

**Research Digest**

**Low Level laser Therapy (LLLT) and photobiomodulation**

**for oral mucositis**

James D Carroll

THOR Photomedicine Ltd (UK)

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# Effect of low-level laser therapy on chemoradiotherapy-induced oral mucositis and salivary inflammatory mediators in head and neck cancer patients.

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**BACKGROUND AND OBJECTIVE:** Oral mucositis (OM) is considered a painful and debilitating side effect in patients receiving head and neck cancer treatment. Low-level laser therapy (LLLT) proved to be effective to prevent and treat chemoradiotherapy-induced OM. The aim of this study was to evaluate the effect of LLLT in the severity of OM in patients with head and neck cancer and on the release of salivary inflammatory mediators. Clinical (score of OM severity) and biochemical parameters (concentration of inflammatory mediators, growth factors, and enzymes in saliva) were used. **MATERIALS AND METHODS:** Thirty patients were randomized into two groups: control and laser. LLLT was performed three times a week in the laser group, while control group received sham irradiation. OM severity was assessed according to the World Health Organization (WHO) and National Cancer Institute (NCI) scales. Pro-inflammatory and anti-inflammatory cytokines (TNF-alpha, IL-6, IL-1beta, IL-10, TGF-beta), growth factors (EGF, FGF, VEGF), and metalloproteinases (MMP2/TIMP2, MMP9/TIMP2) concentrations were assessed using ELISA test. Saliva samples were collected on admission, and at the 7th, 21st, and 35th sessions of radiotherapy. **RESULTS:** The laser group showed a reduction in the severity of OM, which coursed with significantly diminished salivary concentration of EGF and VEGF in the 7th radiotherapy session and of IL-6 and FGF in the 35th. There was a trend for reduced levels of IL-1beta, TNF-alpha, IL-10, TGF-beta, MMP2/TIMP2, MMP9/TIMP2 in the laser group compared to the control, however, no statistically significant differences were found. **CONCLUSIONS:** These findings demonstrated that LLLT was effective in reducing the severity of chemoradiotherapy-induced OM and was associated with the reduction of inflammation and repair. *Lasers Surg. Med.* 47:296-305, 2015. (c) 2015 Wiley Periodicals, Inc.

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# Guideline for the prevention of oral and oropharyngeal mucositis in children receiving treatment for cancer or undergoing haematopoietic stem cell transplantation.

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**PURPOSE:** To develop an evidence-based clinical practice guideline for the prevention of oral mucositis in children (0-18 years) receiving treatment for cancer or undergoing haematopoietic stem cell transplantation (HSCT). **METHODS:** The Mucositis Prevention Guideline Development Group was interdisciplinary and included internationally recognised experts in paediatric mucositis. For the evidence review, we included randomised controlled trials (RCTs) conducted in either children or adults evaluating the following interventions selected according to prespecified criteria: cryotherapy, low level light therapy (LLLT) and keratinocyte growth factor (KGF). We also examined RCTs of any intervention conducted in children. For all systematic reviews, we synthesised the occurrence of severe oral mucositis. The Grades of Recommendation, Assessment, Development and Evaluation approach was used to describe quality of evidence and strength of recommendations. **RESULTS:** We suggest cryotherapy or LLLT may be offered to cooperative children receiving chemotherapy or HSCT conditioning with regimens associated with a high rate of mucositis. We also suggest KGF may be offered to children receiving HSCT conditioning with regimens associated with a high rate of severe mucositis. However, KGF use merits caution as there is a lack of efficacy and toxicity data in children, and a lack of long-term follow-up data in paediatric cancers. No other interventions were recommended for oral mucositis prevention in children. **CONCLUSIONS:** All three specific interventions evaluated in this clinical practice guideline were associated with a weak recommendation for use. There may be important organisational and cost barriers to the adoption of LLLT and KGF. Considerations for implementation and key research gaps are highlighted.

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# Biomodulation of Inflammatory Cytokines Related to Oral Mucositis by Low-Level Laser Therapy.

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This study evaluated the effects of LLLT on the expression of inflammatory cytokines related to the development of oral mucositis by gingival fibroblasts. Primary gingival fibroblasts were seeded on 24-well plates (105 cells/well) for 24 h. Fresh serum-free culture medium (DMEM) was then added, and cells were placed in contact with LPS (*Escherichia coli*, 1  $\mu\text{g mL}^{-1}$ ), followed by LLLT irradiation (LaserTABLE-InGaAsP diode prototype-780 nm, 25 mW) delivering 0, 0.5, 1.5 or 3  $\text{J cm}^{-2}$ . Cells without contact with LPS were also irradiated with the same energy densities. Gene expression of TNF- $\alpha$ , IL-1 $\beta$ , IL-6 and IL-8 was evaluated by Real-Time PCR, and protein synthesis of these cytokines was determined by enzyme-linked immunosorbent (ELISA) assay. Data were statistically analyzed by the Kruskal-Wallis test, complemented by the Mann-Whitney test ( $P < 0.05$ ). LPS treatment increased the gene expression and protein synthesis of TNF- $\alpha$ , IL-6 and IL-8, while the expression of IL-1 $\beta$  was not affected. For LPS-treated groups, LLLT promoted significant decreases in the expression of TNF- $\alpha$ , IL-6, and IL-8 at 1.5  $\text{J cm}^{-2}$  and 3  $\text{J cm}^{-2}$ . These results demonstrate that LLLT promoted a beneficial biomodulatory effect on the expression of inflammatory cytokines related to oral mucositis by human gingival fibroblasts.

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# Low level laser therapy against radiation induced oral mucositis in elderly head and neck cancer patients-a randomized placebo controlled trial.

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**OBJECTIVES:** Radiotherapy (RT) is treatment of choice for Elderly Head and Neck Cancer (HNC) patients. Oral mucositis (OM) during RT affects patient's routine oral activities and overall health. Low Level Laser Therapy (LLL) provided some promising results against cancer therapy induced OM in children and adults. No study specifically evaluated effects of LLL against RT induced OM in elderly HNC patients until date, hence we did this study. **MATERIAL AND METHODS:** This double blinded study randomized 46 elderly HNC patients scheduled for RT [Dosage=66 Gray (2 Gy/fraction), 5 fractions/week, total 33 fractions for 6.5 weeks], into laser (22) and placebo (24) groups. Laser group patients received LLL [Helium-Neon,  $\lambda=632.8$  nm, power density=0.024 W/cm<sup>2</sup>, dosage=3.0 J/point at six anatomical sites bilaterally i.e. 12 locations, total dose/session=36 J, beam aperture diameter=0.6 mm, beam spot size=1 cm<sup>2</sup>, irradiated area diameter=1 cm<sup>2</sup>, irradiation time/point=125 s, 5 sessions/week, non-contact method-distance between probe and irradiated tissues <1 cm, whereas placebo group did not receive laser. OM grades (RTOG/EORTC Scale), oral pain, weight loss, need for morphine analgesics and tube feeding, and RT break were recorded by a blinded assessor. Descriptive statistics and repeated measures ANOVA were used for analysis keeping  $p<0.05$ . **RESULTS:** Significant reduction in the incidence and duration of severe OM ( $p=0.016$ ) and severe pain ( $p=0.023$ ) and weight loss ( $p=0.004$ ) was observed in laser than placebo group. No difference was found for enteral feeding use ( $p=0.667$ ) between two groups. **CONCLUSIONS:** LLL decreased the severity of OM and oral pain in elderly HNC patients. Also, lesser weight loss, morphine analgesic use and radiation break happened in laser group.

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# Oral mucositis in pediatric patients undergoing hematopoietic stem cell transplantation: clinical outcomes in a context of specialized oral care using low-level laser therapy.

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OM is a painful inflammatory condition of the oral mucosa, derived from the toxic effects of chemotherapy and radiotherapy. High OM severity is frequently present in HSCT pediatric patients, who exhibit multiple painful ulcers that limit their mastication and swallowing, leading to poor nutritional status. Few studies have demonstrated OM clinical outcomes in young patients undergoing HSCT. Feasibility of oral care and LLLT on OM prophylaxis and treatment is also poorly discussed. The aim of this study was to describe a specialized oral care protocol that included LLLT for pediatric patients undergoing transplantation and to demonstrate the clinical outcomes after OM prevention and treatment. Data from OM-related morbidity were collected from 51 HSCT pediatric patients treated daily with LLLT, followed by standard oral care protocols. All the patients, even infants and young children, accepted the daily oral care and LLLT well. The majority (80.0%) only exhibited erythema in the oral mucosa, and the maximum OM degree was WHO II. Patients who had undergone autologous and HLA-haploidentical transplants showed OM with the lowest severity. The frequency of total body irradiation and methotrexate prescriptions was higher in adolescents when compared with infants ( $p = 0.044$ ), and adolescents also exhibited OM more severely than infants and young children. We found that good clinical outcomes were obtained using this therapy, mainly in regard to the control of OM severity and pain reduction in the oral cavity. Specialized oral care, including LLLT, is feasible and affordable for HSCT pediatric patients, although some adaptation in the patient's oral hygiene routine must be adopted with help from parents/companions and clinical staff.

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# Oral mucositis prevention and management by therapeutic laser in head and neck cancers.

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**INTRODUCTION:** Oral mucositis is considered a severe complication in cancer patients receiving radiotherapy or chemotherapy for head and neck cancer. The aim of this review study was to assess the effect of low level laser therapy for prevention and management of oral mucositis in cancer patients. **METHODS:** The electronic databases searched included Pubmed, ISI Web of Knowledge and Google scholar with keywords as "oral mucositis", "low level laser therapy" from 2000 to 2013. **RESULTS:** The results of most studies showed that photobiomodulation (PBM) reduced the severity of mucositis. Also, it can delay the appearance of severe mucositis. **CONCLUSION:** Low level laser therapy is a safe approach for management and prevention of oral mucositis.

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[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=25606332](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=25606332)

# Effect of prophylactic low level laser therapy on oral mucositis: a systematic review and meta-analysis.

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**BACKGROUND:** Objective was to determine whether prophylactic low level laser therapy (LLLT) reduces the risk of severe mucositis as compared to placebo or no therapy. **METHODS:** MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials were searched until February 2014 for randomized controlled trials (RCTs) comparing prophylactic LLLT with placebo or no therapy in patients with cancer or undergoing hematopoietic stem cell transplantation (HSCT). All analyses used random effects models. **RESULTS:** Eighteen RCTs (1144 patients) were included. Prophylactic LLLT reduced the overall risk of severe mucositis (risk ratio (RR) 0.37, 95% confidence interval (CI) 0.20 to 0.67;  $P = 0.001$ ). LLLT also reduced the following outcomes when compared to placebo/no therapy: severe mucositis at the time of anticipated maximal mucositis (RR 0.34, 95% CI 0.20 to 0.59), overall mean grade of mucositis (standardized mean difference -1.49, 95% CI -2.02 to -0.95), duration of severe mucositis (weighted mean difference -5.32, 95% CI -9.45 to -1.19) and incidence of severe pain (RR 0.26, 95% CI 0.18 to 0.37). **CONCLUSION:** Prophylactic LLLT reduced severe mucositis and pain in patients with cancer and HSCT recipients. Future research should identify the optimal characteristics of LLLT and determine feasibility in the clinical setting.

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[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=25198431](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=25198431)

# Effect of low-level laser therapy on inflammatory mediator release during chemotherapy-induced oral mucositis: a randomized preliminary study.

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Patients undergoing hematopoietic stem cell transplantation (HSCT) are submitted to a conditioning regimen of high-dose chemotherapy, with or without radiation therapy, which usually results in oral ulcerations and mucosal barrier breakdown. Oral mucositis (OM) is a common and debilitating toxicity side effect of autologous and allogeneic HSCT. The aim of this study was to evaluate the effect of low-level laser therapy (LLLT) on the severity of OM and inflammatory mediator (TNF-alpha, IL-6, IL-1beta, IL-10, TGF-beta, metalloproteinases, and growth factors) levels in saliva and blood of HSCT patients. Thirty patients were randomly assigned to two groups: control (n = 15) and laser (n = 15). LLLT was applied from the first day of the conditioning regimen until day 7 post-HSCT (D + 7). Saliva and blood were collected from patients on admission (AD), D-1, D + 3, D + 7, and on marrow engraftment day (ME). Clinical results showed less severe OM in the laser group ( $p < 0.05$ ). The LLLT group showed increased matrix metalloproteinase 2 (MMP-2) levels in saliva on D + 7 ( $p = 0.04$ ). Significant differences were also observed for IL-10 on D + 7 and on ME in blood plasma, when compared to the control group ( $p < 0.05$ ). No significant differences were seen in saliva or blood for the other inflammatory mediators investigated. LLLT was clinically effective in reducing the severity of chemotherapy-induced OM in HSCT patients, and its mechanism of action does not seem to be completely linked to the modulation of pro- or anti-inflammatory cytokines, growth factors or matrix metalloproteinases.

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# Effects of low-level laser therapy on M1-related cytokine expression in monocytes via histone modification.

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Low-level laser therapy (LLLT) has been used in the treatment of radiotherapy-induced oral mucositis and allergic rhinitis. However, the effects of LLLT on human monocyte polarization into M1 macrophages are unknown. To evaluate the effects of LLLT on M1-related cytokine and chemokine production and elucidate the mechanism, the human monocyte cell line THP-1 was treated with different doses of LLLT. The expression of M1-related cytokines and chemokines (CCL2, CXCL10, and TNF-alpha) was determined by ELISA and real-time PCR. LLLT-associated histone modifications were examined by chromatin immunoprecipitation (ChIP) assays. Mitochondrial involvement in the LLLT-induced M1-related cytokine expression was evaluated by quantitative real-time PCR. Flow cytometry was used to detect the cell surface markers for monocyte polarization. The results showed that LLLT (660 nm) significantly enhanced M1-related cytokine and chemokine expression in mRNA and protein levels. Mitochondrial copy number and mRNA levels of complex I-V protein were increased by LLLT (1 J/cm<sup>2</sup>). Activation of M1 polarization was concomitant with histone modification at TNF-alpha gene locus and IP-10 gene promoter area. This study indicates that LLLT (660 nm) enhanced M1-related cytokine and chemokine expression via mitochondrial biogenesis and histone modification, which may be a potent immune-enhancing agent for the treatment of allergic diseases.

Mediators Inflamm 2014 2014 625048

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=24692853](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=24692853)

# Significant errors and misdirection in class IV laser therapy study.

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This Correspondence relates to the article by Ottaviani et al (Effect of Class IV Laser Therapy on Chemotherapy-Induced Oral Mucositis: A Clinical and Experimental Study. *Am J Pathol* 2013, 183:1747-1757.).

To the Editor-in-Chief:

There are design errors in the recent paper by Ottaviani et al,<sup>1</sup> and the subsequent conclusions are misleading. The authors claim to demonstrate that a 5 W 970 nm class IV high-power laser is more effective than a “standard low-power laser therapy protocol.”

Ottaviani et al<sup>1</sup> compared a 5 W 970 nm laser with a 2.5 mW 635 nm laser delivering 0.45 J per point. This is not a standard protocol for oral mucositis and could not possibly have any clinical effect. The authors referenced a systematic review of low level light therapy (LLLT) for oral mucositis by Bjordal et al<sup>2</sup> in which a careful analysis of effective parameters is reported. The paper concludes that the effective treatment regime for a 635 nm laser is a 10 to 60 mW laser and 3 J per point. The laser power used by Ottaviani et al<sup>1</sup> was only 25% of that recommended, and the energy delivered was only 15% of that recommended.

In addition to the beam being under powered, the 635 nm laser “was taken 1 to 3 cm from the affected areas, and a rotator motion was applied.” This further distributes the already weak (low irradiance) beam over a larger area. In the study’s methods, it is stated that the 635 nm laser was pulsed at 2 Hz, which would have further reduced the energy. It has been consistently shown in LLLT dose-rate studies that irradiances in the range of 5 to 100 mW/cm<sup>2</sup> are more effective at reducing inflammation and repairing tissue than high irradiances.<sup>3,4,5</sup>

Ottaviani et al<sup>1</sup> misdirect the reader by asserting they used a standard protocol when, in fact, they have merely designed a weak protocol to make a class IV laser product appear more effective.

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[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=24655380](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=24655380)

# MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy.

Lalla RV, Bowen J, Barasch A, Elting L, Epstein J, Keefe DM, McGuire DB, Migliorati C, Nicolatou-Galitis O, Peterson DE, Raber-Durlacher JE, Sonis ST, Elad S

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**BACKGROUND:** Mucositis is a highly significant, and sometimes dose-limiting, toxicity of cancer therapy. The goal of this systematic review was to update the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) Clinical Practice Guidelines for mucositis. **METHODS:** A literature search was conducted to identify eligible published articles, based on predefined inclusion/exclusion criteria. Each article was independently reviewed by 2 reviewers. Studies were rated according to the presence of major and minor flaws as per previously published criteria. The body of evidence for each intervention, in each treatment setting, was assigned a level of evidence, based on previously published criteria. Guidelines were developed based on the level of evidence, with 3 possible guideline determinations: recommendation, suggestion, or no guideline possible. **RESULTS:** The literature search identified 8279 papers, 1032 of which were retrieved for detailed evaluation based on titles and abstracts. Of these, 570 qualified for final inclusion in the systematic reviews. Sixteen new guidelines were developed for or against the use of various interventions in specific treatment settings. In total, the MASCC/ISOO Mucositis Guidelines now include 32 guidelines: 22 for oral mucositis and 10 for gastrointestinal mucositis. This article describes these updated guidelines. **CONCLUSIONS:** The updated MASCC/ISOO Clinical Practice Guidelines for mucositis will help clinicians provide evidence-based management of mucositis secondary to cancer therapy.

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[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=24615748](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=24615748)

# Evaluation of nutritional status in head and neck radio-treated patients affected by oral mucositis: efficacy of class IV laser therapy.

Gobbo M, Ottaviani G, Perinetti G, Ciriello F, Beorchia A, Giacca M, Di Lenarda R, Rupel K, Tirelli G, Zacchigna S, Biasotto M

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**PURPOSE:** To retrospectively evaluate the role of class IV laser therapy in the amelioration of nutritional status of patients affected by oral mucositis due to radiotherapy of the head and neck region during oncological treatment. **METHODS:** Sixty-three oncological patients were included in this study. All patients were affected by tumors in the head and neck region and had developed oral mucositis during radiotherapy. Forty-two patients had been treated by high-power laser therapy whereas 21 patients had been managed with traditional medications. Data collection included weight measurement (kilogram) and body mass index (BMI) calculation (mass (kilogram)/(height) (square meter)) on the first and last day of radiotherapy. In addition, gender, age, pathology, and the kind of oncological treatment have been considered. **RESULTS:** Laser-treated patients decreased less in BMI during radiotherapy ( $p = 0.000$ ). Patients treated by combined oncological treatments (radiotherapy and/or chemotherapy and/or surgery) had a higher weight loss during radiotherapy ( $p = 0.015$ ). According to a multivariate regression analysis, the only variable which significantly influenced the reduction of BMI was laser treatment ( $p = 0.000$ ). **CONCLUSIONS:** Laser therapy is actually considered one of the recommended remedies for the healing of oral mucositis due to cancer treatments. Healing of mucositis can deeply influence the feeding capacity of patients, through reduction of pain and improvement of chewing and swallowing capacities. It also allows lowering the costs for hospitalization and supportive care. Laser therapy should become part of nutritional interventions in oncological patients affected by oral mucositis.

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[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=24554204](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=24554204)

# Efficacy of cryotherapy associated with laser therapy for decreasing severity of melphalan-induced oral mucositis during hematological stem-cell transplantation: a prospective clinical study.

de Paula Eduardo F, Bezinelli LM, da Graca Lopes RM, Nascimento Sobrinho JJ, Hamerschlak N, Correa L

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Melphalan followed by hematopoietic stem-cell transplantation (HSCT) is the standard treatment for multiple myeloma and other hematopoietic neoplasms. However, high doses of melphalan cause severe oral mucositis (OM). The objective was to verify the efficacy of cryotherapy plus laser therapy on reduction of OM severity. HSCT patients undergoing melphalan chemotherapy (n = 71) were randomly divided into two groups according to OM treatment: oral cryotherapy performed with ice chips for 1 h 35 min followed by low-level laser therapy (InGaAlP, 660 nm, 40 mW, 6 J/cm<sup>2</sup>) (n = 54) and laser therapy alone with the same protocol (n = 17). A control group (n = 33) was composed of HSCT patients treated with melphalan who received no specific treatment for OM. OM scores and clinical information were collected from D0 to D + 11. The cryotherapy/laser therapy group showed the lowest OM scores (maximum Grade I) and the lowest mean number of days (8 days) with OM in comparison with the other groups (p < 0.001). OM Grades III and IV were present with high frequency only in the control group. The association of cryotherapy with laser therapy was effective in reducing OM severity in HSCT patients who underwent melphalan conditioning. Copyright (c) 2014 John Wiley & Sons, Ltd.

Hematol Oncol 2014 Feb 11

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# Low-level laser therapy: a standard of supportive care for cancer therapy-induced oral mucositis in head and neck cancer patients?

