects like oral mucositis.

Photo biomodulation or low-level laser therapy has shown promise in recent years for prevention of oral mucositis; however, due to its complicated intricacies and multiple parameters, it has not efficiently been implemented in clinical practice. A systematic review by Labrosse, et. al. confirmed two main objectives surrounding PBM: primarily, its place in treatment of oral mucositis and secondarily, the optimal parameters for which it could be replicated in practice [21]. PBM positively treated patients in three-quarters of the studies examined. However, the favorable impact of PBM on pain reduction, analgesic consumption, and patient compliance in radiation therapy (RT) and RT/CT warrants further investigation [22]. Additionally, establishing optimal PBM parameters is challenging due to the diversity of settings, assessment methods for oral mucositis and pain, and the absence of data on analgesic usage and long-term carcinological follow-up. To address these challenges and establish a standardized protocol, future studies should harmonize endpoints and follow-up criteria [22].

Table 1: Alternative Approaches to Manage Oral Mucositis

Treatment modality	Purpose	MASCC/ISOO Guideline Category	Reason	Further Specifications
Cryotherapy [23]	Prevention	Recommendation	Cold-induced local vasoconstriction limits delivery of the chemotherapeutic agent to the oral mucosa	In patients receiving bolus doses of 5-fluorouracil and in patients undergoing autologous HCT conditioned with high-dose melphalan.
Benzydamine 0.15% mouthwash [2]	Prevention	Recommendation/ Suggestion	Anti-inflammatory	Effectively prevents oral mucositis in patients who receive up to 50 Gy RT or CRT. For example, it may be beneficial for patients undergoing palliative RT or RT to the H&N for lymphoma.
KGF-1 [24]	Prevention	Recommendation	Stimulates the proliferation and differentiation of epithelial cells; KGF-1 has antiapoptotic, antioxidant, and anti-proinflammatory effects, inducing tissue protection.	In patients receiving high-dose chemotherapy and TBI-based conditioning regimens before autologous HCT.

Note: Adapted from Elad, S.; Yarom, N.; Zadik, Y.; Kuten-Shorrer, M.; Sonis, S.T. The broadening scope of oral mucositis and oral ulcerative mucosal toxicities of anticancer therapies. *CA Cancer J. Clin.* 2022, 72, 57–77 [25].

Table 1 refers to additional alternative approaches to preventing oral mucositis, as outlined in the evidence-based guidelines from the MASCC/ISOO. These guidelines indicate whether these approaches are suggested or recommended for specific patient populations. Our summary highlights the broad spectrum of treatment modalities that are currently being employed and studied to reduce the burden of oral mucositis in cancer patients undergoing chemoradiation therapy.

Limitations

Methodologic limitations of our literature review on dietary and nutritional recommendations for patients with oral mucositis secondary to cancer treatment therapies must be addressed. The studies included within this review intentionally only included newer literature reviews and clinical trials that took place after 2020. We analyzed the data and literature primarily over the last three years in order to have the most up-to-date and current review on the topic. Furthermore, we only included literature reviews and clinical trial studies that were written or translated to English. Our selection of articles included within our

review may have selection bias present due to the time frame and language preference, as there have been additional studies on this topic in other languages and numerous studies written about diet and nutrition on oral mucositis prior to 2020. Lastly, there is a paucity of research on specific nutritional interventions in large clinical trial settings and additional scientific literature is needed to affirm solid conclusions on the findings we have reviewed and studied.

Conclusion

Radiation and chemotherapy-induced oral mucositis and malnutrition have a significant impact on the quality of life and overall health of patients receiving cancer therapy. Numerous recent studies have indicated that early and consistent nutritional and dietary intervention improves oral mucositis, nutritional status, and mucosal healing. Additional prospective randomized clinical trials would be useful to conduct worldwide to assess the effects of nutritional interventions on oral mucositis for patients receiving radiation therapy, chemotherapy, or combined therapies. Identifying, comparing, and evaluating nutritional interventions on the

improvement of nutritional status, mucosal health, and overall quality of life is essential in developing holistic and easily accessible treatment modalities as recommendations for patients undergoing cancer treatment.

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