HEALING OF ACUTE GINGIVAL LESIONS WITH PHOTOBIOMODULATION AND ANTIMICROBIAL PHOTODYNAMIC THERAPY IN A YOUNG PATIENT UNDERGOING CHEMOTHERAPY: A CASE REPORT WITH TWO YEARS FOLLOW-UP

Cicatrização de lesões gengivais agudas com fotobiomodulação e terapia fotodinâmica antimicrobiana em uma paciente jovem submetida à quimioterapia: relato de caso e acompanhamento de dois anos

Access this article online	
Quick Response Code:	**Website:** https://periodicos.uff.br/ijosd/article/view/62593
	DOI: 10.22409/ijosd.v3i68.62593

Autores:
Caroline Pessoa da Silva
DDS, Private Practice, Rio de Janeiro, RJ, Brazil

Vitor Marcos Barbosa Magalhães Filho
MD, Private Practice, Rio de Janeiro, RJ, Brazil

Elizângela Partata Zuza
Federal University of Uberlândia (UFU), Uberlândia, MG, Brazil

Karla Bianca Fernandes da Costa Fontes
Federal Fluminense University (UFF), Nova Friburgo, RJ, Brazil

Alessandra Areas e Souza
Federal Fluminense University (UFF), Nova Friburgo, RJ, Brazil

Instituição na qual o trabalho foi realizado: Private practice

Endereço para correspondência: Alessandra Areas e SouzaRua Doutor Silvio Henrique Braune, 22, Centro, Nova Friburgo, RJ, Brazil Cep: 28650-625 Tel: 21 98747-6672
E-mail para correspondência: alessandraareas@id.uff.br

RESUMO

Pacientes de todas as idades em tratamento oncológico podem apresentar lesões bucais dolorosas em decorrência dos efeitos da quimioterapia e radioterapia. Tratamentos não invasivos como os lasers podem ser benéficos na melhoria destas condições e, neste contexto, o uso da fotobiomodulação (PBM), isoladamente ou em combinação com a terapia fotodinâmica antimicrobiana (aPDT), pode ter efeitos positivos na cicatrização tecidual, reduzindo dor, edema e inflamação. O objetivo deste relato de caso foi descrever o tratamento de lesões agudas em gengiva inserida, utilizando PBM isoladamente ou em associação com aPDT, em paciente de 23 anos em tratamento quimioterápico para câncer de ovário. O uso de PBM e aPDT mostrou benefícios tanto na melhora de lesões gengivais agudas quanto na prevenção do aparecimento de novas lesões durante a quimioterapia, confirmando seu potencial como terapia auxiliar benéfica no manejo de pacientes com câncer. A intervenção precoce, aos primeiros sintomas das lesões, e também o uso preventivo do laser nos ciclos subsequentes de quimioterapia podem ter sido decisivos para prevenir sequelas periodontais, como recessão gengival, perda de inserção clínica e perda óssea e, também, trouxe conforto e alívio, reduzindo a dor e contribuindo para a cicatrização dos tecidos. Por se tratar de uma terapia de baixo custo e eficaz, seu uso, seguindo os protocolos descritos, deve ser incentivado para melhorar a qualidade de vida dos pacientes durante o tratamento oncológico envolvendo quimioterapia e/ou radioterapia.

Palavras-chave: câncer, quimioterapia, doença gengival, fotobiomodulação, terapia fotodinâmica antimicrobiana.

ABSTRACT

Patients of all ages undergoing cancer treatment can present painful oral lesions as a result of the effects of chemotherapy and radiotherapy. Non-invasive treatments like lasers can be beneficial in improving these conditions and, in this context, the use of photobiomodulation (PBM), alone or in combination with antimicrobial photodynamic therapy (aPDT), can have positive effects on tissue healing, reducing pain, edema and inflammation. The objective of this case report was to describe the treatment of acute lesions in attached gingiva, using PBM alone or in association with aPDT, in a 23-year-old patient undergoing chemotherapy treatment for ovarian cancer. The use of PBM and aPDT showed benefits both in improving acute gingival lesions and in preventing the appearance of new lesions during chemotherapy, confirming its potential as a