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Background and aims: Oral mucositis (OM) is still a common and severe acute side-effect of many oncologic treatments, especially in patients treated for head and neck cancer. It may affect quality of life, require supportive care and impact treatment planning and its efficacy. Low-level laser therapy (LLLT) seems to promote pain relief and reduces OM incidence and its severity. It has been recommended for these patients as a treatment option but without any consensus in the LLLT procedure. New recommendations and perspectives for clinical trials will be discussed. Materials (Subjects) and Methods: Step by step, the efficacy of soft laser in the management of iatrogenic oral mucositis has been evaluated during the last two decades. Its effectiveness and level of recommendation got stronger with time. We will report and discuss some major results and the latest recommendations published on this topic. Results: The major clinical results have been reported and analysed last year in a first meta-analysis (1). 11 randomized placebo-controlled trials were selected with a total of 415 patients treated with chemotherapy and/or radiotherapy for head and neck cancer. The relative risk for developing OM was significantly reduced after LLLT but only for a dose between 1 to 6 Joules per point. Pain, severity and duration of OM grade  $\geq 2$  were also reduced without difference with placebo for possible side-effects. Nine years after the positive results published for patients treated by radiotherapy alone (2)), a new French randomized, multicentric, phase III trial for patients treated with new standard treatment, using LLLT in accordance to recent recommendations is ongoing. Seven centers are specifically established for this trial which should include a hundred patients. Conclusions: The very encouraging results of LLLT in the prevention and treatment of OM in patients treated by chemotherapy or radiotherapy for advanced head and neck cancer could soon be proposed as a new standard of care, according to the multinational Association of Supportive care in Cancer (MASCC) criteria. Modern lasers are less time consuming and extraoral applicators for a possible use by trained paramedical staff could be helpful to complete clinician practice. A preventive dose of 2 J/cm<sup>2</sup> and a curative dose of 4 J/cm<sup>2</sup> if using a red wavelength lasers are now recommended.

Laser Ther 2012 Dec 26 21(4) 297-303

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=24511199](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=24511199)

# Chemotherapy-induced oral mucositis: effect of LED and laser phototherapy treatment protocols.

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**BACKGROUND AND OBJECTIVE:** Over the last few decades, many studies have focused on the effect of lasers on the management of oral mucositis in oncologic patients treated with chemotherapy and/or radiotherapy. However, the effect of light-emitting diode (LED) has been poorly studied, and was not compared with that of laser phototherapy (LPT). For this reason, the aim of the present study was to clinically compare the effect of these two therapies on chemotherapy-induced oral mucositis (CIOM) and pain. **METHODS:** Forty patients with CIOM were divided into two groups: G1, patients treated with LPT; G2, patients treated with LED. The treatment was administered during 10 consecutive days, with exception of weekends. LPT was applied using an InGaAlP laser (660 nm/40 mW/6.6 J cm<sup>-2</sup>/0.24 J per point/0.036 cm<sup>2</sup> of spot size). LED phototherapy was applied using 0.24 J per point/80 mW/630 nm/1 cm<sup>2</sup> of spot size. CIOM was assessed during each session in accordance to the World Health Organization (WHO) score. The patient self-assessed pain was scored on a visual analog scale (VAS). **RESULTS:** The mean VAS and WHO scores were significantly smaller in the LED group (p<0.05). However, both groups required the same number of days to reach score zero for mucositis and pain (p>0.05). Moreover, in the group with severe mucositis (score III), there was a lower frequency of patients with complete healing and pain relief, with the exception of analgesia in G2, in which almost all patients were completely relieved from pain. **CONCLUSIONS:** These findings suggest that LED therapy is more effective than LPT in the treatment of COIM, with the parameters used in the present study.

Photomed Laser Surg 2014 Feb 32(2) 81-7

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=24476495](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=24476495)

# Low-power laser therapy in chemical-induced oral mucositis: a case study.

Medeiros NJ, Medeiros NF, dos Santos CC, Parente GV, de Carvalho JN

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Grande. Universidade Federal de Campina Grande, UFCG).

Braz J Otorhinolaryngol 2013 Nov-Dec 79(6) 792

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?  
cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=24474495](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=24474495)

# Class IV laser therapy as treatment for chemotherapy-induced oral mucositis in onco-haematological paediatric patients: a prospective study.

Chermetz M, Gobbo M, Ronfani L, Ottaviani G, Zanazzo GA, Verzegnassi F, Treister NS, Di Lenarda R, Biasotto M, Zacchigna S

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**BACKGROUND:** Oral mucositis is a debilitating side effect of chemotherapy. Laser therapy has recently demonstrated efficacy in the management of oral mucositis (OM). **AIM:** This prospective study was conducted to evaluate the efficacy of class IV laser therapy in patients affected by OM. **DESIGN:** Eighteen onco-haematological paediatric patients receiving chemotherapy and/or haematopoietic stem cell transplantation, prior to total body irradiation, affected by OM, were enrolled in this study. Patients were treated with class IV laser therapy for four consecutive days; the assessment of OM was performed through WHO Oral Mucositis Grading Objective Scale, and pain was evaluated through visual analogue scale. Patients completed a validated questionnaire, and photographs of lesions were taken during each session. Patients were re-evaluated 11 days after the first day of laser therapy. **RESULTS:** All patients demonstrated improvement in pain sensation, and all mucositis was fully resolved at the 11-day follow-up visit, with no apparent side effects. Laser therapy was well tolerated with remarkable reduction in pain associated with oral mucositis after 1-2 days of laser therapy. **CONCLUSIONS:** Given class IV laser therapy appears to be safe, non-invasive, and potentially effective, prospective, randomized, controlled trials are necessary to further assess efficacy and to determine optimal treatment parameters.

Int J Paediatr Dent 2013 Dec 25

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=24372909](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=24372909)

# High-level Evidence Exists for Low-level Laser Therapy on Chemoradiotherapy-induced Oral Mucositis in Cancer Survivors.

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Indian J Palliat Care 2013 Sep 19(3) 195-6

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=24347912](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=24347912)

# Low-level laser in prevention and treatment of oral mucositis in pediatric patients with acute lymphoblastic leukemia.

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1 Postgraduate Program in Dentistry, Oral Pathology Unit, Federal University of Pernambuco , Recife, Pernambuco, Brazil .

**Abstract Objective:** The aim of this study was to evaluate the influence of low-level laser therapy (LLLT) on the prevention and treatment of oral mucositis (OM) in pediatric cancer patients taking methotrexate. **Background data:** OM is a very common, potentially severe side effect, caused by treatment with radiotherapy and chemotherapy for cancer. **Methods:** Forty patients with acute lymphoblastic leukemia, who received high doses of methotrexate, were distributed into two groups. Group A (Preventive Group) was composed of patients who received preventive laser (red-subgroup A1 or infrared-subgroup A2) for 5 days, beginning on the 1st day of infusion. Group B (Treatment Group) was composed of patients who received laser treatment only if they developed post-chemotherapy mucositis (red-subgroup B1 or infrared-subgroup B2). Laser was used at wavelengths of 660 or 830 nm with output 100 mW, power density 3.57 W/cm<sup>2</sup>, spot size 0.028 cm<sup>2</sup>, energy of 1 J, resulting in an energy density of 35 J/cm<sup>2</sup> for 10 sec in the prophylactic group, and energy of 2 J, resulting in energy density of 70 J/cm<sup>2</sup> for 20 sec in the therapeutic group. **Results:** The percentage of patients who did not develop OM was higher in Group A (60% vs. 25%). In Group B, 3/20 patients developed grade IV OM (15%), and a significant difference was found between the two subgroups at the end of treatment (p=0.019). **Conclusions:** Prophylactic laser produced a better outcome than when patients did not receive any preventive intervention, and red laser (660 nm) was better than infrared (830 nm) in the prevention and treatment of OM.

Photomed Laser Surg 2013 Dec 31(12) 613-8

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=24261310](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=24261310)

# [Use of laser for the prevention and treatment of oral mucositis induced by radiotherapy and chemotherapy of head and neck cancer.]

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One of the complications of radiotherapy and chemotherapy is oral mucositis. Since the low energy laser is one of the most frequently recommended interventions by authors and international societies, the aim of this study is to review the scientific evidence on the use of lasers as a preventive and therapeutic in oral mucositis associated with treatment of cancer. We performed a literature search in PubMed and The Cochrane Collaboration Library, limiting the search to the last 20 years. We finally included 29 articles that contained 30 studies. Low energy laser phototherapy seems a promising intervention in both the prevention and treatment of oral mucositis associated with cancer treatment. Virtually all studies reviewed showed good results with no adverse effects and reductions in both incidence and severity of mucositis in all types of cancer treatments.

Med Clin (Barc) 2013 Nov 8

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=24216016](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=24216016)

# Effect of low level laser therapy in the reduction of oral complications in patients with cancer of the head and neck submitted to radiotherapy.

Oton-Leite AF, Elias LS, Morais MO, Pinezi JC, Leles CR, Silva MA, Mendonca EF

Department of Oral Medicine (Oral Pathology), Dental School, Federal University of Goias.

BrazilThe aim of this study was to assess the effect of low level laser therapy on reducing the occurrence and severity of oral complications in patients with head and neck cancer undergoing radiotherapy. Sixty head and neck cancer outpatients from a cancer hospital receiving radiotherapy were selected and randomly assigned into two groups. The laser group was irradiated with an InGaAlP laser and the control received sham laser. The assessment of complications (oral mucositis, pain) was carried out one week after starting radiotherapy, and at the fifteenth and thirtieth sessions of radiotherapy. All patients from both groups showed some degree of oral mucositis. Better outcomes were observed in the laser group when compared with the control in the follow-up sessions, indicating lower degrees of oral mucositis, pain and higher salivary flow ( $p < .05$ ). These findings support the use of laser therapy as an adjuvant treatment for the control of oral complications.

Spec Care Dentist 2013 Nov 33(6) 294-300

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=24164228](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=24164228)

# Laser therapy in the control of oral mucositis: a meta-analysis.

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**OBJECTIVE:** To conduct a systematic review and meta-analysis of the effectiveness of Laser Therapy in the prevention of oral mucositis (OM) in patients undergoing oncotherapy. **METHODS:** To this systematic review and meta-analysis a search was performed in MEDLINE, LILACS and Cochrane using the keywords "laser therapy" and "Oral mucositis." The case-control studies included were submitted to odds ratio (OR) analysis, which the cut-off point for statistic calculation was OM grade > 3. We carried out a meta-analysis by BioEstat 5.0, using the Random Effect DerSimonian-Laird statistical analysis. **RESULTS:** Twelve (studies were included in this systematic review, and the meta-analysis of seven of them showed that LT in patients undergoing oncotherapy is approximately nine times more effective in the prevention of OM grade > 3 than in patients without laser treatment (OR: 9,5281, confidence interval 95% 1,447 -52,0354, p=0,0093. **CONCLUSION:** These data demonstrated significant prophylatic effect of OM grade > 3 in patients undergoing LT. Further studies, with larger sample sizes, are needed for better evaluation of the prophylatic effect of OM grade > 3 by LT.

Rev Assoc Med Bras 2013 September - October 59(5) 467-474

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=24119379](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=24119379)

# Effect of Class IV Laser Therapy on Chemotherapy-Induced Oral Mucositis: A Clinical and Experimental Study.

Ottaviani G, Gobbo M, Sturnega M, Martinelli V, Mano M, Zanconati F, Bussani R, Perinetti G, Long CS, Di Lenarda R, Giacca M, Biasotto M, Zaccchigna S

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Oral mucositis (OM) is a serious and acute side effect in patients with cancer who receive chemotherapy or radiotherapy, often leading to the suspension of therapy and a need for opioid analgesic and enteral/parenteral nutrition, with an effect on patient survival. Among the various interventions proposed in OM management, laser therapy is becoming a recommended treatment option but has limitations due to its heterogeneous laser parameters. Here, we report on our successful clinical experience on the use of class IV laser therapy to treat OM induced by different chemotherapy regimens. To shed light on the mechanisms of action of laser therapy in improving OM resolution, we have developed an animal model of chemotherapy-induced OM, in which we compare the efficacy of the standard low-power laser therapy protocol with an innovative protocol, defined as high-power laser therapy. We show that high-power laser therapy is more effective than low-power laser therapy in improving OM lesion healing, reducing the inflammatory burden, and preserving tissue integrity. In addition, high-power laser therapy has been particularly effective in promoting the formation of new arterioles within the granulation tissue. Our results provide important insights into the mechanism of action of biostimulating laser therapy on OM *in vivo* and pave a way for clinical experimentation with the use of high-power laser therapy.

Am J Pathol 2013 Oct 3

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=24096076](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=24096076)

# Phase III trial of low-level laser therapy to prevent oral mucositis in head and neck cancer patients treated with concurrent chemoradiation.

Antunes HS, Herchenhorn D, Small IA, Araujo CM, Viegas CM, Cabral E, Rampini MP, Rodrigues PC, Silva TG, Ferreira EM, Dias FL, Ferreira CG

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**Brazil**BACKGROUND: Oral mucositis (OM) is a complication of chemoradiotherapy treatment of head and neck squamous cell carcinoma (HNSCC) patients with no effective therapy. This study was designed to assess the efficacy of preventive low-level laser therapy (LLLT) in reducing the incidence of grade 3-4 OM. MATERIAL AND METHODS: From June 2007 to December 2010, 94 HNSCC patients entered a prospective, randomized, double-blind, placebo-controlled phase III trial. Chemoradiotherapy consisted of conventional radiotherapy plus concurrent cisplatin every 3 weeks. A diode InGaAlP (660nm-100mW -1J-4J/cm<sup>2</sup>) was used. OM evaluation was performed by WHO and OMAS scales and quality of life by EORTC questionnaires (QLQ). RESULTS: A six-fold decrease in the incidence of grades 3-4 OM was detected in the LLLT group compared to the placebo; (6.4% versus 40.5%). LLLT impacted the incidence of grades 3-4 OM to a relative risk ratio of 0.158 (CI 95% 0.050-0.498). After treatment QLQ-C30 showed, differences favoring LLLT in physical, emotional functioning, fatigue, and pain; while the QLQ-H&N35 showed improvements in LLLT arm for pain, swallowing, and trouble with social eating. CONCLUSION: Preventive LLLT in HNSCC patients receiving chemoradiotherapy is an effective tool for reducing the incidence of grade 3-4 OM. Efficacy data were corroborated by improvements seen in quality of life.

Radiother Oncol 2013 Sep 14

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=24044799](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=24044799)

# LED and laser photobiomodulation in the prevention and treatment of oral mucositis: experimental study in hamsters.

Freire MD, Freitas R, Colombo F, Valenca A, Marques AM, Sarmiento VA

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**PURPOSE:** This paper aims to evaluate the effects of laser (660 nm) and light-emitting diode (LED) (670 nm) irradiation in the cheek pouch mucosa of hamsters with oral mucositis (OM) induced by chemotherapy (Che) with 5-fluorouracil (5-FU). **MATERIALS AND METHODS:** In the preventive groups, the photobiomodulation was started 1 day before the drug administration and was performed every 48 h (Ia, IIa, Ib, and IIb). In the therapeutic groups (IIIa, IIIb, IVa, and IVb), the irradiations were started on the third day after the Che d(0) and was performed every 48 h. In both groups, animals were sacrificed 7 or 14 days after Che. In the positive control groups, the hamsters were subjected to Che but did not receive irradiation, and they were sacrificed in 7 days (Va) or 14 days (Vb). In the negative control groups, no procedures were done and the animals were sacrificed 7 days (Vc) or 14 days (Vd) after the experiment started. **RESULTS:** The results indicated loss of body mass, xerostomia, and alopecia in the animals subjected to Che and the healing of OM to different degrees after the photobiomodulation treatment. Histologically, the positive control and experimental groups showed inflammation, predominately with lymphocytes and plasma cells, which tended to diminish with time. Epithelial atrophy, hyperemia, fibroblast proliferation, and vascular congestion were also observed at those intervals. **CONCLUSIONS:** The best results were obtained from the preventive laser and LED photobiomodulation groups; both treatments were effective in diminishing the OM lesions. **CLINICAL RELEVANCE:** A noninvasive and effective method with sparse side effects of OM would be desirable for use in cancer centers around the world.

Clin Oral Investig 2013 Aug 15

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=23949015](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=23949015)

# Effect of laser phototherapy in the prevention and treatment of chemo-induced mucositis in hamsters.

Lopez TC, Martins MD, Pavesi VC, Ferreira LS, Bussadori SK, Moreira MS, Marques MM

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The aim of this study was to investigate the effect of laser phototherapy (LPT) in the prevention and/or treatment of oral mucositis induced by 5-fluorouracil (5-FU; Eurofarma, Sao Paulo, Brazil) in hamsters. Ninety-six hamsters were divided into four groups (n = 24): Control (no treatment); Preventive [LPT from day (D) D-5 to D+5]; Therapeutic (LPT from D+5 to D+15); and Combined (preventive plus therapeutic LPT from D-5 to D+15). The animals received an intraperitoneal injection of 5-FU on Days 0 and 2. The pouch mucosa was scratched on Days 3 and 4. The irradiation parameters were: indium-gallium-aluminum-phosphide (InGaAlP) diode laser (MM Optics, Sao Carlos, Brazil) (660 nm), beam area of 0.036 cm<sup>2</sup>, 40 mW, 1.11 W/cm<sup>2</sup>, 6.6 J/cm<sup>2</sup>, power density applied daily of 39.6 J/cm<sup>2</sup>, in punctual mode (six points and six seconds per point) and contact mode, one application per day. The animals were sacrificed on Days 0, 5, 10 and 15 (n = 6) and weighed, and the pouch mucosa was removed for histopathological analysis. Clinical and corresponding histological scores were compared using ANOVA and Tukey's test (p ≤ 0.05). Similar weight losses ranging from 5% to 10% occurred in all groups. The therapeutic group had significantly lower clinical and histological scores than the other groups at Day 10. This study showed that positive effects on oral mucositis management were obtained only when LPT was applied in the therapeutic protocol (from D+5 to D+15 after chemotherapy).

Braz Oral Res 2013 Jun 11

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=23752482](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=23752482)

# Effects of laser irradiation at different wavelengths (660, 810, 980, and 1,064 nm) on mucositis in an animal model of wound healing.

Usumez A, Cengiz B, Oztuzcu S, Demir T, Aras MH, Gutknecht N

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The aim of the present study was to compare the effectiveness of four different laser wavelengths (660, 810, 980, and 1,064 nm) used for low-level laser therapy (LLLT) on the healing of mucositis in an animal model of wound healing by investigating the expression of platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-beta), and blood-derived fibroblast growth factor (bFGF). Thirty-five male Wistar albino rats with a weight of 250-300 g body mass and 5 months old were used in the study. All animals were intraperitoneally injected with 100 mg/kg of 5-fluorouracil (5-FU) on the first day and 65 mg/kg of 5-FU on the third day. The tip of an 18-gauge needle was used in order to develop a superficial scratching on the left cheek pouch mucosa by dragging twice in a linear movement on third and fifth days. After ulcerative mucositis were clinically detected on the animals' left cheek pouch mucosa, the laser therapy was started. Four different laser wavelengths (660 nm, HELBO, Bredent; 810 nm, Fotona XD, Fotona; 980 nm, ARC Fox; and 1,064 nm, Fidelis Plus 3, Fotona) used for LLLT at ED 8 J/cm<sup>2</sup> daily from the first to the fourth days. Oval excisional biopsy was taken from the site of the wound, and the expression of PDGF, TGF-beta, and bFGF was evaluated. The obtained data were analyzed by one-way ANOVA, and then Tukey HSD tests were used for pairwise comparisons among groups ( $\alpha = 0.05$ ). The one-way ANOVA test indicated that expression values of the growth factors, PDGF and bFGF, were significantly affected by irradiation of different wavelengths of lasers ( $p < 0.001$ ). However, expression value of the TGF-beta was not affected by irradiation of different wavelengths of lasers ( $p > 0.05$ ). The highest PDGF expression was detected in neodymium-doped yttrium aluminum garnet (Nd:YAG) laser group ( $p < 0.05$ ), and there were no statistically significant differences among the other groups ( $p > 0.05$ ). The highest bFGF expression was detected in 980-nm diode and Nd:YAG laser groups ( $p < 0.05$ ), and there were no statistically significant differences among the other groups ( $p > 0.05$ ). These findings suggest that low-level Nd:YAG and 980-nm diode laser therapy accelerate the wound healing process by changing the expression of PDGF and bFGF genes responsible for the stimulation of the cell proliferation and fibroblast growth.

Lasers Med Sci 2013 May 1

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=23636299](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=23636299)

# Cost-effectiveness of the introduction of specialized oral care with laser therapy in hematopoietic stem cell transplantation.

Bezinelli LM, de Paula Eduardo F, da Graca Lopes RM, Biazevic MG, de Paula Eduardo C, Correa L, Hamerschlak N, Michel-Crosato E

Unit of Bone Marrow Transplantation, Hospital Israelita Albert Einstein, Sao Paulo, Brazil; Department of Social Dentistry, Universidade de Sao Paulo, Sao Paulo, Brazil.

Oral mucositis (OM) is one of the side effects of hematopoietic stem cell transplantation (HSCT), resulting in major morbidity. The aim of this study was to determine the cost-effectiveness of the introduction of a specialized oral care program including laser therapy in the care of patients receiving HSCT with regard to morbidity associated with OM. Clinical information was gathered on 167 patients undergoing HSCT and divided according to the presence (n = 91) or absence (n = 76) of laser therapy and oral care. Cost analysis included daily hospital fees, parenteral nutrition (PN) and prescription of opioids. It was observed that the group without laser therapy (group II) showed a higher frequency of severe degrees of OM (relative risk = 16.8, 95% confidence interval -5.8 to 48.9,  $p < 0.001$ ), with a significant association between this severity and the use of PN ( $p = 0.001$ ), prescription of opioids ( $p < 0.001$ ), pain in the oral cavity ( $p = 0.003$ ) and fever  $> 37.8$  degrees C ( $p = 0.005$ ). Hospitalization costs in this group were up to 30% higher. The introduction of oral care by a multidisciplinary staff including laser therapy helps reduce morbidity resulting from OM and, consequently, helps minimize hospitalization costs associated with HSCT, even considering therapy costs. Copyright (c) 2013 John Wiley & Sons, Ltd.

