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Updates on the potency and mechanism of glutamine supplementation in oral mucositis management: A narrative review

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Abstract

Introduction: Chemotherapy and head-and-neck radiotherapy administered to cancer patients can lead to the development of oral mucositis (OM), a condition characterized by extensive and excruciating damage to the oral mucosal tissues. Glutamine, an essential amino acid, plays a crucial role in various facets of cellular metabolism, particularly in cell proliferation, wound healing, and leukocyte function, and has been reported to have preventive and therapeutic benefits in oral mucositis.

Objective: This study aims to comprehensively review current findings on the potential clinical applications and mechanisms of glutamine in the management of oral mucositis.

Review: Several studies have demonstrated the efficacy of glutamine supplementation in diminishing the severity of OM and expediting the healing process. This positive effect is attributed to the modulation of inflammation and the stimulation of pro-regenerative activity in keratinocytes and fibroblasts. Furthermore, glutamine intervention enhances the overall nutritional status of patients, reducing the risk of complications commonly observed in cancer patients. Additionally, it plays a pivotal role in preventing or ameliorating the conditions of sarcopenia and lymphopenia.

Conclusion: Glutamine supplementation emerges as a promising intervention for the management of oral mucositis in patients undergoing chemotherapy or head-and-neck radiotherapy. Its multifaceted impact, including inflammation modulation, pro-regenerative activity, and improvement in nutritional status, positions glutamine as a valuable component in the comprehensive care of cancer patients experiencing oral mucositis.

Keywords: Oral Mucositis; Glutamine; Cancer; Radiotherapy; Chemotherapy

1. Introduction

In the current landscape of cancer management, cytotoxic drugs and radiotherapy remain pivotal treatment modalities [1]. These approaches target rapidly dividing cells, affecting both cancerous and somatic cells [2]. However, a significant drawback of these therapies is the development of oral mucositis (OM), characterized by tissue damage and inflammation of the oral mucosa. The symptoms associated with OM can profoundly impact the well-being of individuals undergoing cancer treatment, affecting both their physical and psychological dimensions. OM not only diminishes the quality of life for patients but also elevates the risk of infections, disrupts treatment schedules, jeopardizes the success of cancer therapy, and necessitates hospitalization, thereby increasing overall treatment costs [3,4].

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To address these challenges, effective management strategies are imperative, aiming to alleviate symptoms and expedite the healing process from tissue damage [3,4]. An intriguing avenue in this regard is the role of glutamine, an amino acid with physiological significance in cell proliferation and wound healing. Numerous clinical studies have explored the potential benefits of glutamine supplementation in diverse cancer populations experiencing OM, consistently demonstrating its positive impact on the resolution of OM symptoms [4,5].

Building upon these findings, this paper delves into the discussion of the role and mechanism of glutamine supplementation in the management of OM, specifically in chemotherapy and head-and-neck radiotherapy patients [4,5]. Through a comprehensive exploration of the existing literature, we aim to contribute insights into the potential of glutamine as a valuable adjunct in mitigating the adverse effects of cancer treatment on the oral mucosa.

2. Discussion

2.1. Oral Mucositis

Oral mucositis (OM) is characterized as damage to the oral mucosa, a secondary effect of chemotherapy or radiotherapy in the head-neck region. This condition involves atrophy of the epithelium, vascular damage, inflammatory cell infiltration, and ulceration [1]. Approximately 20-80% of patients undergoing chemotherapy will experience OM, and nearly all patients receiving head and neck radiotherapy will develop it [2,3]. OM is a highly painful condition that hampers activities related to the stomatognathic system, including speaking, processing food, eating, and maintaining oral hygiene, thereby negatively impacting the quality of life [4,5]. A study by Bellm et al. (2000) emphasized that patients perceive OM as the most severe complication they experience during treatment [6].

Clinically, the onset of OM depends on the type of therapy. Radiotherapy-induced OM typically manifests about 2-3 weeks after treatment initiation (at an accumulative radiation dose of 16-22 Gy) and worsens during the 6-7 weeks of treatment [8]. After the cessation of radiotherapy sessions, OM gradually heals within a few weeks. In contrast, in patients receiving chemotherapy, OM appears within a few days after treatment initiation. The duration is shorter than radiotherapy, and the recovery time is within a few days [8].

