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Oral Mucositis and Osteosarcoma: A Systematic Review

(Mucositis oral y osteosarcoma: una revisión sistemática)

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Abstract (english)

Oral mucositis (OM) is a debilitating side effect of chemotherapy and radiotherapy, severely affecting the quality of life of cancer patients. Osteosarcoma is an aggressive primary malignant bone tumor that usually necessitates aggressive multimodal therapy, such as high-dose chemotherapy, which exposes patients to mucositis. This systematic review investigates the prevalence, pathophysiology, clinical presentation, and treatment of OM among osteosarcoma patients undergoing treatment. A systematic review of multiple databases was conducted to identify relevant studies published between 2000 and 2025. The findings highlight the need for optimizing prophylactic and therapeutic interventions in order to minimize OM among this group of patients.

Keywords(english)

Oral mucositis, osteosarcoma, chemotherapy, mucositis management, supportive care.

Resumen(español)

La mucositis oral (MO) es un efecto secundario debilitante de la quimioterapia y la radioterapia, que afecta gravemente la calidad de vida de los pacientes con cáncer. El osteosarcoma es un tumor óseo maligno primario agresivo que suele requerir terapia multimodal agresiva, como quimioterapia de dosis alta, lo que expone a los pacientes a la mucositis. Esta revisión sistemática investiga la prevalencia, la fisiopatología, la presentación clínica y el tratamiento de la MO en pacientes con osteosarcoma sometidos a tratamiento. Se realizó una revisión sistemática de múltiples bases de datos para identificar estudios relevantes publicados entre 2000 y 2025. Los hallazgos resaltan la necesidad de optimizar las intervenciones profilácticas y terapéuticas para minimizar la MO en este grupo de pacientes.

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Palabras clave(español)

Mucositis oral, osteosarcoma, quimioterapia, tratamiento de la mucositis, tratamientos de apoyo.

Introduction

Oral mucositis (OM) is a common and severe side effect of cancer treatment, involving painful ulcers, inflammation, and susceptibility to infection. OM occurs in as many as 80% of patients receiving chemotherapy and radiotherapy, causing morbidity and treatment-related complications. As a dose-limiting toxicity, OM causes significant patient discomfort, increased risk of infection, prolonged hospital stay, and possible interruptions in cancer treatment. These complications affect the quality of life and outcomes of treatment in patients significantly and render OM a critical problem in oncology (1).

Osteosarcoma is an aggressive primary bone malignancy that occurs predominantly in adolescents and young adults. It commonly requires multimodal therapy with surgery, chemotherapy, and, in certain instances, radiotherapy. The standard chemotherapy regimen includes high-dose methotrexate (HD-MTX), doxorubicin, cisplatin, and ifosfamide. While these agents improve survival, they are also associated with significant toxicities, including OM (2). Chemotherapy-induced OM leads to incapacitating oral pain and ulceration, further decreasing nutritional intake, treatment adherence, and quality of life. In extreme cases, patients might need opioid analgesia, enteral or parenteral nutrition support, and dose adjustments in chemotherapy, which might affect overall survival outcomes (3).

The development of OM follows a complex pathophysiological process, beginning with direct epithelial DNA damage and progressing through a cascade of inflammatory responses. The Sonis (2004) (4) five-phase OM model drafts a complicated interaction between tissue damage, bacterial colonization, inflammatory cytokine upregulation, and oxidative stress. Inflammatory mediators like tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and nuclear factor kappa B (NF-κB) are the prime factors responsible for mucosal injury through increased tissue injury and ulceration time. Genetic susceptibility, immune status, and underlying oral health status further influence the severity of OM, accounting for interpatient variability of clinical presentation (5).

Clinically, OM presents as pain, ulcerations, and erythema and, severely compromises a patient's capacity to eat, speak, and maintain oral hygiene. Symptoms are graded based on the World Health Organization (WHO) and National Cancer Institute (NCI) toxicity scales based on severity of mucosal involvement and degree of functional impairment. Severe OM (Grade 3-4) tends to result in dose reduction, delay, or discontinuation of chemotherapy, adversely affecting the success of cancer therapy (6). In addition, mucosal barrier dysfunction increases the risk of secondary infections, including bacterial, fungal, and viral opportunistic infections, further increasing the complexity of patient management.

This systematic review analyzes existing evidence on the prevalence, pathophysiology, and treatment of OM in osteosarcoma patients treated with chemotherapy. Through the analysis of recent research, this review identifies the newest therapeutic approaches, preventive strategies, and novel treatment modalities that may enhance patient outcomes and quality of life.