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[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=23625880](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=23625880)

# Evaluation of the effect of low level laser on prevention of chemotherapy-induced mucositis.

Arbabi-Kalati F, Arbabi-Kalati F, Moridi T

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Iran Radiotherapy in the head and neck region and chemotherapy might give rise to oral mucositis which is a severe and painful inflammation. There is no known definite cure for mucositis. A number of studies have attempted to evaluate the effect of low-power laser on radiotherapy- and chemotherapy-induced mucositis. The present study was undertaken to evaluate the effect of low-power laser on the prevention of mucositis, xerostomia and pain as a result of chemotherapy. The subjects in this double-blind randomized controlled study were 24 adult patients who underwent chemotherapy during 2009-2010. The results showed that low-power laser was able to decrease the effect of chemotherapy on oral mucositis, xerostomia and pain in a variety of malignancies ( $P < 0.05$ ). It can be concluded that low-power laser might decrease the intensity of mucositis.

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[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=23605599](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=23605599)

# Low-level laser therapy can produce increased aggressiveness of dysplastic and oral cancer cell lines by modulation of Akt/mTOR signaling pathway.

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Low-level laser therapy (LLLT) is a non-thermal phototherapy used in several medical applications, including wound healing, reduction of pain and amelioration of oral mucositis. Nevertheless, the effects of LLLT upon cancer or dysplastic cells have been so far poorly studied. Head and neck cancer patients receiving LLLT for oral mucositis, for example, might have remaining tumor cells that could be stimulated by LLLT. This study demonstrated that LLLT (GaAlAs - 660 nm or 780 nm, 40 mW, 2.05, 3.07 or 6.15 J/cm<sup>2</sup> ) can modify oral dysplastic cells (DOK) and oral cancer cells (SCC9 and SCC25) growth by modulating the Akt/mTOR/CyclinD1 signaling pathway; LLLT significantly modified the expression of proteins related to progression and invasion in all the cell lines, and could aggravate oral cancer cellular behavior, increasing the expression of pAkt, pS6 and Cyclin D1 proteins and producing an aggressive Hsp90 isoform. Apoptosis was detected for SCC25 and was related to pAkt levels. ((c) 2013 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim).

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## In regard to de Lima et al.

Olson RA

To the Editor: The Brazilian investigators should be applauded for pursuing a randomized, double-blind controlled trial, seeking to determine whether low-level laser (LLL) therapy can effectively reduce oral mucositis in head-and-neck cancer patients undergoing concurrent chemoradiation therapy (1). This is certainly an important topic that affects many patients. To date, there have been limited gains in effective preventive treatments for oral mucositis (2, 3). However, several limitations in the study methodology severely hinder the ability to assess whether the intervention is effective or not.

First, the study by de Lima et al (1) was only powered to detect a 30% difference in oral mucositis risk, which left the study unable to detect a more modest yet still clinically meaningful difference. Second, the method used to analyze the primary outcomes reduced the power to detect a significant difference; by performing comparisons of oral mucositis rates at multiple time points, the investigators had to adjust for the multiple pairwise comparisons performed and thereby reduced the likelihood of identifying a significant difference in oral mucositis rates. The investigators would have had a higher chance of finding a significant difference by comparing oral mucositis rates aggregated across the multiple time points in a single analysis. Third, the heterogeneous study population, including patients who did not receive oral cavity radiation therapy, potentially diluted any benefit from LLL in preventing oral mucositis from oral cavity radiation therapy.

If the investigators had powered the study to detect a more conservative difference in oral mucositis and only accrued patients who had their oral cavity in the high-dose radiation therapy volume, then potentially a meaningful difference in the primary outcome would have been detected. Alternatively, a negative study under these conditions would have better allowed readers to conclude that LLL is unlikely to be of benefit to patients, directing the clinical and research community to turn to other potential strategies. Unfortunately, this current study assessing whether LLL can prevent oral mucositis in head-and-neck cancer patients receiving concurrent chemoradiotherapy does not adequately allow us to accept or reject the null hypothesis.

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## In reply to Olson.

de Castro G Jr, Snitcovsky IM

To the Editor: We thank Dr Olson for the interest in our publication (1, 2). As mentioned, the effect of measures to prevent chemoradiation-induced oral mucositis (OM) is limited. When designing the study, we estimated a 30% decrease in the incidence of grade 3 to 4 OM (80% in the control arm vs 50% in the experimental arm), judged as clinically meaningful, considering that the real impact of low-level laser (LLL) therapy in this scenario was unknown.

Another important aspect is related to the time points at which grades 3 to 4 OM are diagnosed during radiation therapy, leading to more frequent treatment interruptions as early as they appear, which is the reason why we decided to perform comparisons of OM rates at different time points in our study.

Respectfully, we partially agree with the possibility of diluting LLL therapy benefits due to the inclusion of patients with primary tumors located neither in the oral cavity nor the oropharynx in our study. In daily practice, OM is also detected when delivering concurrent chemoradiation in patients whose disease is diagnosed with primary tumors located in larynx or nasopharynx, as examples.

Finally, because we did observe significantly fewer unplanned treatment breaks in those patients treated with LLL, a marginal benefit could not be excluded in terms of reduced rates of grades 3 to 4 OM.

Recently reported studies by Gautam et al (3) and Antunes et al (4) were positive in terms of reducing severe OM and associated pain in patients undergoing chemoradiation, receiving LLL prophylaxis with higher energy density (3.5-4.0 J/cm<sup>2</sup>). Standardization of LLL parameters (wavelength and power) is necessary.

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## Oral care in Brazilian bone marrow transplant centers.

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**BACKGROUND:** Oral care is a fundamental procedure for the success of the hematopoietic stem cell transplantation, particularly regarding the control of oral infectious diseases. Information about oral care protocols and the inclusion of dental professionals in transplantation medical staff is poorly known.

**OBJECTIVE:** The aim of this study was to carry out a survey about the protocols of Brazilian dental

professionals with regard to oral care of HSCT patients. **METHODS:** A questionnaire was mailed to 36

Brazilian transplant centers with questions about basic oral care protocols, the indication of specific mouthwashes, antibiotic therapy regimens, laser therapy, and treatment of oral mucositis and graft-versus-host disease. All the respondent centers (n = 12) have dentists as members of the HSCT medical

staff. **RESULTS:** The majority indicate non-alcoholic chlorhexidine (n = 9; 75.0%) and sodium bicarbonate (n = 5; 41.7%) as routine mouthwashes. Laser therapy was frequently indicated (n= 9; 75.0%), mainly in the prevention of oral mucositis and in oral pain control. In the post-transplant period, antibiotic therapy was only indicated for invasive dental treatments (n= 8; 66.7%). Several treatments for graft-versus-host disease were mentioned without a trend towards establishing a standard protocol.

**CONCLUSION:** Basic oral care constitutes regular assessment in the routine treatment of hematopoietic stem cell transplantation patients in Brazilian centers.

Rev Bras Hematol Hemoter 2011 33(1) 15-20

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=23284237](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=23284237)

# Effect of low-level laser therapy on patient reported measures of oral mucositis and quality of life in head and neck cancer patients receiving chemoradiotherapy-a randomized controlled trial.

Gautam AP, Fernandes DJ, Vidyasagar MS, Maiya AG, Nigudgi S

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**IndiaPURPOSE:** Chemoradiotherapy (CRT)-induced oral mucositis (OM) adversely affects a patient's oral functions and quality of life (QOL). Low-level laser therapy (LLLT) showed some preventive and curative effects against clinically reported objective measures of OM in few trials including our recently published study. There is dearth of evidence regarding the effects of LLLT on patient's subjective experience of OM and QOL. Hence, we did this study to evaluate the effects of LLLT on a patient's reported measures of OM and QOL in head and neck cancer (HNC) patients receiving CRT. **METHODS:** This triple blinded study randomized 220 HNC patients scheduled for CRT (three weekly Cisplatin + RT = 66 Gray (2 Gy/session), five fractions/week for 6.5 weeks, total 33 fractions) into laser (110) and placebo (110) groups. The laser group received LLLT (Technomed Electronics Advanced Laser Therapy 1000, He-Ne,  $\lambda = 632.8$  nm, power density = 24 mW/cm<sup>2</sup>, dosage = 3.0 J at each point, total dose/session = 36-40 J, spot size 1 cm<sup>2</sup>, irradiation time/point 125 s) before each radiation session, while the placebo group did not receive laser therapy. Methodology was similar to our recently published study (Gautam et al. *Radiother Oncol* 104:349-354, 2012). In this part of our study, a blinded assessor collected subjective outcomes of the patient's reported measures of OM using Oral Mucositis Weekly Questionnaire-Head and Neck (OMWQ-HN) and QOL using Functional Assessment of Cancer Treatment-Head and Neck (FACT-HN) Questionnaire. Data were analyzed using repeated measure ANOVA through general linear model. Statistical significance was kept at  $p < 0.05$ . **RESULTS:** Results analysis revealed that OMWQ-HN ( $F = 12.199$ ,  $df = 6, 1314$ ,  $p < 0.001$ ) and FACT-HN ( $p < 0.05$ ) scores were significantly lower in LLLT than placebo group patients. Also, a significant reduction ( $p < 0.001$ ) in incidence of severe OM, need for opioid analgesics, and total parenteral nutrition was observed. **CONCLUSIONS:** LLLT was effective in improving the patient's subjective experience of OM and QOL in HNC patients receiving CRT.

Support Care Cancer 2012 Dec 8

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# Systematic review of laser and other light therapy for the management of oral mucositis in cancer patients.

Migliorati C, Hewson I, Lalla RV, Antunes HS, Estilo CL, Hodgson B, Lopes NN, Schubert MM, Bowen J, Elad S

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**BACKGROUND:** The aim of this study was to review the available literature and define clinical practice guidelines for the use of laser and other light therapies for the prevention and treatment of oral mucositis. **METHODS:** A systematic review was conducted by the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology. The body of evidence for each intervention, in each cancer treatment setting, was assigned an evidence level. Based on the evidence level, one of the following three guideline determinations was possible: recommendation, suggestion, and no guideline possible. **RESULTS:** A new recommendation was made for low-level laser (wavelength at 650 nm, power of 40 mW, and each square centimeter treated with the required time to a tissue energy dose of 2 J/cm<sup>2</sup> (2 s/point)) for the prevention of oral mucositis in adult patients receiving hematopoietic stem cell transplantation conditioned with high-dose chemotherapy, with or without total body irradiation. A new suggestion was made for low-level laser (wavelength around 632.8 nm) for the prevention of oral mucositis in patients undergoing radiotherapy, without concomitant chemotherapy, for head and neck cancer. No guideline was possible in other populations and for other light sources due to insufficient evidence. **CONCLUSIONS:** The increasing evidence in favor of low-level laser therapy allowed for the development of two new guidelines supporting this modality in the populations listed above. Evidence for other populations was also generally encouraging over a range of wavelengths and intensities. However, additional well-designed research is needed to evaluate the efficacy of laser and other light therapies in various cancer treatment settings.

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# Prevention of oral mucositis in children receiving cancer therapy: A systematic review and evidence-based analysis.

Qutob AF, Gue S, Revesz T, Logan RM, Keefe D

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This systematic review investigated, critically appraised, and rated the evidence on agents used to prevent oral mucositis in children. A comprehensive search of the relevant literature was performed up to December 2011. Articles were included according to the inclusion/exclusion criteria and were critically appraised for validation and quality assessment using a checklist consisting of 18 categories. Each article was then rated for its strength of evidence. 16,471 articles were retrieved from 19 different databases and then reduced to 27 articles that fit the inclusion criteria. Five articles on oral care protocols supported their use to prevent oral mucositis in children. Seven articles on chlorhexidine mouthwash and three on laser therapy had conflicting evidence of its use. The preventative agents that were supported by one or two articles included: benzydamine mouthwash, iseganan mouthwash, granulocyte-macrophage colony-stimulating factor (GM-CSF) mouthwash, oral/enteral glutamine, oral propantheline and cryotherapy, oral cryotherapy, oral sucralfate suspension, prostaglandin E2 tablets, and chewing gum. The reduction in the rates of occurrence of oral mucositis when using agents of fair (B) to good (A) evidence ranged from 22% to 52%. In conclusion, this review suggests the use of oral care protocols to prevent oral mucositis in children because of their strength of evidence (fair to good). The authors suggest avoiding agents with fair to good evidence against their use (oral sucralfate suspension, prostaglandin E2 tablets, and GM-CSF mouthwash). Agents with conflicting evidence (chlorhexidine mouthwash (used solely), laser therapy, and glutamine) should also be avoided until further research confirms their efficacy.

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[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=22959949](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22959949)

# [Does intraoral low-level laser therapy decrease mucositis during head and neck cancer radiotherapy?]

Boetz F

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[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=22907571](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22907571)

# Low level laser therapy for concurrent chemoradiotherapy induced oral mucositis in head and neck cancer patients - A triple blinded randomized controlled trial.

Gautam AP, Fernandes DJ, Vidyasagar MS, Maiya AG, Vadhiraja BM

Manipal University, Udupi, India.

**India**BACKGROUND AND PURPOSE: Oral mucositis (OM) is most cumbersome acute side effect of concurrent chemoradiotherapy (CCRT) for head and neck cancer (HNC). OM associated pain affects oral functions and nutrition of the patient that may result in discontinuity of treatment. Several modalities have been tried to prevent and treat OM, but none proved completely successful until date. We used prophylactic low level laser therapy (LLLT) for the prevention and treatment of CCRT induced OM. MATERIALS AND METHODS: In this triple blinded study, 221 HNC patients scheduled to undergo CCRT (Cisplatin (1, 22, 43day)+RT=66 Grays (2Gy/fraction), 33 fractions, 5 fractions/week, for 45days) were block randomized into laser (n=111) and placebo (n=110) group. Laser group received LLLT (HeNe, lambda=632.8nm, power-density=24mW, dosage=3.0J/point, total dosage/session=36-40J, spot-size=1cm(2), 5 sessions/week) while placebo received sham treatment daily prior to radiation. OM (RTOG/EORTC Scale), oral pain (VAS), dysphagia (FIS), weight loss and CCRT break were assessed. Data were analyzed using frequencies and percentage, generalized estimating equations (GEE) and odds ratio. RESULTS: There was significant reduction in incidence of severe OM (F=16.64, df=8876, p<0.0001) and its associated pain (F=25.06, df=8876, p<0.0001), dysphagia (F=20.17, df=8876, p<0.0001) and opioid analgesics use (p<0.0001) in laser than placebo group patients. CONCLUSIONS: LLLT decreased the incidence of CCRT induced severe OM and its associated pain, dysphagia and opioid analgesics use.

Radiother Oncol 2012 Aug 9

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=22884841](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22884841)

## [Radio-induced oral and pharyngeal mucositis: management updates].

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Mucositis is a major side effect induced by radiotherapy and/or chemotherapy of head and neck cancer. This toxicity impacts patient's quality of life and may compromise optimal treatments. Pathophysiology, risk factors, incidence and consequences of mucositis will be discussed in this review. Its management remains principally supportive (pain medication and nutritional support); however, in recent years several studies have revealed that the use of low level energy laser is particularly useful in the prevention and treatment of chemo- and radio-induced mucositis.

Cancer Radiother 2012 Sep 16(5-6) 358-63

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=22841560](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22841560)

# Effect of irradiation with red and infrared laser in the treatment of oral mucositis: a pilot study with patients undergoing chemotherapy with 5-FU.

Cunha CB, Eduardo FP, Zezell DM, Bezinelli LM, Shitara PP, Correa L

Aristides Maltez Hospital, Salvador, BA, Brazil.

Lasers Med Sci 2012 Nov 27(6) 1233-40

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?  
cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=22588683](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22588683)

# Low Level Helium Neon Laser therapy for chemoradiotherapy induced oral mucositis in oral cancer patients - A randomized controlled trial.

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**IndiaBACKGROUND:** Patients receiving chemoradiotherapy (CRT) for oral cancer (OC) often develop oral mucositis (OM). OM associated pain severely affects oral functions and nutrition of the patient, resulting in narcotic analgesic use and CRT interruption. Laser therapy has shown some promising results in preventing and treating OM caused by cancer therapies. So in this trial we used prophylactic Low Level Helium Neon (He-Ne) Laser for the prevention and treatment of CRT induced OM in OC patients. **MATERIALS AND METHODS:** This double blinded trial block randomized 121 primary OC patients scheduled to undergo CRT [RT dosage=66Gray/33fractions for 5days/week and chemotherapy (3 weekly Cisplatin)] into laser (n=60) and placebo (n=61) group. Laser group received He-Ne Laser ( $\lambda=632.8\text{nm}$ ,  $P=24\text{mW}$ ,  $ED=3.5\text{J}/\text{cm}^2$ ) while placebo received sham treatment just before radiation for 6.5weeks. OM (RTOG/EORTC Scale), its associated pain, and total parenteral nutrition (TPN), were assessed on every week by a blinded assessor. Also opioid analgesic use, weight loss and any CRT break were recorded. Data was analyzed using descriptive statistics, t-test and Man Whitney U test. Level of significance was set at  $p<0.05$ . **RESULTS:** Incidence of severe OM (29% vs. 89%,  $p<0.001$ ) and its associated pain (18% vs. 71%,  $p<0.001$ ), opioid analgesic use (7% vs. 21%,  $p<0.001$ ) and TPN (30% vs. 39%  $p=0.039$ ) was significantly less in laser than placebo group patients. Also duration of severe OM and pain experienced was less in laser than placebo group. CRT break required only for placebo group (9%) patients. **CONCLUSION:** Low Level He-Ne Laser decreased the incidence of CRT induced severe OM and its associated pain, opioid analgesics use and TPN.

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[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=22502814](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22502814)

# Efficacy of Low-Level Laser Therapy (LLLT) in Oral Mucositis: What Have We Learned from Randomized Studies and Meta-Analyses?

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[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?  
cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=22486724](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22486724)

# Low-level laser therapy in the prevention and treatment of cancer therapy-induced mucositis: 2012 state of the art based on literature review and meta-analysis.

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**PURPOSE OF REVIEW:** To discuss the promising state of the art low-level laser therapy (LLLT) for preventive and therapeutic usage in oral mucositis due to cancer therapy. **RECENT FINDINGS:** Photomedicine using LLLT is very effective with intraoral and extraoral devices in the management of oral mucositis, based on several studies including randomized control studies. A systematic review identified 33 relevant articles that were subjected to meta-analysis based on which laser parameters in routine practice are being defined. Meta-analysis showed that LLLT reduced risk of oral mucositis with relative risk (RR) 2.45 [confidence interval (CI) 1.85-3.18], reduced duration, severity of oral mucositis and reduced number of days with oral mucositis (4.38 days, P = 0.0009). RR was similar between the red (630-670 nm) and infrared (780-830 nm) LLLT. Pain-relieving effect based on the Cohen scale was at 1.22 (CI 0.19-2.25). **SUMMARY:** No adverse side effects of LLLT were reported; hence, we recommend red or infrared LLLT with diode output between 10-100 mW, dose of 2-3 J/cm/cm for prophylaxis and 4 J/cm (maximum limit) for therapeutic effect, application on single spot rather than scanning motion. Lesions must be evaluated by a trained clinician and therapy should be repeated daily or every other day or a minimum of three times per week until resolution. There is moderate-to-strong evidence in favor of LLLT at optimal doses as a well tolerated, relatively inexpensive intervention for cancer therapy-induced oral mucositis. It is envisaged that LLLT will soon become part of routine oral supportive care in cancer.

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[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=22450151](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22450151)

# Prevention and management of antineoplastic therapy induced oral mucositis.

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With the scientific advancements in the management of malignant diseases, the treatment is expensive and bears high morbidity in term of oral mucositis. It is a debilitating condition and has been researched extensively for its pathogenesis and treatment. Various treatment options include barrier forming, mucosal protectants, mouth rinses, growth factors, lasers and midline-sparing procedures. Some agents are used locally while others are administered systemically. Despite the availability of a wide range of treatment options for mucositis, a cost-effective treatment is yet to be evolved.

Natl J Maxillofac Surg 2010 Jul 1(2) 127-34

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=22442583](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22442583)

# Evaluation of low-level laser therapy in the prevention and treatment of radiation-induced mucositis: A double-blind randomized study in head and neck cancer patients.

Carvalho PA, Jaguar GC, Pellizzon AC, Prado JD, Lopes RN, Alves FA

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The purpose of this prospective study was to determine the effect of the low-level laser in the prevention and treatment of mucositis in head and neck cancer patients. A total of 70 patients with malignant neoplasms in the oral cavity or oropharynx were evaluated. The patients were randomized into two low-level laser therapy groups: Group 1 (660nm/15mW/3.8J/cm<sup>2</sup>/spot size 4mm<sup>2</sup>) or Group 2 (660nm/5mW/1.3J/cm<sup>2</sup>/spot size 4mm<sup>2</sup>) starting on the first day of radiotherapy. Oral mucositis was assessed daily and weekly using the NCI and WHO scales. Oral pain was scored daily with a visual analogue scale before laser application. The patients in Group 1 had a mean time of 13.5days (range 6-26days) to present mucositis grade II, while the patients in Group 2 had a mean time of 9.8days (range 4-14days) (both WHO and NCI p=0.005). In addition, Group 2 also presented a higher mucositis grade than Group 1 with significant differences found in weeks 2 (p=0.019), 3 (p=0.005) and 4 (p=0.003) for WHO scale and weeks 2 (p=0.009) and 4 (p=0.013) for NCI scale. The patients in Group 1 reported lower pain levels (p=0.004). Low-level laser therapy during radiotherapy was found to be effective in controlling the intensity of mucositis and pain.