There are two categories of risk factors for OM: therapy-related factors (dose, location, duration of chemotherapy, and simultaneous use of chemotherapy and radiation) and patient-related factors (tobacco use, neutropenia, age, nutritional status, gender, oral hygiene and health, and genetic factors). Genetic factors, such as polymorphisms and deficiencies in drug-metabolizing enzymes, epigenetic factors, and genetic abnormalities related to the expression or activity of cytokines and transcription factors (e.g., TGF-β, NF-κB, p53, COX-2, and MMPs), also contribute to the pathogenesis of OM [9].

Lesions in the form of erythema, erosion, or ulceration may occur throughout the oral mucosa, oropharynx, and hypopharynx in OM. Patients may experience clinical symptoms such as ulceration, severe pain, dysphagia, xerostomia, difficulty speaking, odynophagia, decreased appetite, and bleeding. The World Health Organization (WHO) classifies the severity of OM based on the clinical picture and symptoms, as presented in Table 1 [9]. Ulcer formation can serve as a gateway for pathogenic microbes, leading to secondary infections. In cancer patients undergoing chemotherapy/radiotherapy, these infections may escalate into invasive infections due to the immunosuppressive effects of these drugs, which suppress the development of immune cells [10].

2.2. Pathogenesis of Oral Mucositis

The pathogenesis of oral mucositis (OM) is associated with direct or indirect mucosatoxicity caused by ionizing radiation in radiotherapy and cytotoxic drugs such as methotrexate, doxorubicin, 5-fluoroacil, busulfan, bleomycin, cisplatin, carboplatin, etoposide, EGFR inhibitors, and some types of tyrosine kinase inhibitors. There are two mechanisms that can occur in the pathogenesis of OM, namely the direct mechanism and the indirect mechanism of cytotoxic drugs or ionizing radiation in intervening in the division and maturation of epithelial cells. Both mechanisms will be explained in more detail [9]:

2.3. Direct Mechanism

In this mechanism, cytotoxic drugs and ionizing radiation can directly interfere with the biological activity of cells, particularly during the stages of division and maturation. As cells with a rapid turnover rate (approximately 7-14 days), epithelial cells are among the most vulnerable to undergo apoptosis as an effect of these medications.

2.4. Indirect Mechanism

This mechanism explains that chemotherapy or radiotherapy can induce and exacerbate the condition of OM through the induction of macrophages and neutrophils to release pro-inflammatory cytokines such as tumor necrosis factor (TNF), interleukin-1 beta (IL-1β), and IL-6. Additionally, there is a decrease in major anti-inflammatory cytokines such as IL-10 and transforming growth factor beta (TGF-β). These conditions contribute to the worsening inflammation and tissue damage that occurs in OM.

Sonis (2004) proposed a five-stage model for the indirect mechanism of oral mucositis (OM) pathogenesis. The detailed stages are outlined below [11]:

2.4.1. Initiation

Chemotherapy or radiotherapy induces the formation of reactive oxygen species (ROS) and lipid peroxidation leading to DNA damage. Excessive ROS generates oxidative stress, causing cell damage and the formation of damage-associated molecular patterns (DAMP).

2.4.2. Signalling

DAMPs are molecules recognizable by pattern recognition receptors (PRRs) in various innate immune cells, such as macrophages. The interaction between DAMPs and PRRs activates macrophages, triggering the release of various inflammatory mediators. Additionally, ROS can stimulate the activation of the NF-κB signaling pathway, inducing the production of pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6.

2.4.3. Amplification

Pro-inflammatory cytokines amplify signals, further activating macrophages and neutrophils. The activities of these immune cells can cause more severe tissue damage, activate cytotoxic immune cells (natural killer (NK) cells and CD8+ T lymphocytes), increase vascular permeability, and activate cyclooxygenase-2 (COX-2) enzymes.

2.4.4. Ulceration

Extensive tissue damage leads to ulceration, providing entry points for microorganisms that trigger further immune responses. Microorganism components can be recognized as pathogen-associated molecular patterns (PAMPs) by PRRs. The interaction between these molecules can activate various signaling pathways related to inflammation.

2.4.5. Healing

Diminishing inflammation mediated by various factors, particularly the polarization of macrophages from M1 to M2, stimulates healing. M2 macrophages, or alternative-activated macrophages, exhibit anti-inflammatory and pro-regenerative characteristics. These cells function by releasing various growth factors such as FGF, KGF, VEGF, and HGF, triggering wound healing activities such as angiogenesis, fibroplasia, and re-epithelialization.

2.5. Glutamine

Glutamine is a non-essential amino acid that plays a crucial role as a nitrogen donor in intracellular metabolism. It is abundantly present in its free form in plasma and erythrocytes, and it is the amino acid with the highest concentration in muscles compared to other amino acids. In addition to its role in intracellular metabolism, glutamine contributes to cell proliferation and serves as the primary energy source in the metabolism of various cells with a high turnover rate (e.g., epithelial cells, leukocytes) [10].