beneficial auxiliary therapy for the management of cancer patients. Early intervention, at the first symptoms of the lesions, and also the preventive use of laser in subsequent chemotherapy cycles may have been decisive to prevent periodontal sequelae, such as gingival recession, clinical attachment loss and bone loss and it also brought comfort and relief, by reducing pain and contributing to tissue healing. As it is a low-cost and effective therapy, its use, following described protocols, should be encouraged to improve quality of life of patients during cancer treatment involving chemotherapy and/or radiotherapy.

Key words: cancer, chemotherapy, gingival disease, photobiomodulation, antimicrobial photodynamic therapy.

INTRODUCTION

Photobiomodulation (PBM) is an adjuvant treatment for various mucosal lesions, and can be associated with photodynamic therapy (aPDT), with the use of dyes, such as methylene blue, providing antimicrobial action. The laser promotes tissue repair, as it is capable of inducing an increase in fibroblasts, protein and collagen synthesis, angiogenesis, reduction of edema and repair of nerve fibers, inhibiting proteolytic enzymes and pro-inflammatory cytokines (FIGUEIREDO et al., 2013).

As it is a practical, non-invasive and low-cost method, it has become a frequent indication for the treatment of cancer patients with oral mucositis (PENG et al., 2020; SÁNCHEZ-MARTOS et al., 2023; NASCIMENTO et al., 2023; SHEN et al., 2024). Oral mucositis (OM) is a recurrent complication of chemotherapy and radiotherapy and the lesions usually affect the alveolar and buccal mucosa (SONIS et al., 2003; SROUSSI et al., 2017). There are, however, reports of gingival lesions and periodontal changes in cancer patients, resulting from chemotherapy (KHOURY et al., 2003, STANSBURY et al., 1988, HU et al., 2015; BODDU et al., 2018; EINSFELD et al., 2022). Wounds that appear on the oral mucosa and oropharynx resulting from chemotherapy or radiotherapy cause a lot of pain and discomfort for the patient when eating, which can lead to severe anemic conditions (POULOPOULOS et al., 2017). Therefore, the early action of the health team in monitoring the emergence of oral lesions and their immediate treatment is very important to guarantee the well being of these patients (OWOSHO et al., 2023).

The objective of this case report was to describe the treatment with PBM and aPDT in a young patient undergoing oncological ovary treatment, with lesions on the attached gingiva, triggered by chemotherapy.

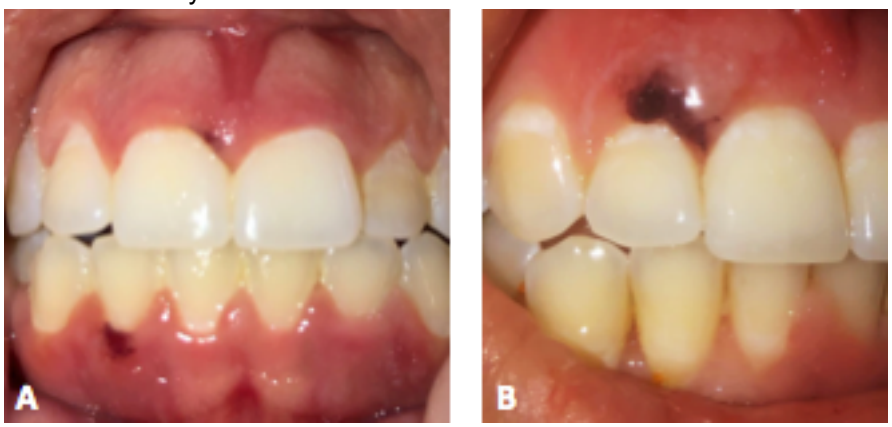
CASE REPORT

The patient in question was treated in accordance with ethical standards and consented to the disclosure of intraoral images relevant to the case. A female patient with 23 years was first submitted to emergency surgery in 2019, due to acute torsion of the right ovary. After surgery, the diagnosis of malignant endodermal sinus tumor or yolk sac tumor in the right ovary was confirmed. She began to be assisted by the oncologist (VMBMF) and underwent adjuvant chemotherapy with the drugs etoposide and cisplatin (EP), for 4 cycles, without oral side effects.