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[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=21911312](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21911312)

# Management of oral and gastrointestinal mucositis: ESMO Clinical Practice Guidelines.

Peterson DE, Bensadoun RJ, Roila F

Department of Oral Health and Diagnostic Sciences, School of Dental Medicine, Neag Comprehensive Cancer Center, University of Connecticut Health Center, Farmington, Connecticut, USA.

No Abstract provided.

Regarding laser the guidelines say: Low-level laser therapy (LLLT) is suggested to reduce incidence of oral mucositis and its associated pain, in patients receiving high-dose chemotherapy or chemoradiotherapy before HSCT, if the treatment centre is able to support the necessary technology and training

Ann Oncol 2011 Sep 22 Suppl 6 vi78-84

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=21908510](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21908510)

## [Treatment and prevention of cancer treatment related oral mucositis].

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One of the most common and troublesome complications of modern intensive anticancer treatments is oral mucositis. The purpose of this review is to summarize current evidence and clinical guidelines regarding its prevention and therapy. The use of keratinocyte growth factor-1, supplementary glutamine and other recently developed treatment modalities are discussed. The injury of the oral mucosa caused by antineoplastic agents promotes the local expression of multiple pro-inflammatory and pro-apoptotic molecules and eventually leads to the development of ulcers. Such lesions predispose patients to several infectious and nutritional complications. Also, they lead to modification of treatment schedules, potentially affecting overall prognosis. Local cryotherapy with ice chips and phototherapy with low energy laser may be useful as preventive measures. Mouthwashes with allopurinol and phototherapy with low energy laser can be used as treatment. In radiotherapy, special radiation administration techniques should be used to minimize mucosal injury. Pain control should always be optimized, with the use of patient controlled analgesia and topical use of morphine. Supplemental glutamine should not be used outside of research protocols. Lastly, thorough attention should be paid to general care and hygiene measures.

Rev Med Chil 2011 Mar 139(3) 373-81

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=21879172](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21879172)

# Amelioration of oral mucositis pain by NASA near-infrared light-emitting diodes in bone marrow transplant patients.

Hodgson BD, Margolis DM, Salzman DE, Eastwood D, Tarima S, Williams LD, Sande JE, Vaughan WP, Whelan HT

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**USAPURPOSE:** This study seeks to investigate the use of extra-orally applied near-infrared phototherapy for the reduction of oral pain secondary to chemotherapy- and radiation therapy-induced mucositis in adult and pediatric hematopoietic stem cell transplant (HSCT) patients. **METHODS:** Eighty HSCT patients were divided into regular (R) and low (L) risk groups, then to experimental (E) and placebo (P) groups, resulting in four groups (ER, EL, PR, PL). Experimental subjects received 670 (+/-10) nm gallium-aluminum-arsinide light-emitting diode device for 80 s at approximately 50 mW/cm<sup>2</sup> energy density and power exposure of 4 J/cm<sup>2</sup>. Placebo patients received the same procedures, but with a placebo phototherapy (identical device but <5 mW/cm<sup>2</sup> energy density). Patients received their respective light therapy once per day starting on the day of the HSCT (day 0) and continued through day +14. Blinded evaluators examined the patients three times per week and scored their oral tissues and patient-reported pain assessments at each evaluation utilizing the WHO, NCI-CTCAE, and OMAS scales. **RESULTS:** Analysis of the mean scores at each observation demonstrate that the extra-oral application of phototherapy resulted in a significant reduction in patient-reported pain between the ER and PR patients ( $p < 0.05$ ) at day +14 when graded via the WHO criteria. The ER and EL patients were improved in almost all other categories and assessment scales, but the differences were not statistically significant. **CONCLUSION:** Phototherapy demonstrated a significant reduction in patient-reported pain as measured by the WHO criteria in this patient population included in this study. Improvement trends were noted in most other assessment measurements.

Support Care Cancer 2011 Jul 3

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=21725826](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21725826)

# A systematic review with meta-analysis of the effect of low-level laser therapy (LLLT) in cancer therapy-induced oral mucositis.

Bjordal JM, Bensadoun RJ, Tuner J, Frigo L, Gjerde K, Lopes-Martins RA

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**PURPOSE:** The purpose of this study is to review the effects of low-level laser therapy (LLLT) in the prevention and treatment of cancer therapy-induced oral mucositis (OM). **METHODS:** A systematic review and meta-analysis of randomised placebo-controlled trials of LLLT performed during chemotherapy or radiation therapy in head and neck cancer patients. **RESULTS:** We found 11 randomised placebo-controlled trials with a total of 415 patients; methodological quality was acceptable at 4.10 (SD +/- 0.74) on the 5-point Jadad scale. The relative risk (RR) for developing OM was significantly ( $p = 0.02$ ) reduced after LLLT compared with placebo LLLT (RR = 2.03 (95% CI, 1.11 to 3.69)). This preventive effect of LLLT improved to RR = 2.72 (95% CI, 1.98 to 3.74) when only trials with adequate doses above 1 J were included. For treatment of OM ulcers, the number of days with OM grade 2 or worse was significantly reduced after LLLT to 4.38 (95% CI, 3.35 to 5.40) days less than placebo LLLT. Oral mucositis severity was also reduced after LLLT with a standardised mean difference of 1.33 (95% CI, 0.68 to 1.98) over placebo LLLT. All studies registered possible side-effects, but they were not significantly different from placebo LLLT. **CONCLUSIONS:** There is consistent evidence from small high-quality studies that red and infrared LLLT can partly prevent development of cancer therapy-induced OM. LLLT also significantly reduced pain, severity and duration of symptoms in patients with cancer therapy-induced OM.

Support Care Cancer 2011 Aug 19(8) 1069-77

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=21660670](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21660670)

# Laser phototherapy as a treatment for radiotherapy-induced oral mucositis.

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Oral mucositis is a harmful side effect of radiotherapy (RT) on the head and neck region. There are encouraging reports on the beneficial aspects of the use of laser light on the treatment of oral mucositis. This paper reports the efficacy of laser phototherapy (LPT) on the treatment of oral mucositis in a patient undergoing RT after surgical removal of a squamous cell carcinoma with osseous invasion of the maxilla. Palatal and commissural lesions were treated with lambda660 nm, 40 mW, slashed circle=4 mm(2), in contact mode, 5 x 2.4 J/cm(2) per point, 14.4 J/cm(2) per session. For treating the lesion on the patient's nasal mucosa, LPT (slashed circle=4 mm(2), lambda780 nm, 70 mW, 3 x 2.1 J/cm(2) per point, 6.3 J/cm(2) per session, contact mode) was used on the external area of the nose. A single dose (2.4 J/cm(2)) with the lambda660 nm laser, as described before, was applied on the entrance of each nostril. LPT was used 3 times/week during 4 weeks. Treatment results indicate that the use of LPT on oral mucositis was effective and allowed the patient to carry on the RT without interruption. However, long-term and controlled clinical trials are necessary to establish both preventive and curative protocols using LPT.

Braz Dent J 2011 22(2) 162-5

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=21537592](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21537592)

# Use of laser phototherapy on a delayed wound healing of oral mucosa previously submitted to radiotherapy: case report.

Ramalho KM, Luiz AC, de Paula Eduardo C, Tuner J, Magalhaes RP, Gallottini Magalhaes M

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Radiotherapy produces both acute and delayed effects on mucosal tissues, disturbing their healing. This report shows a successful treatment with laser phototherapy (LPT) on a delayed wound healing in oral mucosa previously submitted to radiotherapy with a follow up of 3 years. A 47-year-old patient treated 6 months earlier for tongue squamous cell carcinoma by surgery and radiotherapy presented with a mass in the operated area. Biopsy showed chronic inflammatory infiltrate around a residual polyglactin suture. After 2 months there was a painful mucosal dehiscence on the biopsy site. LPT was performed using a semiconductor laser with 660-nm wavelength (InGaAlP) and spot size of 0.04 cm<sup>2</sup>. The parameters applied were 40 mW, 4 J/cm<sup>2</sup> /point, 0.16 J/point, 2.4 J/session. The irradiation was performed punctually, through contact mode in 15 points (4 seconds/point), on top of and around the lesion, during ten sessions. The wound healed completely after ten sessions. This treatment proved to be conservative and effective, inducing healing of a chronic wound in a tissue previously submitted to radiotherapy.

Int Wound J 2011 Apr 15

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=21496209](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21496209)

# Interventions for preventing oral mucositis for patients with cancer receiving treatment.

Worthington HV, Clarkson JE, Bryan G, Furness S, Glenny AM, Littlewood A, McCabe MG, Meyer S, Khalid T

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**BACKGROUND:** Treatment of cancer is increasingly more effective but is associated with short and long term side effects. Oral side effects remain a major source of illness despite the use of a variety of agents to prevent them. One of these side effects is oral mucositis (mouth ulcers). **OBJECTIVES:** To evaluate the effectiveness of prophylactic agents for oral mucositis in patients with cancer receiving treatment, compared with other potentially active interventions, placebo or no treatment. **SEARCH STRATEGY:** Electronic searches of Cochrane Oral Health Group and PaPaS Trials Registers (to 16 February 2011), CENTRAL (The Cochrane Library 2011, Issue 1), MEDLINE via OVID (1950 to 16 February 2011), EMBASE via OVID (1980 to 16 February 2011), CINAHL via EBSCO (1980 to 16 February 2011), CANCERLIT via PubMed (1950 to 16 February 2011), OpenSIGLE (1980 to 2005) and LILACS via the Virtual Health Library (1980 to 16 February 2011) were undertaken. Reference lists from relevant articles were searched and the authors of eligible trials were contacted to identify trials and obtain additional information. **SELECTION CRITERIA:** Randomised controlled trials of interventions to prevent oral mucositis in patients receiving treatment for cancer. **DATA COLLECTION AND ANALYSIS:** Information regarding methods, participants, interventions, outcome measures, results and risk of bias were independently extracted, in duplicate, by two review authors. Authors were contacted for further details where these were unclear. The Cochrane Collaboration statistical guidelines were followed and risk ratios calculated using random-effects models. **MAIN RESULTS:** A total of 131 studies with 10,514 randomised participants are now included. Overall only 8% of these studies were assessed as being at low risk of bias. Ten interventions, where there was more than one trial in the meta-analysis, showed some statistically significant evidence of a benefit (albeit sometimes weak) for either preventing or reducing the severity of mucositis, compared to either a placebo or no treatment. These ten interventions were: aloe vera, amifostine, cryotherapy, granulocyte-colony stimulating factor (G-CSF), intravenous glutamine, honey, keratinocyte growth factor, laser, polymixin/tobramycin/amphotericin (PTA) antibiotic pastille/paste and sucralfate. **AUTHORS' CONCLUSIONS:** Ten interventions were found to have some benefit with regard to preventing or reducing the severity of mucositis associated with cancer treatment. The strength of the evidence was variable and implications for practice include consideration that benefits may be specific for certain cancer types and treatment. There is a need for further well designed, and conducted trials with sufficient numbers of participants to perform subgroup analyses by type of disease and chemotherapeutic agent.

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[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=21491378](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21491378)

# Chemotherapy-induced oral mucositis in a patient with acute lymphoblastic leukaemia.

Rimulo AL, Ferreira MC, Abreu MH, Aguirre-Neto JC, Paiva SM

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**BACKGROUND:** Oral mucositis is the main complication of chemotherapy and radiotherapy used in the treatment of cancer. Phototherapy has proven effective in the treatment of mucositis, as it accelerates the tissue healing process and has both analgesic and anti-inflammatory properties. **CASE REPORT:** This paper reports the case of a paediatric patient with oral mucositis stemming from chemotherapy employed for the treatment of acute lymphoblastic leukaemia. **TREATMENT:** The lesions were treated daily with a light-emitting diode (LED). **FOLLOWUP:** Remission of the lesions occurred after 10 days of treatment. **CONCLUSIONS:** LED was effective in the treatment of mucositis, as it diminished pain symptoms and accelerated the tissue repair process.

Eur Arch Paediatr Dent 2011 Apr 12(2) 124-7

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=21473846](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21473846)

# Low level laser therapy in oral mucositis: a pilot study.

Cauwels RG, Martens LC

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**AIM:** The goal of this pilot study was to investigate the capacity of pain relief and wound healing of low level laser therapy (LLLT) in chemotherapy-induced oral mucositis (OM) in a paediatric oncology population group. **STUDY DESIGN AND METHODS:** 16 children (mean age 9.4 years) from the Gent University Hospital - Department Paediatric Oncology/haematology, suffering from chemotherapy-induced OM were selected. During clinical investigations, the OM grade was assessed using the WHO classification. All children were treated using a GaAlAs diode laser with 830 nm wavelength and a potency of 150 mW. The energy released was adapted according to the severity of the OM lesions. The same protocol was repeated every 48 hrs until healing of each lesion occurred. Subjective pain was monitored before and immediately after treatment by an appropriate pain scale and functional impairment was recorded. At each visit, related blood cell counts were recorded. **RESULTS:** After 12 mths, records were evaluated and information about treatment sequence, treatment sessions and frequencies related to the pain sensation and comfort were registered. Immediately after beaming the OM, pain relief was noticed. Depending on the severity of OM, on average, 2.5 treatments per lesion in a period of 1 week were sufficient to heal a mucositis lesion. **CONCLUSIONS:** LLLT, one of the most recent and promising treatment therapies, has been shown to reduce the severity and duration of mucositis and to relieve pain significantly. In the present study similar effects were obtained with the GaAlAs 830nm diode laser. It became clear that using the latter diode device, new guidelines could be developed as a function of the WHO-OM grades i.e. the lower the grade, the less energy needed. Immediate pain relief and improved wound healing resolved functional impairment that was obtained in all cases.

Eur Arch Paediatr Dent 2011 Apr 12(2) 118-23

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=21473845](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21473845)

# Effect of intraoral low-level laser therapy on quality of life of patients with head and neck cancer undergoing radiotherapy.

Oton-Leite AF, Correa de Castro AC, Morais MO, Pinezi JC, Leles CR, Mendonca EF

Department of Oral Medicine (Oral Pathology), Dental School, Federal University of Goias, Goiania, Brazil.

**BACKGROUND:** Low-level laser therapy has been used to reduce complications of head and neck cancer treatment. The aim was to assess the impact of laser in the quality of life (QOL) of patients receiving radiotherapy. **METHODS:** Sixty outpatients were randomly assigned into 2 groups. The laser group received applications and the placebo group received sham laser. QOL was assessed using the University of Washington QOL questionnaire. A repeated-measures analysis of variance (ANOVA) was used for comparisons of overall QOL scores and Mann-Whitney test compared changes in domain scores. **RESULTS:** A decrease in QOL scores was observed in both groups and the reduction in the laser group was significantly lower ( $p < .01$ ). Changes in QOL scores regarding pain, chewing, and saliva domains were evident in the placebo group. Both health-related QOL and overall QOL were rated higher by patients who received laser therapy. **CONCLUSION:** Laser therapy reduces the impact of radiotherapy on the QOL of patients with head and neck cancer. (c) 2011 Wiley Periodicals, Inc. *Head Neck*, 2011.

*Head Neck* 2011 Apr 5

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=21472883](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21472883)

# Management of chemo- and radiotherapy induced oral mucositis with low-energy laser: initial results of A.C. Camargo Hospital.

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**Background.** Oral mucositis is a common complication of some malignancies treatment, causing therapeutic modifications due to patient's debilitation, which often interferes with the prognosis of the disease. Many attempts have been made to find an optimal treatment or preventive method to minimize the severity of oral mucositis. Several studies have shown good results with the use of low-energy laser, with the aim of accelerating the process of wound healing and promoting pain relief. **Methods.** Patients (n=18) who developed oral mucositis during chemotherapy and/or radiotherapy were submitted to low-energy laser applications until cessation of symptoms. Mucositis severity was scored by an oral mucositis scale based on clinical features and by an oral toxicity scale from the National Cancer Institute based on the ability to swallow; pain severity was scored by subjects on a visual analogue scale before and after the applications. **Results.** Immediate pain relief was achieved in 66.6% of the patients after the first application. Based on the functional scale, mucositis grade III (not capable to eat solids) was reduced in 42.85% of the cases. According to the scale based on the clinical features, mucositis grade IV (ulcerative lesions) was reduced in 75% of the patients that presented this grade of mucositis at the beginning of laser therapy. **Conclusions.** Low-energy laser was well-tolerated and showed beneficial effects on the management of oral mucositis, improving the quality of life during the oncologic treatment.

J Appl Oral Sci 2003 Dec 11(4) 337-41

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=21394411](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21394411)

# Efficacy of low-level laser therapy and aluminum hydroxide in patients with chemotherapy and radiotherapy-induced oral mucositis.

Lima AG, Antequera R, Peres MP, Snitcosky IM, Federico MH, Villar RC

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This study evaluated the efficacy of low-level laser therapy (LLLT) and aluminum hydroxide (AH) in the prevention of oral mucositis (OM). A prospective, comparative and non-randomized study was conducted with 25 patients with head and neck cancer subjected to radiotherapy (RT) or radiochemotherapy (RCT). Twelve patients received LLLT (830 nm, 15 mW, 12 J/cm<sup>2</sup>) daily from the 1st day until the end of RT before each sessions during 5 consecutive days, and the other 13 patients received AH 310 mg/5 mL, 4 times/day, also throughout the duration of RT, including weekends. OM was measured using an oral toxicity scale (OTS) and pain was measured using the visual analogue scale (VAS). EORTC questionnaires were administered to the evaluate impact of OM on quality of life. The LLLT group showed lower mean OTS and VAS scores during the course of RT. A significant difference was observed in pain evaluation in the 13th RT session ( $p=0.036$ ). In both groups, no interruption of RT was needed. The prophylactic use of both treatments proposed in this study seems to reduce the incidence of severe OM lesions. However, the LLLT was more effective in delaying the appearance of severe OM.

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[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=21203698](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21203698)

# A randomized controlled trial of visible-light therapy for the prevention of oral mucositis.

Elad S, Luboshitz-Shon N, Cohen T, Wainchwaig E, Shapira MY, Resnick IB, Radiano R, Lubart R, Or R

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The objective of this study was to assess the efficacy of a novel visible-light therapy (VLT) device for the prevention of oral mucositis in hematopoietic stem cell transplantation (HSCT) patients. A VLT-device suitable for intra-oral use was applied to 20 patients undergoing HSCT. The study design was placebo-controlled, randomized and double-blind. Oral mucositis was assessed using the OMAS and WHO scales. Oral pain and acceptance levels were scored by the patient using a 10-step scale. Patients were evaluated once a week until day 21 post-HSCT. Mucositis rate, severity and pain score were compared. At the third visit, 1 week post-HSCT, mucositis rates were significantly lower in the treatment group (for both WHO and OMAS  $p=0.02$ ). Mucositis was also less severe in the treatment group (for WHO  $p=0.01$ ; for OMAS  $p=0.01$ ). Furthermore, the patients in the treatment group reported lower pain levels ( $p=0.04$ ). The treatment was well tolerated and highly accepted, with no reports of adverse events related to the device. These findings suggest that the VLT-device is safe and effective for the prevention of oral mucositis in patients undergoing HSCT.

Oral Oncol 2010 Dec 15

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=21163686](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21163686)

# Oral Mucositis Prevention by Low-Level Laser Therapy in Head-and-Neck Cancer Patients Undergoing Concurrent Chemoradiotherapy: A Phase III Randomized Study.

Gouvea de Lima A, Villar RC, de Castro G Jr, Antequera R, Gil E, Rosalmeida MC, Federico MH, Snitcovsky IM

Departamento de Radiologia, Disciplina de Oncologia, Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, SP, Brazil.

**PURPOSE:** Oral mucositis is a major complication of concurrent chemoradiotherapy (CRT) in head-and-neck cancer patients. Low-level laser (LLL) therapy is a promising preventive therapy. We aimed to evaluate the efficacy of LLL therapy to decrease severe oral mucositis and its effect on RT interruptions. **METHODS AND MATERIALS:** In the present randomized, double-blind, Phase III study, patients received either gallium-aluminum-arsenide LLL therapy 2.5 J/cm<sup>2</sup> or placebo laser, before each radiation fraction. Eligible patients had to have been diagnosed with squamous cell carcinoma or undifferentiated carcinoma of the oral cavity, pharynx, larynx, or metastases to the neck with an unknown primary site. They were treated with adjuvant or definitive CRT, consisting of conventional RT 60-70 Gy (range, 1.8-2.0 Gy/d, 5 times/wk) and concurrent cisplatin. The primary endpoints were the oral mucositis severity in Weeks 2, 4, and 6 and the number of RT interruptions because of mucositis. The secondary endpoints included patient-reported pain scores. To detect a decrease in the incidence of Grade 3 or 4 oral mucositis from 80% to 50%, we planned to enroll 74 patients. **RESULTS:** A total of 75 patients were included, and 37 patients received preventive LLL therapy. The mean delivered radiation dose was greater in the patients treated with LLL (69.4 vs. 67.9 Gy,  $p = .03$ ). During CRT, the number of patients diagnosed with Grade 3 or 4 oral mucositis treated with LLL vs. placebo was 4 vs. 5 (Week 2,  $p = 1.0$ ), 4 vs. 12 (Week 4,  $p = .08$ ), and 8 vs. 9 (Week 6,  $p = 1.0$ ), respectively. More of the patients treated with placebo had RT interruptions because of mucositis (6 vs. 0,  $p = .02$ ). No difference was detected between the treatment arms in the incidence of severe pain. **CONCLUSIONS:** LLL therapy was not effective in reducing severe oral mucositis, although a marginal benefit could not be excluded. It reduced RT interruptions in these head-and-neck cancer patients, which might translate into improved CRT efficacy.