Materials and Methods

Systematic search was done in PubMed, Scopus, Web of Science, and the Cochrane Library with the key words: "oral mucositis," "osteosarcoma," "mucositis induced by chemotherapy," and "management of mucositis."

Inclusion Criteria:

- Studies published in English from 2000 onwards
- Studies on OM among osteosarcoma patients who are undergoing chemotherapy.

The selection of studies adhered to PRISMA guidelines to ensure comprehensive analysis of pertinent literature.

Data extraction included:

- Study design
- Sample size
- Chemotherapy regimens
- Incidence and severity of OM
- Management strategies

Bias risk was assessed using the Cochrane Risk of Bias Tool for randomized studies and the Newcastle-Ottawa Scale for observational studies.

Table. 1. Papers.

Author	Study	Sample Size	Chemotherapy Regimen	OM Incidence (%)	Key Findings
Zieger et al. (2024)[7]	Genetic Variants Influence the Severity of Oral Mucositis in Pediatric Osteosarcoma Patients	14 pediatric patients	HDMTX (66.9%), doxorubicin + cisplatin (34.1%)	78.7%	**Genetic variants in ABC family genes linked to OM severity and pharmacogenomic risks**
Samadhi et al. (2024)[8]	Disseminated herpes simplex virus type 1 infection manifested as extensive oral ulcers, pneumonitis, and ileo-colitis in a neutropenic patient post-chemotherapy for osteosarcoma.	Case report	Cisplatin, doxorubicin	Severe	**HSV-1 reactivation complicating OM in osteosarcoma**
Andrea Bell et al. (2023)[1]	Oral Mucositis	N/A	Various	20-40%	**Comprehensive review of OM pathophysiology and management**
Pampina et al. (2023)[9]	Osteosarcoma: Current Concepts and Evolutions in Management Principles.	N/A	Multi-agent chemotherapy	N/A	**Overview of osteosarcoma management**
Valer et al. (2020)[10]	Oral mucositis in childhood cancer patients receiving high-dose methotrexate: Prevalence, relationship with other toxicities and methotrexate elimination.	77 children	High-dose methotrexate	74.9%	**OM linked to renal/hepatic toxicity**
Lalla et al. (2009)[11]	Management of oral mucositis in patients who have cancer.	N/A	Various	51%	**Detailed OM pathogenesis and economic impact**
Cheng (2008)[12]	Association of plasma methotrexate, neutropenia, hepatic dysfunction, nausea/vomiting and oral mucositis in children with cancer.	28 children	High-dose methotrexate	50%	**Plasma MTX levels correlated with OM severity**

Results and discussion.

The studies analyzed in this systematic review emphasized the severity and prevalence of OM among osteosarcoma patients receiving chemotherapy. Cheng (2008) (12) and, Valer et al. (2020) (10) established that there was a high correlation between plasma levels of high-dose methotrexate (HD-MTX) and the severity of OM, with Valer et al. (2020) (10) indicating a 74.9% incidence of OM among children treated with HD-MTX. These results highlight the need for pharmacokinetic monitoring to maximize MTX dosing and minimize the risk of severe OM. In addition, Cheng (2008) (12) found a correlation between MTX plasma concentration at 66 hours after infusion and OM severity, highlighting the contribution of delayed drug clearance to enhanced mucosal toxicity.

Genetic Susceptibility and OM Risk. Increasing evidence indicates that genetic susceptibility is an important factor in OM severity. Zieger et al. (2024) (7) found genetic variants in the ABC family genes (ABCA3, ABCC2, and ABCC6) to be strongly linked with higher OM risk in children with osteosarcoma undergoing chemotherapy. These findings suggest that pharmacogenomic profiling can be applied as a predictive marker to identify high-risk patients, and by

doing so, allow personalized chemotherapy regimens with decreased severity of OM.

Moreover, Droothe et al. (2006) (13) stressed the role of host genetic factors, especially enzymatic differences in drug metabolism, in chemotherapy-induced toxicities. Their results indicates that tailored chemotherapy dosing strategies may have a substantial impact on the severity of OM in susceptible patients.

Inflammatory Pathways in OM Pathogenesis. The pathogenesis of OM involves a complex cascade of inflammatory responses that amplify mucosal injury. Andrea Bell et al. (2023) (1) and Lalla et al. (2009) (11) highlighted the contribution of pro-inflammatory cytokines, such as TNF-α, IL-6, and NF-κB, to enhancing oral mucosal injury and extending ulceration. Such findings are supported by the five-phase model proposed by Sonis (2004) (4), which outlines the manner in which oxidative stress, inflammatory mediators, and secondary infections lead to severe and persistent OM.