After one year, in 2020, the disease reoccurred in the peritoneum and contralateral ovary, requiring a total hysterectomy and left oophorectomy. The same chemotherapy regimen was performed, due to the favorable previous results. No oral side effects were observed.

After 6 months of the end of the treatment, in 2021, patient presented a new cancer recurrence in the peritoneum, undergoing another chemotherapy regimen with the drugs cisplatin, ifosfamide and paclitaxel (TIP) for 4 cycles. The cycle of this last chemotherapy lasted five days, with the three drugs being administered on the first day, and from the second to the fifth day, only cisplatin and ifosfamide. From the second day onwards, the patient began to experience pain in the attached gingiva and, shortly thereafter, fever. The oncologist administered antibiotics (Clavulanate potassium 875 mg, 1 tablet, 12/12 hours, 7 days). However, from the fourth day of chemotherapy, dark purple spots appeared on the attached gingiva and papillae (Figures 1A, 1B). Within 24 hours, these spots spread in both maxilla and mandible gingiva (Figure 2A).

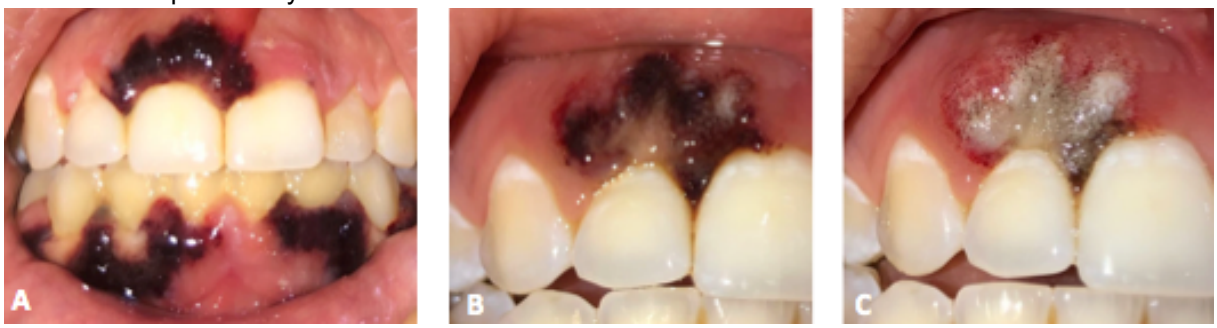
Figure 1. A) Beginning of the gingival lesion with dark stains in day 1; **B)** Evolution of the gingival lesion in a few hours in day 1.



In day 3, these spots evolved to form whitish plaques, with a necrotic appearance (Figure 2B). On day 4, patient felt pain and could not eat properly neither clean her teeth, She photographed her mouth (Figure 2C), sent to the oncologist and were therefore referred to a periodontist (CPS).

After clinical examination, on day 5, an acute gingival lesion induced by chemotherapy was diagnosed. As the lesions did not extend to the mucosa, oral mucositis (OM) was not considered as a definite diagnosis, even though it is a possible one. Lesions were painful and had a necrotic appearance, with a pseudomembrane and an unpleasant odor, clinically similar to necrotizing gingivitis, but without the appearance of papillary loss due to necrosis. As the patient could not undergo any invasive treatment, such as biopsies or procedures that caused bleeding, and because etiologic agent was the chemotherapy, clinical diagnosis was established as acute gingival lesion.

Figure 2. A) Rapid evolution after 24 hours, in attached gingiva and papilla in day 2; **B)** Lesions progressed with pseudomembrane appearance, pain and fever in day 3; **C)** Worsening of the condition and pain in day 4.