Int J Radiat Oncol Biol Phys 2010 Dec 14

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=21163585](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21163585)

# Interventions for preventing oral mucositis for patients with cancer receiving treatment.

Worthington HV, Clarkson JE, Bryan G, Furness S, Glenny AM, Littlewood A, McCabe MG, Meyer S, Khalid T

Cochrane Oral Health Group, School of Dentistry, The University of Manchester, Coupland III Building, Oxford Road, Manchester, UK, M13 9PL.

**BACKGROUND:** Treatment of cancer is increasingly more effective but is associated with short and long term side effects. Oral side effects remain a major source of illness despite the use of a variety of agents to prevent them. One of these side effects is oral mucositis (mouth ulcers). **OBJECTIVES:** To evaluate the effectiveness of prophylactic agents for oral mucositis in patients with cancer receiving treatment, compared with other potentially active interventions, placebo or no treatment. **SEARCH STRATEGY:** Electronic searches of Cochrane Oral Health Group and PaPaS Trials Registers (to 1 June 2010), CENTRAL (The Cochrane Library 2010, Issue 2), MEDLINE via OVID (1950 to 1 June 2010), EMBASE via OVID (1980 to 1 June 2010), CINAHL via EBSCO (1980 to 1 June 2010), CANCELIT via PubMed (1950 to 1 June 2010), OpenSIGLE (1980 to 2005) and LILACS via the Virtual Health Library (1980 to 1 June 2010) were undertaken. Reference lists from relevant articles were searched and the authors of eligible trials were contacted to identify trials and obtain additional information. **SELECTION CRITERIA:** Randomised controlled trials of interventions to prevent oral mucositis in patients receiving treatment for cancer. **DATA COLLECTION AND ANALYSIS:** Information regarding methods, participants, interventions, outcome measures, results and risk of bias were independently extracted, in duplicate, by two review authors. Authors were contacted for further details where these were unclear. The Cochrane Collaboration statistical guidelines were followed and risk ratios calculated using random-effects models. **MAIN RESULTS:** A total of 131 studies with 10,514 randomised participants are now included. Nine interventions, where there was more than one trial in the meta-analysis, showed some statistically significant evidence of a benefit (albeit sometimes weak) for either preventing or reducing the severity of mucositis, compared to either a placebo or no treatment. These nine interventions were: allopurinol, aloe vera, amifostine, cryotherapy, glutamine (intravenous), honey, keratinocyte growth factor, laser, and polymixin/tobramycin/amphotericin (PTA) antibiotic pastille/paste. **AUTHORS' CONCLUSIONS:** Nine interventions were found to have some benefit with regard to preventing or reducing the severity of mucositis associated with cancer treatment. The strength of the evidence was variable and implications for practice include consideration that benefits may be specific for certain cancer types and treatment. There is a need for further well designed, and conducted trials with sufficient numbers of participants to perform subgroup analyses by type of disease and chemotherapeutic agent.

Cochrane Database Syst Rev 2010 (12) CD000978

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=21154347](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21154347)

# The Prevention of Induced Oral Mucositis with Low-Level Laser Therapy in Bone Marrow Transplantation Patients: A Randomized Clinical Trial.

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**Brazil Abstract Background Data and Objective:** Patients who have received high doses of chemotherapy, either alone or in combination with total body irradiation often cite oral mucositis (OM) as the most debilitating side effect. The aim of this study was to investigate the clinical effects of low-level laser therapy (LLLT) on the prevention of conditioning-induced OM in hematopoietic stem cell transplantation (HSCT). **Methods:** We randomized 42 patients who underwent autologous or allogeneic HSCT. A low-level InGaAlP diode laser was used, emitting light at 660 nm, 40 mW, and 4 J/cm<sup>2</sup>. An evaluation of OM was carried out using the World Health Organization scale. **Results and Conclusion:** In the LLLT group, 57.1% of patients had an OM grade 0, 9.6% had grade 1, and 33.3% had grade 2, whereas in the control group, only 4.8% of patients were free of OM (grade 0). Our results indicate that the preventive use of LLLT in patients who have undergone HSCT is a powerful instrument in reducing OM incidence.

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[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=20969443](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20969443)

# Interventions for treating oral mucositis for patients with cancer receiving treatment.

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**BACKGROUND:** Treatment of cancer is increasingly effective but associated with short and long term side effects. Oral side effects, including oral mucositis (mouth ulceration), remain a major source of illness despite the use of a variety of agents to treat them. **OBJECTIVES:** To assess the effectiveness of interventions for treating oral mucositis or its associated pain in patients with cancer receiving chemotherapy or radiotherapy or both. **SEARCH STRATEGY:** Electronic searches of Cochrane Oral Health Group and PaPaS Trials Registers (to 1 June 2010), CENTRAL via The Cochrane Library (to Issue 2, 2010), MEDLINE via OVID (1950 to 1 June 2010), EMBASE via OVID (1980 to 1 June 2010), CINAHL via EBSCO (1980 to 1 June 2010), CANCERLIT via PubMed (1950 to 1 June 2010), OpenSIGLE (1980 to 1 June 2010) and LILACS via the Virtual Health Library (1980 to 1 June 2010) were undertaken. Reference lists from relevant articles were searched and the authors of eligible trials were contacted to identify trials and obtain additional information. **SELECTION CRITERIA:** All randomised controlled trials comparing agents prescribed to treat oral mucositis in people receiving chemotherapy or radiotherapy or both. Outcomes were oral mucositis, time to heal mucositis, oral pain, duration of pain control, dysphagia, systemic infection, amount of analgesia, length of hospitalisation, cost and quality of life. **DATA COLLECTION AND ANALYSIS:** Data were independently extracted, in duplicate, by two review authors. Authors were contacted for details of randomisation, blindness and withdrawals. Risk of bias assessment was carried out on six domains. The Cochrane Collaboration statistical guidelines were followed and risk ratio (RR) values calculated using fixed-effect models (less than 3 trials in each meta-analysis). **MAIN RESULTS:** Thirty-two trials involving 1505 patients satisfied the inclusion criteria. Three comparisons for mucositis treatment including two or more trials were: benzydamine HCl versus placebo, sucralfate versus placebo and low level laser versus sham procedure. Only the low level laser showed a reduction in severe mucositis when compared with the sham procedure, RR 5.28 (95% confidence interval (CI) 2.30 to 12.13). Only 3 comparisons included more than one trial for pain control: patient controlled analgesia (PCA) compared to the continuous infusion method, therapist versus control, cognitive behaviour therapy versus control. There was no evidence of a difference in mean pain score between PCA and continuous infusion, however, less opiate was used per hour for PCA, mean difference 0.65 mg/hour (95% CI 0.09 to 1.20), and the duration of pain was less 1.9 days (95% CI 0.3 to 3.5). **AUTHORS' CONCLUSIONS:** There is weak and unreliable evidence that low level laser treatment reduces the severity of the mucositis. Less opiate is used for PCA versus continuous infusion. Further, well designed, placebo or no treatment controlled trials assessing the effectiveness of interventions investigated in this review and new interventions for treating mucositis are needed.

Cochrane Database Syst Rev 2010 8 CD001973

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=20687070](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20687070)

# Effects of low-level laser therapy on collagen expression and neutrophil infiltrate in 5-fluorouracil-induced oral mucositis in hamsters.

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**BACKGROUND AND OBJECTIVES:** Several studies have suggested that low-level laser therapy (LLLT) can ameliorate oral mucositis; however, the mechanisms involved are not well understood. The aim of this study was to investigate the mechanisms of action of LLLT on chemotherapy-induced oral mucositis, as related to effects on collagen expression and inflammation. **MATERIALS AND METHODS:** A hamster cheek pouch model of oral mucositis was used with all animals receiving intraperitoneal 5-fluorouracil, followed by surface irritation. Animals were randomly allocated into three groups, and treated with an InGaAlP diode laser at a wavelength of 660 nm and output power of 35 or 100 mW laser, or no laser. Clinical severity of mucositis was assessed at four time-points by a blinded examiner. Buccal pouch tissue was harvested from a subgroup of animals in each group at four time-points. Collagen was qualitatively and quantitatively evaluated after picosirius staining. The density of the neutrophil infiltrate was also scored. **RESULTS:** Peak clinical severity of mucositis was reduced in the 35 mW laser group as compared to the 100 mW and control groups. The reduced peak clinical severity of mucositis in the 35 mW laser group was accompanied by a decrease in the number of neutrophils and an increase in the proportion of mature collagen as compared to the other two groups. The total quantity of collagen was significantly higher in the control (no laser) group at the day 11 time-point, as compared to the 35 mW laser group, consistent with a more prolonged inflammatory response in the control group. **CONCLUSION:** This study supports two mechanisms of action for LLLT in reducing mucositis severity. The increase in collagen organization in response to the 35 mW laser indicates that LLLT promotes wound healing. In addition, LLLT also appears to have an anti-inflammatory effect, as evidenced by the reduction in neutrophil infiltrate.

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[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=20662031](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20662031)

## Oral mucositis. Review of literature.

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The standard treatment for malignant neoplasia of the cervicofacial area is surgery in association with radio- and/or chemotherapy. These therapies can cause local and systemic complications. Mucositis is the most common dose-correlated complication to the oral cavity. It is particularly difficult to treat in patients who are already physically and psychologically exhausted by the tumoral pathology. This study illustrates, through a review of the literature, the attack rate, the pathogenesis and the clinical course of the mucositis, as well as the correct dental approach and clinical-therapeutic management of these patients, with the aim of improving the quality of their lives.

N Y State Dent J 2010 Jan 76(1) 34-8

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=20359063](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20359063)

# Rehabilitation of exacerbated case of oral mucositis associated with renal failure following bone marrow transplantation.

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Inflammation of oral mucosa induced by anti neoplastic drugs is an important, dose limiting and costly side effect of cancer therapy. Here is presented an exacerbated case of oral mucositis associated with renal failure in a patient who underwent bone marrow transplantation. The clinical aspects and an integrated rehabilitation program are discussed below.

Indian J Dent Res 2009 Jul-Sep 20(3) 365-9

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=19884725](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19884725)

# Use of therapeutic laser for prevention and treatment of oral mucositis.

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Oral mucositis (OM) affects patients who are submitted to hematopoietic stem cell transplantation (HSCT) due to high doses of chemotherapy and/or radiotherapy. The purpose of this investigation was to perform a comparative study of the frequency and evolution of OM among patients subjected to therapeutic laser and to the conventional therapy (use of mouthwash called 'Mucositis Formula'). The patients were subjected to a myeloablative conditioning regimen before the allogeneic HSCT. Twenty-two patients were selected and divided into 2 groups: group I was irradiated with InGaAlP laser (660 nm) and GaAlAs laser (780 nm), 25 mW potency, 6.3J/cm<sup>2</sup> dose, in 10-s irradiation time, followed to conventional treatment; group II was subjected only to the conventional treatment. Both World Health Organization (WHO) scale and the Oral Mucositis Assessment Scale (OMAS) were used to evaluate the results. Data were analyzed by the non-parametric Wilcoxon test, with  $p < 0.05$  considered as statistically significant. Group I presented a lower frequency of OM ( $p = 0.02$ ) and lower mean scores, according to WHO and OMAS scales ( $p < 0.01$  and  $p = 0.01$ , respectively). In conclusion, laser reduced the frequency and severity of OM, suggesting that therapeutic laser can be used both as a new form of prevention and treatment of OM.

Braz Dent J 2009 20(3) 215-20

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=19784467](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19784467)

# Use of 660-nm Diode Laser in the Prevention and Treatment of Human Oral Mucositis Induced by Radiotherapy and Chemotherapy.

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**Abstract Objective:** The aim of this multidisciplinary study was to evaluate quantitatively and qualitatively the effect of a 660-nm diode laser in the prevention and treatment of human oral mucositis (OM) in patients suffering from head and neck cancer who had undergone radiotherapy and chemotherapy. **Background Data:** OM is a severe oral lesion resulting from the toxic effects of treatment for cancer in the head and neck region. Low-level laser therapy is indicated to prevent and treat this oral complication and may be used alone or in association with conventional drug treatment, producing pain relief and wound repair. **Methods:** This study included 72 patients with head and neck cancer treated at the Cancer Hospital of Mato-Grosso, Brazil, and divided into a control group (C; n = 36) and a laser group (L; n = 36). Laser therapy was performed in combination with radiotherapy and chemotherapy twice a week using a diode laser ( $\lambda = 660$  nm, power = 30 mW, spot size = 2 mm, energy = 2 J per point). **Results:** Statistically significant differences were observed between the two groups. Patients in group L usually did not present with OM or pain, but all patients in group C presented with OM ranging from Level I to III associated with pain. This difference was significant from week 1 on, increased until week 4 and remained stable up to week 7. **Conclusion:** Laser therapy was effective in preventing and treating oral effects induced by radiotherapy and chemotherapy, thus improving the patient's quality of life.

Photomed Laser Surg 2009 Sep 21

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=19764899](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19764899)

# Low-power laser to prevent oral mucositis in autologous hematopoietic stem cell transplantation.

Chor A, Torres SR, Maiolino A, Nucci M

Brazil

Eur J Haematol 2010 Feb 1 84(2) 178-9

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?  
cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=19682060](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19682060)

# Laser phototherapy as topical prophylaxis against head and neck cancer radiotherapy-induced oral mucositis: comparison between low and high/low power lasers.

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**BACKGROUND AND OBJECTIVE:** Oral mucositis is a dose-limiting and painful side effect of radiotherapy (RT) and/or chemotherapy in cancer patients. The purpose of the present study was to analyze the effect of different protocols of laser phototherapy (LPT) on the grade of mucositis and degree of pain in patients under RT. **PATIENTS AND METHODS:** Thirty-nine patients were divided into three groups: G1, where the irradiations were done three times a week using low power laser; G2, where combined high and low power lasers were used three time a week; and G3, where patients received low power laser irradiation once a week. The low power LPT was done using an InGaAlP laser (660 nm/40 mW/6 J cm<sup>-2</sup>/0.24 J per point). In the combined protocol, the high power LPT was done using a GaAlAs laser (808 nm, 1 W/cm<sup>2</sup>). Oral mucositis was assessed at each LPT session in accordance to the oral-mucositis scale of the National Institute of the Cancer-Common Toxicity criteria (NIC-CTC). The patient self-assessed pain was measured by means of the visual analogue scale. **RESULTS:** All protocols of LPT led to the maintenance of oral mucositis scores in the same levels until the last RT session. Moreover, LPT three times a week also maintained the pain levels. However, the patients submitted to the once a week LPT had significant pain increase; and the association of low/high LPT led to increased healing time. **CONCLUSIONS:** These findings are desired when dealing with oncologic patients under RT avoiding unplanned radiation treatment breaks and additional hospital costs.

Lasers Surg Med 2009 Apr 41(4) 264-70

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=19347940](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19347940)

# Cyclooxygenase-2 and vascular endothelial growth factor expression in 5-fluorouracil-induced oral mucositis in hamsters: evaluation of two low-intensity laser protocols.

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**GOAL OF WORK:** The aim of this study was to investigate the mechanisms whereby low-intensity laser therapy may affect the severity of oral mucositis. **MATERIALS AND METHODS:** A hamster cheek pouch model of oral mucositis was used with all animals receiving intraperitoneal 5-fluorouracil followed by surface irritation. Animals were randomly allocated into three groups and treated with a 35 mW laser, 100 mW laser, or no laser. Clinical severity of mucositis was assessed at four time-points by a blinded examiner. Buccal pouch tissue was harvested from a subgroup of animals in each group at four time-points. This tissue was used for immunohistochemistry for cyclooxygenase-2 (COX-2), vascular endothelial growth factor (VEGF), and factor VIII (marker of microvessel density) and the resulting staining was quantified. **MAIN RESULTS:** Peak severity of mucositis was reduced in the 35 mW laser group as compared to the 100 mW laser and control groups. This reduced peak clinical severity of mucositis in the 35 mW laser group was accompanied by a significantly lower level of COX-2 staining. The 100 mW laser did not have an effect on the severity of clinical mucositis, but was associated with a decrease in VEGF levels at the later time-points, as compared to the other groups. There was no clear relationship of VEGF levels or microvessel density to clinical mucositis severity. **CONCLUSION:** The tissue response to laser therapy appears to vary by dose. Low-intensity laser therapy appears to reduce the severity of mucositis, at least in part, by reducing COX-2 levels and associated inhibition of the inflammatory response.

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[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=19234862](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19234862)

# Low-level infrared laser therapy in chemotherapy-induced oral mucositis: a randomized placebo-controlled trial in children.

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**BACKGROUND:** Oral mucositis (OM) is one of the most frequent complications of chemotherapy for which there is no standard therapy; treatment is mostly conservative. This study was conducted to determine whether low-intensity laser therapy (LLLT) can reduce the duration of chemotherapy-induced OM. **PROCEDURE:** A placebo-controlled randomized trial was carried out using LLLT or placebo (sham treatment). Children and adolescents with cancer receiving chemotherapy or hematopoietic stem-cell transplantation between October 2005 and May 2006 were eligible as soon as they developed OM. Patients received intervention for 5 days. The LLLT group was treated with laser GaAlAs, wavelength ( $\lambda$ ): 830 nm (infrared), power: 100 mW, dose: 4 J/cm, and placebo group underwent sham treatment. The grade of OM was clinically assessed by the National Cancer Institute, Common Toxicity Criteria scale. **RESULTS:** Twenty-one patients developed OM and were evaluable for analysis; 18 (86%) patients had a diagnosis of leukemia or lymphoma and 3(14%) had solid tumors. The mean age was 8.2 (+/-3.1) years. Nine patients were randomized in the laser group and 12 in the placebo-control group. Once OM was diagnosed, the patients had daily OM grading assessments before laser or sham application and thereafter until complete healing of the lesions. On day 7 after OM diagnosis, 1/9 of patients remained with lesions in laser group and 9/12 of patients in the placebo-control group ( $P=0.029$ ). In the laser group, the mean of OM duration was 5.8+/-2 days and in the placebo group was 8.9+/-2.4 days ( $P=0.004$ ). **CONCLUSIONS:** Our study has shown evidence that laser therapy in addition to oral care can decrease the duration of chemotherapy-induced OM. Our results confirm the promising results observed in adult cancer patients and should encourage pediatric oncologists to use laser therapy as first-line option in children with chemotherapy-induced OM.

J Pediatr Hematol Oncol 2009 Jan 31(1) 33-7

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=19125084](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19125084)

# LED phototherapy to prevent mucositis: a case report.

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**OBJECTIVE:** The purpose of this case report was to evaluate the efficacy of phototherapy using light-emitting diodes (LEDs) to prevent oral mucositis in a Hodgkin's disease patient treated with the ABVD (doxorubicin [Adriamycin], bleomycin, vinblastine, and dacarbazine) chemotherapy regimen.

**BACKGROUND DATA:** Mucositis is a common dose-limiting complication of cancer treatment, and if severe it can lead to alterations in treatment planning or suspension of cancer therapy, with serious consequences for tumor response and survival. Therefore, low-power lasers and more recently LEDs, have been used for oral mucositis prevention and management, with good results.

**MATERIALS AND METHODS:** In this study, a 34-year-old man received intraoral irradiation with an infrared LED array (880 nm, 3.6 J/cm<sup>2</sup>, 74 mW) for five consecutive days, starting on chemotherapy day 1. In each chemotherapy cycle, he received the ABVD protocol on days 1 and 15, and received LED treatment for 5 d during each cycle. To analyze the results, the World Health Organization (WHO) scale was used to grade his mucositis, and a visual analogue scale (VAS) was used for pain evaluation, on days 1, 3, 7, 10, and 13 post-chemotherapy. **RESULTS:** The results showed that the patient did not develop oral mucositis during the five chemotherapy cycles, and he had no pain symptoms. **CONCLUSION:** LED therapy was a safe and effective method for preventing oral mucositis in this case report. However, further randomized studies with more patients are needed to prove the efficacy of this method.

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[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=19025412](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19025412)

# Low-intensity red laser on the prevention and treatment of induced-oral mucositis in hamsters.

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**OBJECTIVE:** The purpose of this study was to investigate the effects of laser phototherapy as preventive and therapeutic regime on induced-oral mucositis in hamsters. **DESIGN:** The animals were divided into four groups: preventive cryotherapy, preventive laser, therapeutic laser and therapeutic control group. Mucositis was induced in hamsters by intraperitoneal injection of 5-fluorouracil (5-FU) and superficial scratching. All preventive treatment was performed on the right cheek pouch mucosa. The left pouch mucosa was used for a spontaneous development of mucositis and did not receive any preventive therapy. Laser parameters were:  $\lambda=660\text{nm}$ ,  $P=30\text{mW}$ ,  $D=1.2\text{J}/\text{cm}^2$ ,  $\Delta t=40\text{s}$ , spot size  $3\text{mm}^2$ ,  $I=1\text{W}/\text{cm}^2$ . Cryotherapy was done positioning ice packs in the hamster mucosa 5min before 5-FU infusion and 10min afterward. To study the healing of mucositis, the left pouch mucosa of each of the hamsters in the TLG received laser irradiation on the injured area. Irradiation parameters were kept the same as abovementioned. The control hamsters in the TCG did not receive any treatment. The mucositis degree and the animal's body mass were evaluated. An assessment of blood vessels was made based on immunohistochemical staining. **RESULTS:** The CG animals lost 15.16% of their initial body mass while the LG animals lost 8.97% during the first 5 days. The laser treated animals had a better clinical outcome with a faster healing, and more granulation tissue. The quantity of blood vessels at both LG and CG were higher than in healthy mucosa. Regarding the therapeutic analysis, the severity of the mucositis in the TLG was always lower than TCG. TLG presented higher organization of the granulation tissue, parallel collagen fibrils, and increased angiogenesis. **CONCLUSION:** The results suggest that laser phototherapy had a positive effect in reducing mucositis severity, and a more pronounced effect in treating established mucositis.