2.6. Nutritional Status of Glutamine in Cancer Patients Receiving Chemotherapy and/or Radiotherapy

Glutamine plays a central role in nitrogen homeostasis, and a catabolic state can decrease intracellular glutamine levels (muscles) by more than 50% and plasma glutamine levels by 20-30%. Catabolic conditions induced by cancer, nausea, cellular injury, or poor enteral glutamine intake can lead to a decline in nutritional status, disrupting various physiological systems in the body [10,12]. Glutamine is crucial in various cellular metabolisms, particularly in tissues that either consume glutamine (high glutaminase activity in most organs, leukocytes, and fibroblasts) or export glutamine (high glutamine synthetase activity in muscles and the brain) [13]. Reduced nutrient intake and loss of body composition, especially muscle loss in cancer patients, can lead to a deficiency in glutamine. Glutamine serves as the primary energy source for lymphocytes and cells in the gastrointestinal tract, contributing significantly to cellular immunity and mucosal health [14].

2.7. Clinical evidence of Glutamine in Oral Mucositis Management

Several clinical studies have evaluated the use of glutamine to prevent or treat oral mucositis (OM) in various cancer populations. The Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) has published a systematic review on various interventions for OM and evidence-based clinical practice guidelines [10]. This includes new guidelines related to glutamine. For patients undergoing chemotherapy and simultaneous radiation for head and neck cancer, it is recommended to use oral (PO) and/or glutamine mouthwash for OM prevention [10-14]. This recommendation is based on Level II evidence derived from two randomized controlled trials (RCTs). Chattopadhyay et al. (2014) and Tsujimoto et al. (2015) reported that oral glutamine use significantly reduced the severity of OM [13,14]. Additionally, glutamine use also reduced the duration of OM and pain in research studies. In one study of head and neck cancer patients, glutamine was administered as an oral "swish and swallow" formulation, suggesting a potential topical application effect [16]. Several RCTs investigated the effects of parenteral glutamine on OM. The results showed that four RCTs stated that glutamine administration had no beneficial effects, while only two RCTs reported that parenteral glutamine was effective in managing OM [10]. From these studies, the MASCC/ISOO panel does not recommend the use of parenteral glutamine in OM management. Indications from various studies suggest that oral or swish-and-swallow glutamine administration may be a beneficial method in OM management [17].

According to a study by Anderson & Lalla (2020), the role played by glutamine in supporting OM healing is its ability to induce epithelial cell activity and enhance mucosal immune function [10]. A study by Todorova et al. (2003) reported that glutamine can reduce pro-inflammatory cytokines in normal cells and increase pro-apoptotic proteins in tumor cells [18]. Additionally, glutamine supplementation can support increased glutathione synthesis, an enzyme crucial for tissue detoxification. Tissue damage caused by chemotherapy or radiotherapy can result from excessive ROS formation in tissues. Increased glutathione in tissues can reduce oxidative stress levels and tissue damage, supporting wound healing [19-21].

The required amount of glutamine for a healthy population in a normal diet is around 10 g/day [22]. For patients in catabolic conditions, such as cancer patients undergoing chemotherapy/radiotherapy, a higher amount of glutamine is needed, considering the increased needs of mucosal and leukocyte tissues for glutamine [22,23]. Glutamine or protein deficiency can lead to conditions such as sarcopenia and lymphopenia, increasing the risk of complications and higher mortality. Therefore, it is recommended that patients in such conditions consume 20-40 g/day of glutamine from their diet. Topical glutamine supplementation + disaccharide (e.g., trehalose, sucrose) that is safe and rational can be given at 4 g per topical use (swish and swallow) performed twice a day. The addition of disaccharide to glutamine supplementation is necessary to enhance glutamine absorption in the mucosa, where glutamine is absorbed more than 100 times compared to single glutamine use [10,24,25].

3. Conclusion

The topical treatment of glutamine independently or in combination with disaccharides, such as trehalose and sucrose, holds promise in alleviating the severity and symptoms of oral mucositis (OM) in cancer patients undergoing chemotherapy or head-and-neck radiotherapy. Glutamine supplementation plays a crucial role in mitigating inflammation by modulating resident immune cells. Additionally, it aids in the wound healing process by enhancing the capabilities of epithelial and fibroblast cells to heal wounds. Furthermore, it optimizes mucosal immunity, empowering the system to effectively combat pathogens.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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