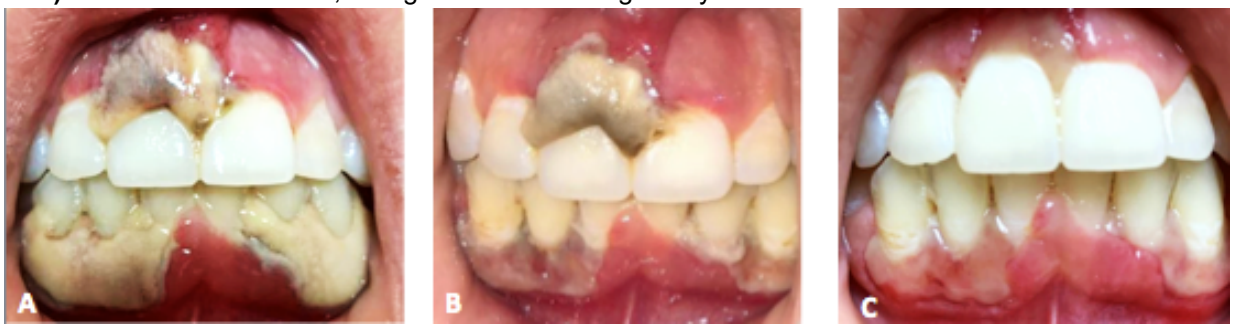


As the patient was symptomatic and there was a contraindication to scrapings and more invasive treatments, it was decided to treat her with laser, using PBM in areas without apparent contamination and aPDT to promote microbial reduction in areas with acute lesions.

In day 5, aPDT application was performed with 0.01% methylene blue solution (Chimiolux 10, DMC, São Paulo, Brasil), applied over the entire length of the whitish plaques (Figure 3A). After five minutes, the photossensitizer excess was removed and tissue was irradiated in several spots, with 1 cm between them, with red diode laser 660nm, Indium Galium Alumínum Phosper (InGaAlP), 100mW, 3mm^2, 9J/spot, 320 J/cm^2, 90 seconds/spot (Therapy EC, São Carlos, São Paulo, Brasil). After aPDT, loose necrotic plaques were carefully removed with a cottom embedded with 10 volume hydrogen peroxyde solution and the patient was instructed to remove dettached plaques the same way when she was home (Figure 3B).

The interval between appointments for aPDT was 48 hours after the appearance of the lesions and the interval increased to 72 hours, from the moment there were no more plaques and dark gingival spots. In the second session, on day 8, healing was satisfactory, but a new session of PBM and aPDT in healing lesions was performed (Figure 3C). With the improvement of the initial acute condition, in the third consultation, 12 days after the onset of the lesions, the patient no longer presented pain and there was clinically visible healing of the gingival tissue, with re-epithelialization of the affected area and the normalization of the pale pink color, indicative of healthy gingival tissue (Figure 4A).

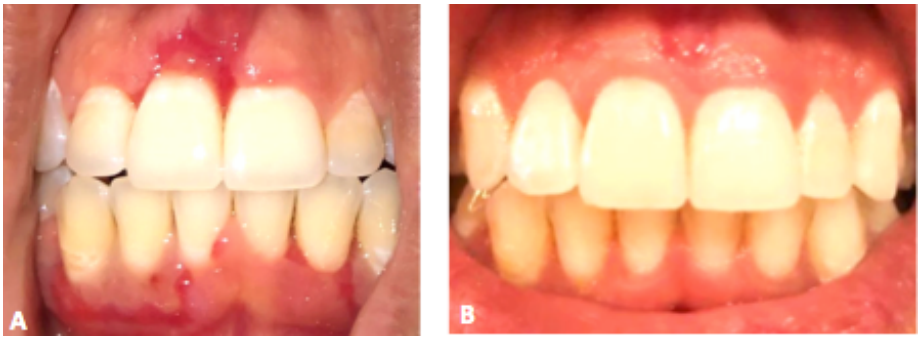
Figure 3. A) First day of aPDT application in day 5. **B)** Detached plaque in the lower arch in day 6. **C)** Second aPDT session, with good tissue healing in day 8.