J Photochem Photobiol B 2009 Jan 9 94(1) 25-31

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18976931](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18976931)

# Light-emitting diode therapy in chemotherapy-induced mucositis.

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**BACKGROUND AND OBJECTIVE:** Mucositis is the most common oral complication of cancer chemotherapy, which causes pain on mastication and swallowing, impairs patients' ability to eat and take oral drugs and may determine interruption of the treatment. The aim of this study was to evaluate the effect of light-emitting diode (LED) therapy on chemotherapy-induced mucositis in hamsters. **STUDY DESIGN/MATERIALS AND METHODS:** Animals of both experimental (Group I; n = 32) and positive control (Group II; n = 32) groups received intraperitoneal injections of 5-fluorouracil on days 0 and 2. All animals had their right and left cheek pouch irritated by superficial scratching on days 3 and 4. In Group I, LED irradiation (630 nm $\pm$ 10 nm, 160 mW, 12 J/cm<sup>2</sup>) was applied during 37.5 seconds at days 3, 4, 6, 8, 10, 12, and 14. In Group II, mucositis was induced, but LED therapy was not performed. The oral mucosa was photographed from day 4 to 14 at 2-day intervals. Photographs were randomly scored according to the severity of induced mucositis (0 to 5). In the negative control group (Group III; n = 6), no mucositis was induced. Biopsies of the cheek pouches of 8 animals (Group I and Group II) were surgically obtained on days 5, 9, 13 and 15 and processed for histological examination. **RESULTS:** The statistical analysis showed significant differences between irradiated and non-irradiated groups (P<0.05). However, muscular degeneration was observed in 18% of the samples of Group I. **CONCLUSION:** It may be concluded that the LED therapy protocol established for this in vivo study was effective in reducing the severity of oral mucositis, although the oral lesions were not completely prevented.

Lasers Surg Med 2008 Nov 40(9) 625-33

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18951429](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18951429)

# Low-level laser therapy in the prevention and treatment of chemotherapy-induced oral mucositis in young patients.

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**OBJECTIVE:** A pilot clinical study was conducted to evaluate the efficacy and feasibility of low-level laser therapy (LLLT) in the prevention and treatment of chemotherapy (CT)-induced oral mucositis (OM) in young patients. **BACKGROUND DATA:** Besides compromising the patient's nutrition and well-being, oral mucositis represents a portal of entry into the body for microorganisms present in the mouth, which may lead to sepsis if there is hematological involvement. Oncologic treatment tolerance decreases and systemic complications may arise that interfere with the success of cancer treatment. LLLT appears to be an interesting alternative to other approaches to treating OM, due to its trophic, anti-inflammatory, and analgesic properties. **MATERIALS AND METHODS:** Patients undergoing chemotherapy (22 cycles) without mucositis were randomized into a group receiving prophylactic laser-irradiation (group 1), and a group receiving placebo light treatment (group 2). Patients who had already presented with mucositis were placed in a group receiving irradiation for therapeutic purposes (group 3, with 10 cycles of CT). Serum granulocyte levels were taken and compared to the progression of mucositis. **RESULTS:** In group 1, most patients (73%) presented with mucositis of grade 0 ( $p = 0.03$  when compared with the placebo group), and 18% presented with grade 1. In group 2, 27% had no OM and did not require therapy. In group 3, the patients had marked pain relief (as assessed by a visual analogue scale), and a decrease in the severity of OM, even when they had severe granulocytopenia. **CONCLUSION:** The ease of use of LLLT, high patient acceptance, and the positive results achieved, make this therapy feasible for the prevention and treatment of OM in young patients.

Photomed Laser Surg 2008 Aug 26(4) 393-400

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18754720](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18754720)

# Non-surgical treatment of peri-implant mucositis and peri-implantitis: a literature review.

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**OBJECTIVES:** To review the literature on non-surgical treatment of peri-implant mucositis and peri-implantitis. **MATERIAL AND METHODS:** A search of PubMed and The Cochrane Library of the Cochrane Collaboration (CENTRAL) as well as a hand search of articles were conducted. Publications and articles accepted for publication up to November 2007 were included. **RESULTS:** Out of 437 studies retrieved a total of 24 studies were selected for the review. Thus the available evidence for non-surgical treatment of peri-implant mucositis and peri-implantitis is scarce. **CONCLUSIONS:** It was observed that mechanical non-surgical therapy could be effective in the treatment of peri-implant mucositis lesions. Furthermore, the adjunctive use of antimicrobial mouth rinses enhanced the outcome of mechanical therapy of such mucositis lesions. In peri-implantitis lesions non-surgical therapy was not found to be effective. Adjunctive chlorhexidine application had only limited effects on clinical and microbiological parameters. However, adjunctive local or systemic antibiotics were shown to reduce bleeding on probing and probing depths. Minor beneficial effects of laser therapy on peri-implantitis have been shown; this approach needs to be further evaluated. There is a need for randomized-controlled studies evaluating treatment models of non-surgical therapy of peri-implant mucositis and peri-implantitis.

J Clin Periodontol 2008 Sep 35(8 Suppl) 305-15

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18724858](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18724858)

# Severity of Oral Mucositis in Patients Undergoing Hematopoietic Cell Transplantation and an Oral Laser Phototherapy Protocol: A Survey of 30 Patients.

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**Abstract Background Data and Objective:** Oral mucositis (OM) is one of the worst cytotoxic effects of chemotherapy and radiotherapy in patients undergoing hematopoietic cell transplantation (HCT), and it causes severe morbidity. Laser phototherapy has been considered as an alternative therapy for prevention and treatment of OM. The aim of this study was to describe the incidence and severity of OM in HCT patients subjected to laser phototherapy, and to discuss its effect on the oral mucosa. **Patients and Methods:** Information concerning patient age and gender, type of basic disease, conditioning regimen, type of transplant, absence or presence of pain related to the oral cavity, OM grade, and adverse reactions or unusual events were collected from 30 patients undergoing HCT (allogeneic or autologous). These patients were given oral laser phototherapy with a InGaAlP laser (660 nm and 40 mW) daily. The data were tabulated and their frequency expressed as percentages. **Results:** In the analysis of those with OM, it was observed that 33.4% exhibited grade I, 40% grade II, 23.3% grade III, and 3.3% grade IV disease. On the most critical post-HCT days (D+5 and D+8), it was observed that 63.3% of patients had grade I and 33.3% had grade II disease; no patients had grade III or IV disease in this period. This severity of OM was similar to that seen in other studies of laser phototherapy and OM. **Conclusion:** The low grades of OM observed in this survey show the beneficial effects of laser phototherapy, but randomized clinical trials are necessary to confirm these findings.

Photomed Laser Surg 2008 Aug 12

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18699729](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18699729)

# The treatment of peri-mucositis and peri-implantitis 1.

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SADJ 2008 May 63(4) 250, 252

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?  
cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18689342](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18689342)

# The use of low-energy laser (LEL) for the prevention of chemotherapy- and/or radiotherapy-induced oral mucositis in cancer patients: results from two prospective studies.

Genot-Klastersky MT, Klastersky J, Awada F, Awada A, Crombez P, Martinez MD, Jaivenois MF, Delmelle M, Vogt G, Meuleman N, Paesmans M

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**BACKGROUND:** Low-energy laser (LEL) treatment has been suggested as an effective and safe method to prevent and/or treat oral mucositis induced by chemotherapy and/or radiotherapy; however, it has not gained wide acceptance so far. **MATERIALS AND METHODS:** We conducted two clinical trials testing the LEL technique: firstly, as a secondary prevention in patients with various solid tumors treated with chemotherapy who all developed severe mucositis after a previous identical chemotherapy and, secondly, as therapeutic intervention (compared to sham illumination in a randomized way) in patients with hematological tumors receiving intensive chemotherapy and having developed low-grade oral mucositis. **RESULTS:** We entered 26 eligible patients in the first study and 36 were randomized in the second study. The success rate was 81% (95%CI = 61-93%) when LEL was given as a preventive treatment. In the second study, in patients with existing lesions, the therapeutic success rate was 83% (95%CI = 59-96%), which was significantly different from the success rate reached in the sham-treated patients (11%; 95%CI = 1-35%); the time to development of grade 3 mucositis was also significantly shorter in the sham-treated patients ( $p < 0.001$ ). **CONCLUSION:** Our results strongly support the already available literature, suggesting that LEL is an effective and safe approach to prevent or treat oral mucositis resulting from cancer chemotherapy.

Support Care Cancer 2008 Dec 16(12) 1381-7

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18458964](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18458964)

## Literature news.

Sardella A

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**AIM:** To evaluate the clinical effects of laser therapy on the prevention and reduction of oral mucositis in patients who underwent hematopoietic stem cell transplantation (HSCT). **Patients and methods:** From January 2003 to September 2004, 24 patients received prophylactic laser therapy (L+ group). The applications started from the beginning of the conditioning regimen up to day +2. The oral assessment was performed daily until day +30. This group was compared with historical controls, namely 25 patients, who did not receive laser therapy (L? group). **RESULTS:** All patients developed some grade of mucositis. However, the L? group presented initial mucositis by 4.36 days, whereas the L+ group presented it in 6.12 days ( $P = 0.01$ ). The maximum mucositis occurred between day +2 and day +6 with healing by day +25 in the L? group and between day +2 and day +7 with healing by day +14 for the L+ group ( $P = 0.84$ ). Laser therapy also reduced the time of oral pain from 5.64 to 2.45 days ( $P = 0.04$ ), and decreased the consumption of morphine ( $P = 0.07$ ). **CONCLUSION:** This study suggests that laser therapy can be useful in oral mucositis to HSCT patients and improve the patient's quality of life. However, controlled randomized trials should be performed to confirm the real efficacy of laser therapy.

Minerva Stomatol 2008 Jan-Feb 57(1-2) 77-8

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18427375](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18427375)

# The Impact of low power laser in the treatment of conditioning-induced oral mucositis: a report of 11 clinical cases and their review.

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We have investigated the clinical effects of low power laser therapy (LPLT) on the treatment of conditioning-induced oral mucositis (OM) in patients submitted to hematopoietic stem cell transplantation (HSCT). The evaluation of OM was done using the Oral Mucositis Assessment Scale (OMAS) and World Health Organization (WHO) scale. In the context of a randomized placebo-controlled trial with 38 patients for the evaluation of preventive LPLT, eleven individuals were submitted to allogeneic (AL) HSCT and developed oral mucositis grade 4 (WHO) or a total area of OM of 12 cm (OMAS) and due to that were treated with LPLT with the purpose of symptom relief. The irradiation used was a diode InGaAlP, emitting light at 660 nm, 50 mW and 8 J/cm<sup>2</sup> measured at the end of fiber optic with 0.196 cm<sup>2</sup> of section area during the treatment. The tip of the laser device touched the oral mucosa and patients recovered on average 6 days (3-12 days) from the beginning of the laser application. Our results have indicated that the use of LPLT in HSCT patients is a powerful instrument in the treatment of overt OM and is now a standard procedure in this group of patients in our hospital.

Med Oral Patol Oral Cir Bucal 2008 Mar 13(3) E189-92

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18305441](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18305441)

# Efficacy of He-Ne Laser in the prevention and treatment of radiotherapy-induced oral mucositis in oral cancer patients.

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**OBJECTIVE:** The objective of this study was to evaluate the efficacy of low-level lasers for the prevention and treatment of radiotherapy-induced oral mucositis in oral cancer patients. **MATERIAL AND METHODS:** Twenty-four hospitalized patients with oral cancer, scheduled to undergo radiotherapy at KMC, Manipal, were enrolled in the present study and assigned to laser (Group I)/control group (Group II). They were treated using He-Ne laser ( $\lambda = 632.8\text{nm}$ , output = 10 mW and energy density =  $1.8\text{ J/cm}^2$ ). Patients were subjected to treatment using laser scanner for 8 days and subsequently were treated using laser probe at 6 anatomic sites in the oral cavity for 5 minutes each. The patients were evaluated on each day of treatment for pain severity (NRS), functional impairment (FIS), and oral mucositis (RTOG) and were followed until the end of cancer treatment. Statistical analysis was done using SPSS version 10. **RESULTS:** Laser therapy applied prophylactically during radiotherapy can reduce the severity of oral mucositis, severity of pain, and functional impairment.

Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008 Feb 105(2) 180-6, 186.e1

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18230388](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18230388)

# Low-energy laser therapy for prevention of oral mucositis in hematopoietic stem cell transplantation.

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**Aim:** To evaluate the clinical effects of laser therapy on the prevention and reduction of oral mucositis in patients who underwent hematopoietic stem cell transplantation (HSCT). **Patients and methods:** From January 2003 to September 2004, 24 patients received prophylactic laser therapy (L+ group). The applications started from the beginning of the conditioning regimen up to day +2. The oral assessment was performed daily until day +30. This group was compared with historical controls, namely 25 patients, who did not receive laser therapy (L- group). **Results:** All patients developed some grade of mucositis. However, the L- group presented initial mucositis by 4.36 days, whereas the L+ group presented it in 6.12 days ( $P = 0.01$ ). The maximum mucositis occurred between day +2 and day +6 with healing by day +25 in the L- group and between day +2 and day +7 with healing by day +14 for the L+ group ( $P = 0.84$ ). Laser therapy also reduced the time of oral pain from 5.64 to 2.45 days ( $P = 0.04$ ), and decreased the consumption of morphine ( $P = 0.07$ ). **Conclusion:** This study suggests that laser therapy can be useful in oral mucositis to HSCT patients and improve the patient's quality of life. However, controlled randomized trials should be performed to confirm the real efficacy of laser therapy.

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[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=17944669](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17944669)

## Cancer treatment-induced oral mucositis.

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Oral mucositis is one of the main complications in non-surgical cancer treatments. It represents the major dose-limiting toxicity for some chemotherapeutic agents, for radiotherapy of the head and neck region and for some radiochemotherapy combined treatments. Many reviews and clinical studies have been published in order to define the best clinical protocol for prophylaxis or treatment of mucositis, but a consensus has not yet been obtained. This paper represents an updated review of prophylaxis and treatment of antineoplastic-therapy-related mucositis using a MEDLINE search up to May 2006, in which more than 260 clinical studies have been found. They have been divided according to antineoplastic therapy (chemotherapy, radiotherapy, chemo-radiotherapy, high-dose chemotherapy). The prophylactic or therapeutic use of the analysed agents, the number of enrolled patients and the study design (randomized or not) were also specified for most studies. Accurate pre-treatment assessment of oral cavity hygiene, frequent review of symptoms during treatment, use of traditional mouthwashes to obtain mechanical cleaning of the oral cavity and administration of some agents like benzydamine, imidazole antibiotics, tryazolic antimycotics, povidone iodine, keratinocyte growth factor and vitamin E seem to reduce the intensity of mucositis. Physical approaches like cryotherapy, low energy Helium-Neon laser or the use of modern radiotherapy techniques with the exclusion of the oral cavity from radiation fields have been shown to be efficacious in preventing mucositis onset. Nevertheless a consensus protocol of prophylaxis and treatment of oral mucositis has not yet been obtained.

Anticancer Res 2007 Mar-Apr 27(2) 1105-25

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=17465250](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17465250)

# A phase III randomized double-blind placebo-controlled clinical trial to determine the efficacy of low level laser therapy for the prevention of oral mucositis in patients undergoing hematopoietic cell transplantation.

Schubert MM, Eduardo FP, Guthrie KA, Franquin JC, Bensadoun RJ, Migliorati CA, Lloid CM, Eduardo CP, Walter NF, Marques MM, Hamdi M

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**INTRODUCTION:** Oral mucositis (OM) is a significant early complication of hematopoietic cell transplantation (HCT). This phase III randomized double-blind placebo-controlled study was designed to compare the ability of 2 different low level GaAlAs diode lasers (650 nm and 780 nm) to prevent oral mucositis in HCT patients conditioned with chemotherapy or chemoradiotherapy. **MATERIALS AND METHODS:** Seventy patients were enrolled and randomized into 1 of 3 treatment groups: 650 nm laser, 780 nm laser or placebo. All active laser treatment patients received daily direct laser treatment to the lower labial mucosa, right and left buccal mucosa, lateral and ventral surfaces of the tongue, and floor of mouth with energy densities of 2 J/cm<sup>2</sup>. Study treatment began on the first day of conditioning and continued through day +2 post HCT. Mucositis and oral pain was measured on days 0, 4, 7, 11, 14, 18, and 21 post HCT. **RESULTS:** The 650 nm wavelength reduced the severity of oral mucositis and pain scores. Low level laser therapy was well-tolerated and no adverse events were noted. **DISCUSSION:** While these results are encouraging, further study is needed to truly establish the efficacy of this mucositis prevention strategy. Future research needs to determine the effects of modification of laser parameters (e.g., wavelength, fluence, repetition rate of energy delivery, etc.) on the effectiveness of LLE laser to prevent OM.

Support Care Cancer 2007 Oct 15(10) 1145-54

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=17393191](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17393191)

# Macroscopic and microscopic effects of GaAIAs diode laser and dexamethasone therapies on oral mucositis induced by fluorouracil in rats.

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**PURPOSE:** To present an animal model for mucositis induced by fluorouracil in rats, and test two therapeutic options, the GaAIAs laser and topical dexamethasone, analysing them with regard to the quality and quantity of tissue alterations and comparing them with the phases of mucositis. **MATERIALS AND METHODS:** Forty-five Wistar rats (250 g) were treated with fluorouracil (60 mg/kg) and, in order to mimic the clinical effect of chronic irritation, the palatal mucosa was irritated by superficial scratching with an 18-gauge needle. When all of the rats presented oral ulcers of mucositis, they were randomly allocated to one of three groups: group I was treated with laser (GaAIAs), group II was treated with topical dexamethasone, and group III was not treated. Excisional biopsies of the palatal mucosa were then performed, and the rats were killed. Tissue sections were stained with haematoxylin and eosin for morphological analyses, and with toluidine blue for mast-cell counts. **RESULTS:** Group I specimens showed higher prevalence of ulcers, bacterial biofilm, necrosis and vascularisation, while group II specimens showed higher prevalence of granulation tissue formation. There were no significant statistical differences in the numbers of mast cells and epithelial thickness between groups. **CONCLUSION:** For the present model of mucositis, rats with palatal mucositis treated with laser (GaAIAs) showed characteristics compatible with the ulcerative phase of oral mucositis, and rats treated with topical dexamethasone showed characteristics compatible with the healing phase of mucositis. Topical dexamethasone was more efficient in the treatment of rats' oral mucositis than the laser.

Oral Health Prev Dent 2007 5(1) 63-71

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=17366763](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17366763)

## Melatonin as a principal component of red light therapy.

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Melatonin is well recognized for its role as a potent antioxidant and is directly implicated in the free radical theory of aging [1] [Reiter RJ, Pablos MI, Agapito TT, Guerrero JM. Melatonin in the context of the free radical theory of aging. *Ann N Y Acad Sci* 1996;786:362-78]. Moreover, melatonin has been shown to retard age-related increases in lipid peroxidation and oxidative damage [2] [Okatani Y, Wakatsuki A, Reiter RJ. Melatonin protects hepatic mitochondrial respiratory chain activity in senescence-accelerated mice. *J Pineal Res* 2002;32:143-8] and to act directly upon the immune system [3] [Poon AM, Liu ZM, Pang CS, Brown GM, Pang SF. Evidence for a direct action of melatonin on the immune system. *Biol Signals* 1994;3:107-17]. This report focuses on characterizing documented functions of melatonin in the context of red light therapy and proposes that melatonin is a potential mediator of red light's therapeutic effects, a hypothesis that is as yet untested. Red light therapy (670 nm, 4J/cm<sup>2</sup>) has been shown to restore glutathione redox balance upon toxicological insult and enhance both cytochrome c oxidase and energy production, all of which may be affected by melatonin. The red light treatment has also been successfully implemented in the clinical setting for its effectiveness in reducing both the number of incidences and severity of oral mucositis resulting in part from the chemotherapy and/or radiation administered prior to bone marrow transplants. Moreover, red light therapy improves wound healing and is being further tested for its ability to ameliorate toxicant-induced retinal and visual cortical neuron damage. Researchers in the growing field of light therapy may be in a position to draw from and collaborate with melatonin researchers to better characterize this alternative treatment.

*Med Hypotheses* 2007 69(2) 372-6

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=17321060](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17321060)

# Effect of low level helium-neon (He-Ne) laser therapy in the prevention & treatment of radiation induced mucositis in head & neck cancer patients.

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**India**BACKGROUND & OBJECTIVES: Oral mucositis is a common debilitating complication of radiotherapy occurring in about 60 per cent of cancer patients. Considerable buccal toxicity of radiotherapy or chemotherapy in cancer patients to become discouraged and can affect their quality of life. In addition, such toxicity can alter the treatment plan. At present, there is no clinically appropriate prophylaxis efficacious antidote for mucositis. The low level laser (LEL) appears to be a simple, non-traumatic technique for the prevention and treatment of radiation induced mucositis. Therefore the present study was carried out to find out the effect of low-level helium-neon (He-Ne) laser in the prevention and treatment of radiation induced mucositis in head and neck cancer patients. METHODS: The patients with carcinoma of oral cavity with stages II-IV a being uniformly treated with curative total tumour dose of 66 Gy in 33 fractions over 6 wk were selected for the study. The patients were divided based on computer generated randomization into laser (study group) and control groups with 25 patients in each group. Both study and control groups were comparable in terms of site of the lesion, stage of the cancer and histology. The study group patients were treated with He-Ne laser (wavelength 632.8 nm and output of 10mW) and control group patients were given oral analgesics, local application of anaesthetics, 0.9 per cent saline and povidine wash during the course of radiotherapy. RESULTS: All patients tolerated the laser treatment without any adverse effect or reactions. The result showed a significant difference in pain and mucositis ( $P<0.001$ ) between the two groups. At the end of radiotherapy (after 6 wk) mean pain score and mucositis grade were significantly lower ( $P<0.001$ ) in the study group compared to control. INTERPRETATION & CONCLUSION: The low-level He-Ne laser therapy during the radiotherapy treatment was found to be effective in preventing and treating the mucositis in head and neck cancer patients. Further studies need to be done on a larger sample to find the mechanism.