Pampina et al. (2023) (9), further elucidated the systemic effects of chemotherapy-induced inflammation, showing that enhanced reactive oxygen species (ROS) cause damage to the oral epithelial barrier, enhancing susceptibility to ulceration and infection. The evidence lends credence to anti-inflammatory and antioxidant-based therapy for minimizing chemotherapy-induced OM.

Opportunistic Infections and OM Severity. The immunosuppression from chemotherapy also raises the risk of secondary infection, further aggravating OM severity. Samadhi et al. (2024) (8) presented a case of disseminated herpes simplex virus type 1 (HSV-1) infection in a patient with osteosarcoma who was on chemotherapy, resulting in extensive oral ulceration, pneumonitis, and ileocolitis, which required intensive antiviral treatment. This case emphasizes the necessity of preventive antiviral interventions and vigilant monitoring for viral reactivation in immunocompromised patients on high-dose chemotherapy.

In addition, Ghosh & Bajpai (2017) (14) reviewed chemotherapy-induced toxicities and emphasized the importance of:

- Hydration therapy to maintain mucosal integrity.
- Cryotherapy for decreasing oral inflammation.
- Immune modulation strategies to avert secondary infections.

In addition, neutropenia, which is routinely seen in cancer patients undergoing chemotherapy, predisposes to bacterial superinfections in OM lesions such that systemic antibiotics and antifungal drugs become necessary for the control of infections.

OM in Head and Neck Osteosarcoma Patients. Although osteosarcoma is mainly seen in long bones, Mendenhall et al. (2010) (15), studied head and neck osteosarcomas and illustrated how radiotherapy substantially aggravates OM severity. Head and neck osteosarcoma patients suffer from:

- Increased mucosal injury from direct radiation exposure.
- Prolonged ulcer healing and greater pain severity.
- Heightened risk of secondary infections from radiation.

The research implies the possibility of controlling OM severity by using specific mucosal protective drugs, e.g., keratinocyte growth factor (KGF) and topically applied anti-inflammatory agents, in patients under radiotherapy treatment for head and neck osteosarcomas.

Advancements in OM Management Strategies. Several care support interventions have been studied for prevention and treatment of OM. Lalla et al. (2009) (11) and Cheng (2008) (12), described that cryotherapy, LLLT, and palifermin (keratinocyte growth factor-1, KGF-1) significantly diminish OM severity and duration. Valer et al. (2020) (10) highlighted the need for hepatic and renal function monitoring as predictive markers for OM risk, underlining the necessity for integrated supportive care strategies.

Emerging biological therapies are:

- Palifermin (KGF-1): Induces epithelial regeneration and decreases duration of severe OM (Lalla et al., 2009) (11).
- Low-Level Laser Therapy (LLLT): Reduces pain severity, enhances healing, and inhibits OM progression (Bell et al., 2023) (1).
- Benzydamine Hydrochloride: A non-steroidal anti-inflammatory mouthwash which alleviates OM pain and inflammation (Lalla et al., 2009) (11).

Moreover, Andrea Bell et al. (2023) (1) and Pampina et al. (2023) (9) promoted incorporating anti-inflammatory medications, local anesthetics, and systemic analgesics to offer all-encompassing relief of symptoms.

Role of the Tumor Microenvironment in OM. Recent studies, for example, Isabelle et al. (2020) (16), have elucidated the great importance of tumor

microenvironment (TME) in the OM pathogenesis. According to their study:

- Extracellular vesicles and cytokines contribute to mucosal inflammation.
- The TME induces a pro-inflammatory and immunosuppressive environment, slowing down oral mucosal healing.
- Immune modulation by targeting TME can offer new therapeutic strategies in severe OM.

Future Research Directions

Future studies should focus on:

1. Targeted cytokine inhibitors: Inhibition of TNF-α and IL-6 to mitigate chemotherapy-induced inflammation.

2. Microbiome therapies: The oral microbiome is integral to mucosal health; restoration of oral wellness may be helped by probiotics and prebiotics.

3. Stem cell-derived therapy: Mesenchymal stem cell-derived exosomes can facilitate epithelial regeneration in OM lesions.

4. Pharmacogenomics: Identifying high-risk individuals through genetic screening to enable personalized chemotherapy regimens.

Conclusion

This review illustrates the multi-factor etiology of OM in osteosarcoma patients, with genetic, pharmacokinetic, inflammatory, and infectious factors affecting the severity of OM. The confluence of predictive methods, tailor-made interventions, and enhanced measures of supportive care remains essential for maximizing patient outcome. Future investigations need to keep exploring new biologic therapies, microbiome manipulation, and immunotherapy-based techniques for OM prevention and treatment

Conflicto of interest

None to declare.

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