The patient underwent four cycles of this chemotherapy regimen. For each five-day chemotherapy cycle, there was a fourteen-day interval. No oral treatment was administered during the five days of chemotherapy. During the fourteen-day interval between chemotherapy sessions, patient was monitored and had PBM preventively, with the same protocol described above. In the four cycles, patient presented dark stains on the attached gums and papilla, however the whitish plaques began to appear less intensely, and when they did appear, they were quite small in size.

After 3 months of treatment and 11 applications of aPDT and/or PBM, patient recovered from acute gingival lesions, without any sequelae with the described treatment. After treatment, she presented a healthy periodontium, with normal probing depth, without clinical attachment loss or gingival recessions in any area affected by the lesions. The patient has been under control of her oncological treatment since 2022, and did not have a recurrence of cancer in these last two years (Figura 4B).

Figure 4. A) Tissue appearance in day 12; **B)** Patient under control, two years later.



DISCUSSION

Lesions in the oral cavity of individuals undergoing antineoplastic chemotherapy are frequent complications, due to the high sensitivity of oral tissues and structures to the toxic effects of chemotherapy drugs (SROUSSI et al., 2017, CURRA et al., 2018). Although OM is the most described condition, there are case reports on periodontal involvement and atypical gingival lesions in individuals undergoing chemotherapy (STANSBURY et al., 1988; HU et al., 2015, STOUFI, 2023).

The risk of developing oral complications during chemotherapy varies greatly between patients and the occurrence and severity of lesions appear to be influenced by factors associated with the patient and the treatment regimen (Sonis 2003). Patient-related variables include tumor diagnosis, patient age, sex, patient's oral condition before cancer therapy, level of oral care during therapy, xerostomia, and baseline neutrophil count. Patients with hematologic malignancies, like leukemia and lymphoma have a higher risk of developing oral complications, when compared to patients with solid tumors, except for head and neck tumors. It seems likely that tumor-related myelosuppression is at least partially the basis for this observation (SONIS et al., 2003).

The objective of chemotherapy is to inhibit cell proliferation and tumor multiplication, thus preventing invasion and metastasis, but it also results in toxic effects (CURRA et al., 2018). Chemotherapy drugs attack cancer cells, which divide quickly, but also act on other cells in the body, such as those in the bone marrow, where blood and defense cells are produced, and cells in the lining of the mouth and intestines and hair follicles. The side effects of chemotherapy depend on the type and dose of medication used and the duration of administration. These side effects may include: increased chance of infections, mouth ulcers, bruises or bleeding in the skin and mucous membranes, hair loss, nausea, vomiting, diarrhea, fatigue. Oral complications caused by chemotherapy

include bleeding, mucositis, sensorial disturbances and increased risk of infections due to immunosuppression (ELAD et al., 2017, 2022).

Not all chemotherapy agents are equally toxic or cause the same effects on oral tissues. Agents that frequently generate severe gastrointestinal toxicity and mucositis are methotrexate, 5-fluorouracil, cisplatin, and alkaloids (MCCARTHY et al., 1998; STOUFFI 2023). In the reported case, the drugs used were paclitaxel, ifosfamide and cisplatin, which can be related to the gingival lesion observed.

The role of age as a risk factor for mucositis is unclear. There are few studies that compare the rate of OM among patients of different ages with similar diagnoses. However, the rate of OM among children may be higher than among older patients treated for the same cancer (MCCARTHY et al., 1998). There are reports that the mitotic activity of oral mucosa cells in young patients is significantly greater than in older individuals, which may result in an increased susceptibility of the basal epithelium in young patients. Furthermore, quantification of epithelium-related growth factors has shown higher amounts in younger individuals, which could, in part, be responsible for the rapidity with which these patients recover after ulcerative mucositis compared to older individuals (HU et al., 2015; EINSFELD et al., 2022).