Indian J Med Res 2006 Oct 124(4) 399-402

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=17159259](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17159259)

# Low level laser therapy (LLLT): a new paradigm in the management of cancer therapy-induced mucositis ?

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[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=17159255](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17159255)

## Low-power laser in the prevention of induced oral mucositis in bone marrow transplantation patients: a randomized trial.

Antunes HS, de Azevedo AM, da Silva Bouzas LF, Adao CA, Pinheiro CT, Mayhe R, Pinheiro LH, Azevedo R, D'Aiuto de Matos V, Rodrigues PC, Small IA, Zangaro RA, Ferreira CG.

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Brazil We investigated the clinical effects of low-power laser therapy (LPLT) on prevention and reduction of severity of conditioning-induced oral mucositis (OM) for hematopoietic stem cell transplantation (HSCT). We randomized 38 patients who underwent autologous (AT) or allogeneic (AL) HSCT. A diode InGaAlP was used, emitting light at 660 nm, 50 mW, and 4 J/cm<sup>2</sup>, measured at the fiberoptic end with 0.196 cm<sup>2</sup> of section area. The evaluation of OM was done using the Oral Mucositis Assessment Scale (OMAS) and the World Health Organization (WHO) scale. In the LPLT group, 94.7% of patients had an OM grade (WHO) lower than or equal to grade 2, including 63.2% with grade 0 and 1, whereas in the controls group, 31.5% of patients had an OM grade lower than or equal to grade 2 ( $P < .001$ ). Remarkably, the hazard ratio (HR) for grades 2, 3, and 4 OM was 0.41 (range, 0.22-0.75;  $P = .002$ ) and for grades 3 and 4 it was 0.07 (range, 0.11-0.53;  $P < .001$ ). Using OMAS by the calculation of ulcerous area, 5.3% of the laser group presented with ulcers of 9.1 cm<sup>2</sup> to 18 cm<sup>2</sup>, whereas 73.6% of the control group presented with ulcers from 9.1 cm<sup>2</sup> to 18 cm<sup>2</sup> ( $P = .003$ ). Our results indicate that the use of upfront LPLT in patients who have undergone HSCT is a powerful instrument in reducing the incidence of OM and is now standard in our center.

Blood 2007 Mar 109 (5) 2250-55

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=PureSearch&db=pubmed&details\\_term=17053058%5BUID%5D](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=PureSearch&db=pubmed&details_term=17053058%5BUID%5D)

# Influence of low-energy laser in the prevention of oral mucositis in children with cancer receiving chemotherapy.

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**Brazil**BACKGROUND: This study assessed the use of low-energy laser in the prevention or reduction of the severity of oral mucositis. PROCEDURE: A randomized clinical trial was carried out. Patients from 3 to 18 years of age treated with chemotherapy or hematopoietic stem-cell transplantation between May, 2003 and February, 2005 were eligible. The intervention group received laser application for 5 days following the start of chemotherapy. The grade of oral mucositis was assessed by the WHO per NCI-CTC common toxicity criteria and the assessments were made on days 1, 8 and 15 by a trained examiner blind to the intervention. RESULTS: Sixty patients were evaluable for analysis; thirty-nine (65%) were males, 35 (58%) patients had a diagnosis of leukemia or lymphoma, and 25 (42%) had solid tumors. The mean age was 8.7 +/- 4.3 years. Twenty-nine patients were randomized in the laser group and 31 in the control group. On day 1, no patients presented with mucositis. On day 8, of 20 patients (36%) who developed mucositis, 13 of them were from the laser group and 7 from the control group. On day 15, of 24 patients (41%) who developed mucositis, 13 of them were from the laser group and 11 from the control group. There was no significant difference between groups concerning the grades of mucositis on day 8 (P = 0.234) or on day 15 (P = 0.208). CONCLUSIONS: This study showed no evidence of benefit from the prophylactic use of low-energy laser in children and adolescents with cancer treated with chemotherapy when optimal dental and oral care was provided.

Pediatr Blood Cancer 2007 Apr 48(4) 435-40

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=16862549](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16862549)

## Patients with moderate chemotherapy-induced mucositis

Corti L, Chiarion-Sileni V, Aversa S, Ponzoni A, D'Arcais R, Pagnutti S, Fiore D, Sotti G

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**OBJECTIVE:** The aim of this study was to assess the clinical effectiveness of phototherapy with noncoherent light in the alleviation of chemotherapy-induced mucositis in patients with metastatic cancer. **BACKGROUND DATA:** Mucositis occurs in more than 40% of chemotherapy-treated patients, significantly reducing the quality of their lives. Many different interventions have been evaluated to reduce oral mucositis. Recently, good results have been achieved by phototherapy with photoradiation, a technique which has virtually no side effects. Some clinical results seem to indicate that also phototherapy through noncoherent light emissions which can be produced by less expensive light sources such as light-emitting diodes (LEDs) may be effective. However, until now, no studies have been available on this subject. **METHODS:** Twelve patients, aged from 34 to 82, selected on the basis of a diagnosis of chemotherapy-induced oral mucositis, were treated intra-orally through a noncoherent LED emission, wavelength 645 +/- 15 nm, 7.8 mW, fluence 0.99 J/cm<sup>2</sup>, three times a day for 1 week. Mucositis was scored daily using the Daily Mucositis Index (DMI), a scale that evaluates the disease evolution through 16 different items. The primary end-point assessed was the time to recovery, from the start of LED treatment, compared to a nonrandomized control group of 12 patients with comparable stomatitis. **RESULTS:** The median healing time, expressed as the DMI decrease, was 1.7 (range 1-2.8) and, in seven LED-treated patients, was shorter than in the control group. The healing rate (measured as the ratio of the DMIs) increased from 117% to 164%. **CONCLUSION:** This pilot study shows that LED treatment is safe and capable of reducing the duration of chemotherapy-induced mucositis. This result needs to be confirmed in an adequate phase III study.

Photomed Laser Surg 2006 Apr 24(2) 207-13

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=16706701](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16706701)

## Clinical and experimental applications of NIR-LED photobiomodulation.

Desmet KD, Paz DA, Corry JJ, Eells JT, Wong-Riley MT, Henry MM, Buchmann EV, Connelly MP, Dovi JV, Liang HL, Henshel DS, Yeager RL, Millsap DS, Lim J, Gould LJ, Das R, Jett M, Hodgson BD, Margolis D, Whelan HT

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This review presents current research on the use of far-red to near-infrared (NIR) light treatment in various in vitro and in vivo models. Low-intensity light therapy, commonly referred to as "photobiomodulation," uses light in the far-red to near-infrared region of the spectrum (630-1000 nm) and modulates numerous cellular functions. Positive effects of NIR-light-emitting diode (LED) light treatment include acceleration of wound healing, improved recovery from ischemic injury of the heart, and attenuated degeneration of injured optic nerves by improving mitochondrial energy metabolism and production. Various in vitro and in vivo models of mitochondrial dysfunction were treated with a variety of wavelengths of NIR-LED light. These studies were performed to determine the effect of NIR-LED light treatment on physiologic and pathologic processes. NIRLED light treatment stimulates the photoacceptor cytochrome c oxidase, resulting in increased energy metabolism and production. NIR-LED light treatment accelerates wound healing in ischemic rat and murine diabetic wound healing models, attenuates the retinotoxic effects of methanol-derived formic acid in rat models, and attenuates the developmental toxicity of dioxin in chicken embryos. Furthermore, NIR-LED light treatment prevents the development of oral mucositis in pediatric bone marrow transplant patients. The experimental results demonstrate that NIR-LED light treatment stimulates mitochondrial oxidative metabolism in vitro, and accelerates cell and tissue repair in vivo. NIR-LED light represents a novel, noninvasive, therapeutic intervention for the treatment of numerous diseases linked to mitochondrial dysfunction.

Photomed Laser Surg 2006 Apr 24(2) 121-8

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=16706690](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16706690)

# The role of alternative and natural agents, cryotherapy, and/or laser for management of alimentary mucositis.

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**GOALS OF WORK:** To review the literature and update the current guidelines of alternative/natural agents, cryotherapy, and/or laser therapy in the management of alimentary mucositis (AM). **MATERIALS AND METHODS:** The original guidelines developed by the Multinational Association for Supportive Care in Cancer (MASCC)/International Society for Oral Oncology (ISOO) mucositis study group were the basis for this study. A medical librarian conducted an initial Medline search to identify research articles published between 2002 and 2005 in English language. A search term combination that included stomatitis, mucositis, mucous membrane, neoplasm, lasers, complimentary therapies, amino acids, antioxidants, vitamins, minerals, plant extracts, and cryotherapy was conducted. This initial search identified articles with a strong scientific methodology that included both preclinical and clinical research. Using standardized scoring forms, authors reviewed and scored individual articles. A consensus result of the review was achieved in a meeting of reviewers in June of 2005. **RESULTS:** The initial search identified a total of 167 new articles. Of these, 14 were selected and reviewed: alternative/natural therapy (one preclinical study); cryotherapy (four clinical studies); lasers (two clinical studies); and alternative/natural agents (seven clinical studies). A new guideline could be established for the use of cryotherapy in the management of AM in hematopoietic stem cell transplant (HSCT) patients receiving melphalan in the conditioning phase. **CONCLUSION:** The rapid progress in the understanding of AM created a need for new prevention and management protocols. Frequent literature review is now necessary to identify agents and protocols being developed in this important area of supportive care in cancer.

Support Care Cancer 2006 Jun 14(6) 533-40

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=16572313](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16572313)

## [Radiation-induced mucositis of the aerodigestive tract: prevention and treatment. MASCC/ISOO mucositis group's recommendations]

Bensadoun RJ, Le Page F, Darcourt V, Bensadoun F, Ciais G, Rostom YA, Poissonnet G, Dassonville O, Demard F

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Acute mucositis is the main intensity-limiting toxicity in the management of head and neck (H&N) and digestive track carcinomas with radiotherapy. New radiation modalities (hyperfractionation and/or acceleration) as well as combined modality regimens in this situation induce higher rates of acute toxicity. Hyperfractionation for example allows higher control rates, with few late toxicities, but it slightly increases acute mucositis. The addition of chemotherapy introduces systemic toxicity and can exacerbate local tissue reactions when used concurrently with radiation. Mucositis is recognized as the principal limiting factor to further treatment intensification. As local-regional control and overall survival are related to dose-intensity in this case, further research into the assessment, analysis, prevention and treatment of mucosal toxicity is not only crucial to the improvement in quality of life, but certainly to improved rates of disease control as well. Several topical and systemic treatments are directed to the decrease and the acceptance of this acute toxicity, but few have shown significant preventive effect. Improvement of technical aspects of H&N radiotherapy (3D conformal radiation, intensity-modulated radiotherapy) should have a major impact in the prevention of mucositis. The efficacy of low level laser therapy in the management of such a toxicity could hence yield important development of this method in the field of oncology. MASCC/ISOO mucositis group's recommendations for the management of acute radiation-induced mucositis are here summarized.

Bull Cancer 2006 Feb 1 93(2) 201-11

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=16517417](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16517417)

# Mitochondrial signal transduction in accelerated wound and retinal healing by near-infrared light therapy.

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Photobiomodulation by light in the red to near infrared range (630-1000 nm) using low energy lasers or light-emitting diode (LED) arrays has been shown to accelerate wound healing, improve recovery from ischemic injury in the heart and attenuate degeneration in the injured optic nerve. Recent evidence indicates that the therapeutic effects of red to near infrared light result, in part, from intracellular signaling mechanisms triggered by the interaction of NIR light with the mitochondrial photoacceptor molecule cytochrome c oxidase. We have demonstrated that NIR-LED photo-irradiation increases the production of cytochrome oxidase in cultured primary neurons and reverses the reduction of cytochrome oxidase activity produced by metabolic inhibitors. We have also shown that NIR-LED treatment prevents the development of oral mucositis in pediatric bone marrow transplant patients. Photobiomodulation improves wound healing in genetically diabetic mice by upregulating genes important in the promotion of wound healing. More recent studies have provided evidence for the therapeutic benefit of NIR-LED treatment in the survival and functional recovery of the retina and optic nerve in vivo after acute injury by the mitochondrial toxin, formic acid generated in the course of methanol intoxication. Gene discovery studies conducted using microarray technology documented a significant upregulation of gene expression in pathways involved in mitochondrial energy production and antioxidant cellular protection. These findings provide a link between the actions of red to near infrared light on mitochondrial oxidative metabolism in vitro and cell injury in vivo. Based on these findings and the strong evidence that mitochondrial dysfunction is involved in the pathogenesis of numerous diseases processes, we propose that NIR-LED photobiomodulation represents an innovative and non-invasive therapeutic approach for the treatment of tissue injury and disease processes in which mitochondrial dysfunction is postulated to play a role including diabetic retinopathy, age-related macular degeneration, Leber's hereditary optic neuropathy and Parkinson's disease.

Mitochondrion 2004 Sep 4(5-6) 559-67

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=16120414](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16120414)

# Chemotherapy- and radiotherapy-induced oral mucositis: review of preventive strategies and treatment.

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Oral mucositis is a frequently encountered and potentially severe complication associated with administration of chemotherapy and radiotherapy. Although many pharmacologic interventions have been used for the prevention and treatment of oral mucositis, there is not one universally accepted strategy for its management. Most preventive and treatment strategies are based on limited, often anecdotal, clinical data. Basic oral hygiene and comprehensive patient education are important components of care for any patient with cancer at risk for development of oral mucositis. Nonpharmacologic approaches for the prevention of oral mucositis include oral cryotherapy for patients receiving chemotherapy with bolus 5-fluorouracil, and low-level laser therapy for patients undergoing hematopoietic stem cell transplantation. Chlorhexidine, amifostine, hematologic growth factors, pentoxifylline, glutamine, and several other agents have all been investigated for prevention of oral mucositis. Results have been conflicting, inconclusive, or of limited benefit. Treatment of established mucositis remains a challenge and focuses on a palliative management approach. Topical anesthetics, mixtures (also called cocktails), and mucosal coating agents have been used despite the lack of experimental evidence supporting their efficacy. Investigational agents are targeting the specific mechanisms of mucosal injury; among the most promising of these is recombinant human keratinocyte growth factor.

Pharmacotherapy 2005 Apr 25(4) 540-54

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=15977916](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15977916)

# Low-level laser for prevention and therapy of oral mucositis induced by chemotherapy or radiotherapy.

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**PURPOSE OF REVIEW:** Oral mucositis is a common morbid condition associated with chemotherapy or radiotherapy for which there is no standard prophylaxis or treatment. There is increasing evidence that the use of low-level laser can reduced the severity of mucositis associated with chemotherapy or radiation therapy. The purpose of this review is to examine the available evidence for it. **RECENT**

**FINDINGS:** For most approaches commonly used to prevent or treat chemotherapy-associated or radiotherapy-associated oral mucositis, a recent panel of experts could not find sufficient levels of evidence to recommend or suggest their use. As for low-level laser therapy, the results are difficult to assess and compare because of interoperator variability and because clinical trials are difficult to conduct in that field. Nevertheless, there is accumulating evidence in support of low-level laser therapy.

**SUMMARY:** On the basis of literature data, it is reasonable to conclude that the evidence that low-level laser therapy may be useful in decreasing the severity of chemotherapy-associated or radiotherapy-associated mucositis is substantial, even though there have been few controlled studies in the field of prevention.

Curr Opin Oncol 2005 May 17(3) 236-40

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=15818167](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15818167)

# Patients with moderate chemotherapy-induced mucositis: pain therapy using low intensity lasers.

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**BACKGROUND:** Intensive cancer therapy normally affects malignant and normal cells with high replication rates. Cells in the gastrointestinal tract are therefore commonly affected by cytotoxins. This often results in the development of chemotherapy-induced oral mucositis (COM). COM is the inflammatory response of the oral mucous membrane to the chemotherapy drugs. Low level laser therapy (LLLT) has proved to be effective in treating and repairing biologically damaged tissue and to reduce pain. LLLT has also proven to be an efficient method for the prevention of oral mucositis. **OBJECTIVE:** To investigate the effect of LLLT on pain relief among patients who have developed COM. **METHOD:** The study was performed as a clinical test with a sample consisting of 13 adult patients receiving oncology treatment. The patients were treated during a 5-day period, and the pain was measured before and after each laser application. The laser used was an AsGaAl, with a wavelength of 830 nm and a potency of 250 mW. The energy given was 35 J cm<sup>-2</sup>. **ANALYSIS:** The results were analysed using the Wilcoxon test. **RESULTS:** There was a significant (P = 0.007) 67% decrease in the daily average experience of pain felt before and after each treatment, confirming that LLLT can relieve pain among patients who have developed COM. **STUDY LIMITATIONS:** The low number of COM patients at the hospital did not allow a control group to be included in the study, and therefore the results contain a potential placebo effect. **IMPLICATIONS FOR NURSING CARE:** The most important benefit the authors consider to be the value for the patients of better and quicker treatment with a drastic reduction in painful mucositis.

Int Nurs Rev 2005 Mar 52(1) 68-72

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=15725279](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15725279)

# Oral and intestinal mucositis - causes and possible treatments.

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Chemotherapy and radiotherapy, whilst highly effective in the treatment of neoplasia, can also cause damage to healthy tissue. In particular, the alimentary tract may be badly affected. Severe inflammation, lesioning and ulceration can occur. Patients may experience intense pain, nausea and gastro-enteritis. They are also highly susceptible to infection. The disorder (mucositis) is a dose-limiting toxicity of therapy and affects around 500 000 patients world-wide annually. Oral and intestinal mucositis is multi-factorial in nature. The disruption or loss of rapidly dividing epithelial progenitor cells is a trigger for the onset of the disorder. However, the actual dysfunction that manifests and its severity and duration are greatly influenced by changes in other cell populations, immune responses and the effects of oral/gut flora. This complexity has hampered the development of effective palliative or preventative measures. Recent studies have concentrated on the use of bioactive/growth factors, hormones or interleukins to modify epithelial metabolism and reduce the susceptibility of the tract to mucositis. Some of these treatments appear to have considerable potential and are at present under clinical evaluation. This overview deals with the cellular changes and host responses that may lead to the development of mucositis of the oral cavity and gastrointestinal tract, and the potential of existing and novel palliative measures to limit or prevent the disorder. Presently available treatments do not prevent mucositis, but can limit its severity if used in combination. Poor oral health and existing epithelial damage predispose patients to mucositis. The elimination of dental problems or the minimization of existing damage to the alimentary tract, prior to the commencement of therapy, lowers their susceptibility. Measures that reduce the flora of the tract, before therapy, can also be helpful. Increased production of free radicals and the induction of inflammation are early events in the onset of mucositis. Prophylactic administration of scavengers or anti-inflammatories can partially counteract or limit some of these therapy-mediated effects, as can the use of cryotherapy. The regular use of mouthwashes, mouth coatings, antibiotics and analgesics is essential, prior to and during loss and ablation of the epithelial layer. Granulocyte-macrophage colony-stimulating factor/granulocyte colony-stimulating factor or the use of laser light therapy may aid restitution and repair. Glutamine supplements may be beneficial in the repair/recovery phase.

Aliment Pharmacol Ther 2003 Nov 1 18(9) 853-74

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=14616150](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14616150)

# NASA light-emitting diodes for the prevention of oral mucositis in pediatric bone marrow transplant patients.

Whelan HT, Connelly JF, Hodgson BD, Barbeau L, Post AC, Bullard G, Buchmann EV, Kane M, Whelan NT, Warwick A, Margolis D

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**OBJECTIVE:** The purpose of this study was to determine the effects of prophylactic near-infrared light therapy from light-emitting diodes (LEDs) in pediatric bone marrow transplant (BMT) recipients. **BACKGROUND DATA:** Oral mucositis (OM) is a frequent side effect of chemotherapy that leads to increased morbidity. Near-infrared light has been shown to produce biostimulatory effects in tissues, and previous results using near-infrared lasers have shown improvement in OM indices. However, LEDs may hold greater potential for clinical applications. **MATERIALS AND METHODS:** We recruited 32 consecutive pediatric patients undergoing myeloablative therapy in preparation for BMT. Patients were examined by two of three pediatric dentists trained in assessing the Schubert oral mucositis index (OMI) for left and right buccal and lateral tongue mucosal surfaces, while the patients were asked to rate their current left and right mouth pain, left and right xerostomia, and throat pain. LED therapy consisted of daily treatment at a fluence of 4 J/cm<sup>2</sup> using a 670-nm LED array held to the left extraoral epithelium starting on the day of transplant, with a concurrent sham treatment on the right. Patients were assessed before BMT and every 2-3 days through posttransplant day 14. Outcomes included the percentage of patients with ulcerative oral mucositis (UOM) compared to historical epidemiological controls, the comparison of left and right buccal pain to throat pain, and the comparison between sides of the buccal and lateral tongue OMI and buccal pain. **RESULTS:** The incidence of UOM was 53%, compared to an expected rate of 70-90%. There was also a 48% and 39% reduction of treated left and right buccal pain, respectively, compared to untreated throat pain at about posttransplant day 7 ( $p < 0.05$ ). There were no significant differences between sides in OMI or pain. **CONCLUSION:** Although more studies are needed, LED therapy appears useful in the prevention of OM in pediatric BMT patients.