The diagnosis of OM is based on clinical exam and, frequently, lesions appear after a few days of antineoplastic treatment, associated with myelosuppression, direct cytotoxicity through the drugs used in therapy, immunological suppression or hyperactivity. Clinically, there is inflammation and ulceration of the oral mucosa, where it appears edematous, erythematous and friable, associated with pain, discomfort, dysphagia and systemic weakness. In association with neutropenia, the development of infections caused by opportunistic microorganisms such as Candida Albicans, Herpes Simplex, Varicella Zoster, among others, is observed. Furthermore, it is also possible to observe intraoral hemorrhage developed secondary to thrombocytopenia due to bone marrow suppression (SONIS et al, 2003). In this present case, as blood tests were not provided and there was no possibility of performing biopsies, the clinical exam of the lesions resembled gingival necrosis, affecting attached and free gingiva. The pain and discomfort reported by the patient resembled necrotizing gingivitis, but no papillary necrosis or permanent loss of gingival tissue was observed. Other studies reported uncommon gingival lesions in cancer patients, especially with leukemia (STANSBURY et al., 1998; KHOURY et al., 2003; HU et al., 2015; BODDU et al., 2018). The patient did not present increased periodontal probing depths, only healthy sulcus up to 3 mm. No clinical attachment loss or bone loss

associated lesions were observed. Therefore, we diagnosed acute gingival lesions, as it was an atypical and unclassified form of injury.

PBM is well established and recommended for the treatment of oral mucositis (ELAD et al., 2020; SÁNCHEZ-MARTOS et al., 2023; SHEN et al., 2024). Low-power lasers in general are efficient contributors to wound repair, inducing fibroblast growth, collagen synthesis, angiogenesis and subsequent re-epithelialization to close the wound (PENG et al., 2020). The Multinational Association for Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO) conducted a systematic review and updated clinical guidelines to provide practitioners with a set of mucositis interventions with strong evidence to support or refute their use. In certain clinical circumstances, PBM protocols to prevent OM in specific patient populations have been defined, but individual variations can be considered for specific cases (PERALTA-MAMANI et al., 2019; ELAD et al., 2020). Still, laser use for prevention of oral lesions in cancer patients have also been discussed (MIGLIORATI et al., 2013; NETTO et al., 2014).

Shen et al. (2024) examined the effectiveness of PBM in chemotherapy-induced OM reduction in patients with head and neck cancer and considered a total of 14 studies covering 869 patients. The incidence of OM in PBM group was significantly lower from the second week compared to the control group, keeping it until the seventh week. Furthermore, the occurrence of severe mucositis in PBM group decreased from the third week until the conclusion of the intervention, showing beneficial effects on pain relief. Although PBM has demonstrated considerable effectiveness in reducing the incidence, severity and pain associated with OM, the authors highlighted the need for standardization of application protocols. Similar conclusions were described in a previous overview of systematic reviews (NASCIMENTO et al., 2023).

The level of oral care during therapy has a marked influence on the outcome regarding oral complications and infections (MORAIS et al., 2020; ELAD et al., 2020). The ability of the patient and their healthcare professionals to reduce oral flora favorably affects local and systemic infections (SONIS et al., 2003). Oral hygiene techniques, including mechanical and chemical interventions, can successfully reduce oral flora, but a chlorhexidine use is not indicated (ELAD et al., 2022), and, therefore, was not used in the patient in this case report.

To improve the quality of life of cancer patients, a reduction in treatment-induced side effects is necessary. To achieve this, monitoring patients is of great importance, especially during and between treatment cycles, to observe early signs of toxicities development. Healthcare professionals must be aware of the

side effects of different components of cancer therapy received by each patient, in order to propose a prophylactic therapy, to minimize side effects and reduce pain and discomfort in cancer patients (VAN DEN BOOGAARD et al., 2022; OWOSHO et al., 2023).

CONCLUSION

The use of PBM, alone or in association with aPDT, proved to be effective in treating acute gingival lesions in a young patient undergoing cancer treatment. Early intervention, at the first symptoms of the lesions, and also the preventive use of laser in subsequent chemotherapy cycles may have been decisive to prevent periodontal sequelae, such as gingival recession, clinical attachment loss and bone loss and it also brought comfort and relief, by reducing pain and contributing to tissue healing. As it is a low-cost and effective therapy, its use, following described protocols, should be encouraged to improve quality of life of patients during cancer treatment involving chemotherapy and/or radiotherapy.

REFERENCES

1. FIGUEIREDO, A.L.P.; LINS, L.; CATTONY, A.C. et al. Laser therapy in the control of oral mucositis: a meta-analysis study. **Magazine of the Brazilian Medical Association**, v. 59, n. 5, p. 467-74, 2013. doi: https://doi.org/10.1016/j.ramb.2013.08.003

2. PENG, J.; SHI, Y.; WANG, J. et al. Low-level laser therapy in the prevention and treatment of oral mucositis: a systematic review and meta-analysis. **Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology.** v. 130, n. 4, p. 387-397e9, 2020. doi: 10.1016/j.oooo.2020.05.014

3. SÁNCHEZ-MARTOS, R; LAMDAOUI, W. et al Therapeutic Outcomes of Photobiomodulation in Cancer Treatment-induced Oral Mucositis: A Systematic Review. **Journal of Clinical and Experimental Dentistry.** v. 15, n. 9, p. e749-e759, 2023. doi: 10.4317/jced.60710

4. NASCIMENTO, M.V.; COSTA, F.W.G.; DE OLIVEIRA FILHO, O.V. et al. Management of Cancer Therapy-Induced Oral Mucositis Using Photobiomodulation Therapy: An Overview of Systematic Reviews. **Photobiomodulation and Photomedicine in Laser Surgery**, v.41, n.10, p.513-538, 2023. doi: 10.1089/photob.2023.0091

5. SHEN, B.; ZHOU, Y.; WU, D.; LIU, J.. Efficacy of photobiomodulation therapy in the management of oral mucositis in patients with head and neck cancer: A systematic review and meta-analysis of randomized controlled trials. **Head & Neck**, p. 1-15, 2024. doi:10.1002/hed.27655

6. SONIS, S.T.; COSTA, J.W. Oral complications of cancer chemotherapy. IN: KUFE, DW, POLLOCK, RE, WEICHSELBAUM, RR et al., editors. **Holland-Frei Cancer Medicine.** 6th edition. Hamilton (ON): BC Decker; 2003. Available from: https://www.ncbi.nlm.nih.gov/books/NBK13131/

7. SROUSSI, H.Y.; EPSTEIN, J.B.; BENSADOUN, R.J. et al. Common oral complications of head and neck cancer radiation therapy: mucositis, infections, saliva change, fibrosis, sensory dysfunctions, dental caries, periodontal disease, and osteoradionecrosis. **Cancer Medicine,** v. 6, n. 12, p.2918-2931, 2017. doi: 10.1002/cam4.1221.

8. KHOURY, H.; POH, C.F.; WILLIAMS, M. et al. Acute Myelogenous Leukemia Complicated by Acute Necrotizing Ulcerative Gingivitis Due to Aspergillus terreus, **Leukemia & Lymphoma**, v. 44, n. 4, p. 709-713, 2003. doi: 10.1080/1042819031000060573

9. STANSBURY, D.M.; PETERSON, D.E.; SUZUKI J.B. Rapidly Progressive Acute Periodontal Infection in a Patient with Acute Leukemia. **Journal of Periodontology,** v. 59, n. 8, p. 544-47, 1988. https://doi-org.ez24.periodicos.capes.gov.br/10.1902/jop.1988.59.8.544

10. HU, J.; KENT, P.; LENNON, J.M. et al. Acute necrotizing ulcerative gingivitis in an immunocompromised young adult. **BMJ Case Reports**, v. 16, n. 2015:bcr2015211092, 2015. doi: 10.1136/bcr-2015-211092.

11. BODDU, P.; CHEN, P.L.; NAGARAJAN, P. et al. Necrotizing fungal gingivitis in a patient with Acute Myelogenous Leukemia: visible yet obscure. **Journal of Oral and Maxillofacial Surgery and Medical Pathology**, v. 30, n. 1, p. 50-54, 2018. doi: 10.1016/j.ajoms.2017.08.007.

12. EINSFELD, V.; SILVA, M.C.P.; GONÇALVES, K.W. et al. Acute necrotizing ulcerative gingivitis in oncopediatric patients: challenges in treatment, **Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology**, v 134, n. 3, p. e147, 2022. ISSN 2212-4403, https://doi.org/10.1016/j.oooo.2022.01.355.

13. POULOPOULOS, A.; PAPADOPOULOS, P.; ANDREADIS, D. Chemotherapy: oral side effects and dental interventions-a review of the literature. **Stomatological Diseases Science,** v. 1, p. 35-49, 2017. http://dx.doi.org/10.20517/2573-0002.2017.03

14. OWOSHO, A.A.; DECOLIBUS, K.; HEDGEPETH, B. et al. The Role of Dental Practitioners in the Management of Oncology Patients: The Head and Neck Radiation Oncology Patient and the Medical Oncology Patient. **Dentistry Journal (Basel),** v. 11, n. 5, p. 136, 2023. doi: 10.3390/dj11050136

15. CURRA, M.; SOARES JUNIOR, L.A.V.; MARTINS, M.D. et al. Chemotherapy protocols and incidence of oral mucositis. An integrative review. **Einstein (São Paulo**). v. 16, n. 1, p. eRW4007, 2018. doi: https://doi.org/10.1590/ s1679-45082018rw4007

16. STOUFI, E. Radiation and Chemotherapy-Induced Gingival Lesions. In: **Periodontal Manifestations of Local and Systemic Diseases.** Springer, Cham, 2023. https://doi.org/10.1007/978-3-031-10828-0_17

17. ELAD, S. The MASCC/ISOO mucositis guidelines 2019: the second set of articles and future directions. **Support Care in Cancer,** v. 28, p. 2445–2447, 2020. https://doi.org/10.1007/s00520-019-05153-w

18. ELAD, S.; ZADIK, Y.; YAROM, N. et al. The Broadening Scope of Oral Mucositis and Oral Ulcerative Mucosal Toxicities of Anticancer Therapies. **CA: A Cancer Journal for Clinicians.** v. 72, n. 1, p. 57-77, 2022.

19. MCCARTHY, G.M.; AWDE, J.D.; GHANDI. H. et al. Risk factors associated with mucositis in cancer patients receiving 5-fluorouracil. **Oral Oncology,** v. 34 , p. 484 - 490, 1998. doi:10.1016/s1368-8375(98)00068-2

20. PERALTA-MAMANI, M.; SILVA, B.M.; PINTO, A.C.S. et al. Low-level laser therapy dosimetry most used for oral mucositis due to radiotherapy for head and neck cancer: a systematic review and meta-analysis. **Critical Reviews in Oncology/Hematology**, v. 138, p. 14-23, 2019, ISSN 1040-8428, https://doi.org/10.1016/j.critrevonc.2019.03.009.

21. NETTO, G.; BEYENE, J. et al. Effect of prophylactic low level laser therapy on oral mucositis: a systematic review and meta-analysis. **PLoS One,** v.

9, n. 9, p. e107418, 2014. doi : http://doi.org/10.1371/journal.pone.0107418

22. MORAIS, M.O.; MARTINS, A.F.L.; DE JESUS, A.P.G. et al. A prospective study on oral adverse effects in head and neck cancer patients submitted to a preventive oral care protocol. **Supportive Care in Cancer**, v. 28, n. 9, p. 4263–73, 2020. https://doi.org/10.1007/s00520-019-05283-1.

23. VAN DEN BOOGAARD, W.M.C.; KOMNINOS, D.S.J.; VERMEIJ, W.P. Chemotherapy Side-Effects: Not All DNA Damage Is Equal. **Cancers (Basel).** 2022, v.14; n. 3, p. 627. doi: 10.3390/cancers14030627.