J Clin Laser Med Surg 2002 Dec 20(6) 319-24

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=12513918](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12513918)

# Pilot study of laser effects on oral mucositis in patients receiving chemotherapy.

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**PURPOSE:** The purpose of this study was to examine the effectiveness of laser therapy in the prevention and/or healing of chemotherapy-induced oral mucositis lesions. This study also evaluated the ease and feasibility of the laser therapy and the impact of the treatment on improving the patient's quality of life. **PATIENTS AND METHODS:** Fifteen patients with an episode of prior chemotherapy-induced grade 3 or 4 mucositis with 5-fluorouracil continuous infusion consented to participate in this study. All patients were provided with standardized mouth care instructions at the initiation of chemotherapy treatments. Enrolled patients received laser therapy treatments 24 hours before the chemotherapy and then recommenced weekly with evenly distributed exposure to the standardized designated areas by one operator during the entire cycle of chemotherapy at the same doses until the mucositis resolved or the chemotherapy cycle was completed. Intraoral perfusion was measured by laser Doppler technology. Patients were assessed for response to laser therapy according to standardized mucositis grading criteria by evaluating development of lesions, extent and duration of lesions, and time to healing. The effect of laser therapy on ability to continue planned chemotherapy, the reduction in dose, delays, and ability to maintain planned dose intensity were assessed. The impact of laser therapy on pain control was evaluated using the visual analogue score. A quality-of-life survey was completed by each patient at the initiation of chemotherapy and then weekly throughout the chemotherapy. **RESULTS:** Eleven of 15 patients experienced grade 0 mucositis, three patients experienced grade 1 to 2 mucositis, and one patient experienced grade 3 to 4 mucositis. Fourteen patients completed the lasertherapy as planned, and none of the patients withdrew from the laser therapy treatments because of noncompliance. One patient continued to experience grade 4 mucositis that necessitated an interruption in the planned chemotherapy regimen and, consequently, the laser treatment. Patients tolerated the laser therapy very well and did not report any increased discomfort. No significant changes in perfusion were observed as a result of laser therapy. **DISCUSSION:** In this pilot study, laser therapy significantly reduced the incidence and the severity of mucositis in chemotherapy patients. The laser therapy does not appear to promote wound healing by affecting the intraoral perfusion, as assessed by Doppler measurements. The mechanisms involved in the mediating of the observed effects remain unknown at this time. Continued research is warranted to determine the optimal laser wavelength and parameters.

Cancer J 2002 May-Jun 8(3) 247-54

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=12074324](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12074324)

# Low level laser therapy: a real hope in the management of chemo-induced and radiation-induced mucositis?

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Cancer J 2002 May-Jun 8(3) 236-8

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?  
cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=12074321](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12074321)

## [Current approaches in prevention and therapy of chemo- and radiotherapy-induced oral mucositis].

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Oral mucositis is a major, often dose-limiting toxicity in modern cancer-therapy, leading to dose reductions or delay in further cancer treatment. It predisposes to life-threatening septic complication during aplasia and substantially reduces quality of life for cancer patients. At present the basic strategies in oral mucositis aim at pain relief and prevention of infectious complications. However, no effective causal prophylaxis or treatment of oral mucositis is widely accepted. The introduction of cytokines, e.g. granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF), the use of cytoprotective agents, e.g. amifostine and the stimulation of basal-cell proliferation by soft-laser irradiation or silver nitrate offer new and hopeful approaches in oral mucositis. Large-scale clinical trials to confirm effectiveness and optimize treatment schedules have to be done.

Wien Med Wochenschr 2001 151(3-4) 53-65

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=11789420](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11789420)

## Effect of NASA light-emitting diode irradiation on wound healing.

Whelan HT, Smits RL Jr, Buchman EV, Whelan NT, Turner SG, Margolis DA, Cevenini V, Stinson H, Ignatius R, Martin T, Cwiklinski J, Philippi AF, Graf WR, Hodgson B, Gould L, Kane M, Chen G, Caviness J

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**OBJECTIVE:** The purpose of this study was to assess the effects of hyperbaric oxygen (HBO) and near-infrared light therapy on wound healing. **BACKGROUND DATA:** Light-emitting diodes (LED), originally developed for NASA plant growth experiments in space show promise for delivering light deep into tissues of the body to promote wound healing and human tissue growth. In this paper, we review and present our new data of LED treatment on cells grown in culture, on ischemic and diabetic wounds in rat models, and on acute and chronic wounds in humans. **MATERIALS AND METHODS:** In vitro and in vivo (animal and human) studies utilized a variety of LED wavelength, power intensity, and energy density parameters to begin to identify conditions for each biological tissue that are optimal for biostimulation. **Results:** LED produced in vitro increases of cell growth of 140-200% in mouse-derived fibroblasts, rat-derived osteoblasts, and rat-derived skeletal muscle cells, and increases in growth of 155-171% of normal human epithelial cells. Wound size decreased up to 36% in conjunction with HBO in ischemic rat models. LED produced improvement of greater than 40% in musculoskeletal training injuries in Navy SEAL team members, and decreased wound healing time in crew members aboard a U.S. Naval submarine. LED produced a 47% reduction in pain of children suffering from oral mucositis. **CONCLUSION:** We believe that the use of NASA LED for light therapy alone, and in conjunction with hyperbaric oxygen, will greatly enhance the natural wound healing process, and more quickly return the patient to a preinjury/illness level of activity. This work is supported and managed through the NASA Marshall Space Flight Center-SBIR Program.

J Clin Laser Med Surg 2001 Dec 19(6) 305-14

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=11776448](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11776448)

# Chemotherapy- and radiotherapy-induced mucositis in head and neck cancer patients: new trends in pathophysiology, prevention and treatment.

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Mucositis is the intensity-limiting toxicity in the management of locally advanced non-resectable head and neck cancer with radiotherapy and chemotherapy. New radiation modalities (hyperfractionation and/or acceleration) as well as combined modality regimens in this situation induce higher rates of acute toxicity. Hyperfractionation, for example, allows higher control rates, with few late toxicities, but it slightly increases acute mucositis. The addition of chemotherapy introduces systemic toxicity and can exacerbate local tissue reactions when used concurrently with radiotherapy. Mucositis is recognized as the principal limiting factor to further treatment intensification. As local regional control and overall survival are related to dose-intensity in this case, further research into the assessment, analysis, prevention and treatment of mucosal toxicity is not only crucial to improvement in quality of life, but certainly also to improved rates of disease control. Several topical and systemic treatments are directed to the decrease and the acceptance of this acute toxicity, but few have shown a significant preventive effect. The efficacy of low-level laser therapy in the management of such toxicity could hence yield important developments with this method in the field of oncology.

Eur Arch Otorhinolaryngol 2001 Nov 258(9) 481-7

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=11769997](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11769997)

## [Combined drug therapy in patients with chronic otitis media and mucositis]

Korviakov VS, Sidorina NG

The data of the authors own studies using conservative therapy in patients with chronic otitis media (COM) and mucositis are presented. The efficiency of treatment of these patients is shown depending on the method of treatment (the highest efficiency being noted in the main group of patients in whom the altered middle ear mucosa was concurrently exposed to autoserum (AS) and magnetic laser therapy (MLT). The efficiency of this or that conservative treatment was found to be related to the magnitude of altered middle ear mucosal changes: the more marked the signs of mucositis are, the more difficult it is to achieve a positive result. The results of treatment were assessed visually (under an operating microscope), bacteriologically, cytologically, and crystallographically. There was a correlation between the visual assessment of obtained treatment results and crystallographic findings. The high efficiency of the proposed treatment in patients with COM and mucositis is determined by the concurrent combined AS and MLT exposure of the entire thickness of the changed mucosa and by the stimulating action of MLT on AS. This conservative therapy can pretend to be the method of choice in treating patients with COM and mucositis.

Vestn Otorinolaringol 2000 -5 47-9

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=11051858](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11051858)

# Prevention and treatment of chemotherapy- and radiotherapy-induced oral mucositis: a review.

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Oral mucositis is a distressing toxic effect of systemic chemotherapy with many commonly utilized drugs and of head and neck irradiation in patients with cancer. The agents and methods that have been used and studied in chemotherapy- and radiotherapy-induced oral mucositis, their mechanisms of action, and the current knowledge of their efficiency to reduce the incidence, severity or shorten the duration of oral mucositis are reviewed in this article. Oral cooling is a cheap and available method to lower the severity of bolus 5-fluorouracil-induced oral mucositis. However, more effective methods are needed. Results of studies with granulocyte-macrophage colony-stimulating factor or granulocyte colony-stimulating factor are promising. Lasers are partly beneficial, but equipment-demanding. Modification of the chemotherapy regimen resulting in shortening of the exposition time to chemotherapy agents or chronomodulation of chemotherapy has been shown to lower mucosal toxicity of some regimens. Results of animal studies with locally applied transforming growth factor beta 3 and interleukin-11 are also promising. Based on the findings of the role of the inflammatory cascade in the response of normal tissues to chemotherapy and radiotherapy, anti-inflammatory drugs might be beneficial. At the present time, no agent has been shown to be uniformly efficacious and can be accepted as standard therapy of chemotherapy- and radiotherapy-induced oral mucositis. Further intensive research is needed.

Oral Oncol 1999 Sep 35(5) 453-70

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=10694945](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10694945)

## Research controversies in management of oral mucositis.

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The management of mucositis is the subject of many controversies, and the optimal treatment is still not known. Several evaluation scoring systems have been described, but no one of these is appropriate to all clinical situations: a simple scale such as that devised by the WHO can be used routinely, and more sophisticated ones can be implemented by trained experimenters working in research. We have considered the impact of each of the treatments currently available on each stage of mucositis. In attempts at prevention, self-care, in the sense of oral hygiene, must remain atraumatic. It is probably advisable to differentiate patients with good previous oral care, in whom tooth brushing is beneficial, from others, in whom the risk of hemorrhage and infection excludes any brushing. Before the dosage of chemotherapy is reduced, the curative or palliative intent of the strategy must be carefully evaluated. In the vascular phase protection of the proliferating cells is attempted by means of vasoconstriction (cryotherapy), cytoprotection (prostaglandin E2 and other antioxidants) or epithelial cell-inhibiting factors such as TGF- $\beta$ 3. Treatments applied in the epithelial phase are directed at increasing the cell proliferation to accelerate epithelial restoration by sucralfate and several growth factors: hematopoietic GF, which has demonstrated a direct effect on the mucosa (GM-CSF), or epithelial growth factors such as keratinocyte GF. In the ulcerative and bacteriological phase attempts are made to attenuate sepsis by means of antiseptics (chlorhexidine), amphotericin B and antiviral agents or antibiotic lozenges. In the healing phase application of the low-energy helium-neon laser has demonstrably been followed by a later time of onset, less pronounced peak severity and shorter duration of oral mucositis. After cancer treatment, oral hygiene, inhibition of oral flora, and pain relief are the main goals. Physiopathogen-specific treatment is the next step, with the emphasis on the inhibition of epithelial cell proliferation during drug exposure and facilitation of epithelial maturation and healing.

Support Care Cancer 2000 Jan 8(1) 68-71

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=10650902](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10650902)

# Oral mucositis in myelosuppressive cancer therapy.

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Because the etiology of mucositis is multifactorial, approaches to prevention and management have also been multifactorial. Effective prevention and management of mucositis will reduce the pain and suffering experienced during cancer treatment. Oropharyngeal pain in cancer patients frequently requires systemic analgesics, adjunctive medications, physical therapy, and psychologic therapy in addition to oral care and topical treatments. Good oral hygiene reduces the severity of oral mucositis and does not increase the risk of bacteremia. Current approaches to management include frequent oral rinsing with saline or bicarbonate rinses, maintaining excellent oral hygiene, and using topical anesthetics and analgesics. Cryotherapy is a potential adjunctive approach in some cases. There are a number of approaches that appear to represent viable candidates for further study. Biologic response modifiers offer the potential for prevention and for acceleration of healing. Various cytokines will enter clinical trials in the near future; these offer the potential for reduction of epithelial cell sensitivity to the toxic effects of cancer therapy or for stimulation of repair of the damaged tissue. Other approaches include the use of medications to reduce exposure of the oral mucosa to chemotherapeutic drugs that are secreted in saliva. Antimicrobial approaches have met with conflicting results, little effect being seen with chlorhexidine and systemic antimicrobials in the prevention of mucositis in radiation patients. In patients with BMT and patients with leukemia, chlorhexidine may not be effective in preventing mucositis, although there may be reduction in oral colonization by *Candida*. Initial studies of topical antimicrobials that affect the gram-negative oral flora have shown reductions in ulcerative mucositis during radiation therapy but have not been assessed in leukemia/BMT. Among other approaches that require further study are low-energy lasers and anti-inflammatory medications. These approaches to management have undergone initial study, but additional investigation is needed to determine their effectiveness with respect to the prevention of mucositis and symptom management and to determine appropriate doses and frequencies of intervention. Current studies and our increasing understanding of the pathogenesis of oral mucositis will lead to new approaches to management and improved quality of life for these patients.

Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999 Sep 88(3) 273-6

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=10503852](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10503852)

## Low-energy He/Ne laser in the prevention of radiation-induced mucositis. A multicenter phase III randomized study in patients with head and neck cancer.

Bensadoun RJ, Franquin JC, Ciais G, Darcourt V, Schubert MM, Viot M, Dejoux J, Tardieu C, Benezery K, Nguyen TD, Laudoyer Y, Dassonville O, Poissonnet G, Vallicioni J, Thyss A, Hamdi M, Chauvel P, Demard F

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Use of the low-energy helium-neon laser (LEL) appears to be a simple atraumatic technique for the prevention and treatment of mucositis of various origins. Preliminary findings, and significant results obtained for chemotherapy-induced mucositis in a previous phase III study, prompted a randomized multicenter double-blind trial to evaluate LEL in the prevention of acute radiation-induced stomatitis. Irradiation by LEL corresponds to local application of a high-photon-density monochromatic light source. Activation of epithelial healing for LEL-treated surfaces, the most commonly recognized effect, has been confirmed by numerous in vitro studies. The mechanism of action at a molecular and enzymatic level is presently being studied. From September 1994 to March 1998, 30 patients were randomized. Technical specification: 60 mW (25 mW at Reims, 1 patient), He-Ne, wavelength 632.8 nm. The trial was open to patients with carcinoma of the oropharynx, hypopharynx and oral cavity, treated by radiotherapy alone (65 Gy at a rate of 2 Gy/fraction, 5 fractions per week) without prior surgery or concomitant chemotherapy. The malignant tumor had to be located outside the tested laser application areas (9 points): posterior third of the internal surfaces of the cheeks, soft palate and anterior tonsillar pillars. Patients were randomized to LEL or placebo light treatment, starting on the first day of radiotherapy and before each session. The treatment time (t) for each application point was given by the equation :  $t(s) = \text{energy (J/cm}^2) \times \text{surface (cm}^2) / \text{Power (W)}$ . Objective assessment of the degree of mucositis was recorded weekly by a physician blinded to the type of treatment, using the WHO scale for grading of mucositis and a segmented visual analogue scale for pain evaluation. Protocol feasibility and compliance were excellent. Grade 3 mucositis occurred with a frequency of 35.2% without LEL and of 7.6% with LEL ( $P < 0.01$ ). The frequency of "severe pain" (grade 3) was 23.8% without LEL, falling to 1.9% with LEL ( $P < 0.05$ ). Pain relief was significantly reduced throughout the treatment period (weeks 2-7). LEL therapy is capable of reducing the severity and duration of oral mucositis associated with radiation therapy. In addition, there is a tremendous potential for using LEL in combined treatment protocols utilizing concomitant chemotherapy and radiotherapy.

Support Care Cancer 1999 Jul 7(4) 244-52

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=10423050](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10423050)

# Low energy Helium-Neon laser in the prevention of oral mucositis in patients undergoing bone marrow transplant: results of a double blind randomized trial.

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**PURPOSE:** To evaluate the efficiency of Helium-Neon (He-Ne) laser in the prevention of oral mucositis induced by high dose chemoradiotherapy before autologous bone marrow transplantation (BMT). **METHODS AND MATERIALS:** Between 1993 and 1995, 30 consecutive patients receiving an autologous peripheral stem-cell or bone marrow transplant (BMT) after high dose chemoradiotherapy were randomized to possibly receive prophylactic laser to the oral mucosa after giving informed consent. Chemotherapy consisted of cyclophosphamide, 60 mg/kg intravenously (I.V.) on day (d)-5 and d-4 in 27 cases, or melphalan 140 mg/kg I.V. on d-4 in three cases. Total body irradiation (TBI) consisted of 12 Gy midplane dose in six fractions (4 Gy/day for three days). He-Ne laser (632.8 nm wavelength, power 60 mW) applications were performed daily from d-5 to d-1 on five anatomic sites of the oral mucosa. Oral examination was performed daily from d0 to d + 20. Mucositis was scored according to an oral exam guide with a 16 item scale of which four were assessed by the patients themselves. Mean daily self assessment scores for oral pain, ability to swallow and oral dryness were measured. A daily mucositis index (DMI) and a cumulative oral mucositis score (COMS) were established. Requirement for narcotics and parenteral nutrition was recorded. **RESULTS:** The COMS was significantly reduced among laser treated (L+) patients ( $p = 0.04$ ). The improvement of DMI in L+ patients was also statistically significant ( $p < 0.05$ ) from d + 2 to d + 7. Occurrence and duration of grade III oral mucositis were reduced in L+ patients ( $p = 0.01$ ). Laser applications reduced oral pain as assessed by patients ( $p = 0.05$ ) and L+ patients required less morphine ( $p = 0.05$ ). Xerostomia and ability to swallow were improved among the L+ patients ( $p = 0.005$  and  $p = 0.01$ , respectively). Requirement for parenteral nutrition was not reduced ( $p = \text{NS}$ ). **CONCLUSION:** Helium-Neon laser treatment was well tolerated, feasible in all cases, and reduced high dose chemoradiotherapy-induced oral mucositis. Optimal laser treatment schedules still needs to be defined.

Int J Radiat Oncol Biol Phys 1997 Jul 1 38(4) 697-703

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=9240635](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9240635)

# Helium-neon laser effects on conditioning-induced oral mucositis in bone marrow transplantation patients.

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**BACKGROUND.** Oral mucositis is a common complication of bone marrow transplantation (BMT) conditioning therapy. Sequelae consist of increased risk for infection, moderate to severe pain, compromised oral function, and bleeding. This study investigated helium-neon laser treatment for prevention of conditioning-induced oral mucositis in BMT patients. Patterns and severity of mucositis for specific conditioning drug regimens also were analyzed. **METHODS.** Twenty patients received laser radiation to their oral mucosa, either left or right of midline. The contralateral side was sham-treated and served as a control. Mucositis severity was scored independently by two modified versions of the Oral Mucositis Index Scale (OMI-A and OMI-B) and the Eastern Cooperative Oncology Group (ECOG) Oral Toxicity Scale; pain severity was scored by subjects on a visual analogue scale (VAS). Cumulative scores were analyzed for differences between the laser-treated and sham-treated sides. **RESULTS.** Oral mucositis and pain scores were significantly lower for the treated versus the untreated side by OMI-A and B ( $P < 0.005$ ) and VAS ( $P = 0.027$ ) criteria, respectively. Ulcerative lesions occurred in all patients bilaterally; severity increased until Day +6, and lesions resolved by Day +21. Mucositis was more severe for patients conditioned with busulfan/carboplatin/thiotepa than for patients conditioned with busulfan/cyclophosphamide/etoposide. **CONCLUSIONS.** Helium-neon laser treatment was well-tolerated and reduced the severity of conditioning-induced oral mucositis in BMT patients.

Cancer 1995 Dec 15 76(12) 2550-6

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=8625084](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8625084)

# Cancer therapy and oral mucositis. An appraisal of drug prophylaxis.

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Oral mucositis as a consequence of cytotoxic therapy is a major cause of morbidity in cancer patients. Cancer therapy-induced tissue damage leading to mucositis can occur through either direct or indirect stomatotoxicity. Once mucositis has occurred, treatment consists of measures to palliate symptoms. The prevention of cancer therapy-induced oral mucositis is less standardised. Numerous drugs have been used as prophylactic agents to prevent chemo- and radiotherapy-induced mucositis. Controlled trials have shown some degree of prophylactic efficacy for sucralfate, chlorhexidine and benzydamine. Positive but non-placebo-controlled trials requiring more study have been conducted with dinoprostone (prostaglandin E2), silver nitrate, beta-carotene, pentoxifylline and lozenges containing polymixin B, tobramycin and amphotericin B. Current studies have shown a lack of efficacy with allopurinol and granulocyte colony-stimulating factor (G-CSF). Nonpharmacological methods such as oral cryotherapy and helium-neon laser treatments have shown some promise. At the present time no agent has been shown to be uniformly efficacious and can be accepted as standard therapy. Additional studies combining several agents or incorporating nonpharmacological manoeuvres for mucositis prevention are needed.

Drug Saf 1993 Sep 9(3) 185-95

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=8240724](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=8240724)

# Soft-laser therapy for iatrogenic mucositis in cancer patients receiving high-dose fluorouracil: a preliminary report.

Pourreau-Schneider N, Soudry M, Franquin JC, Zattara H, Martin PM, Ciais G, Namer M, Schneider M, Chauvel P, Demard F

J Natl Cancer Inst 1992 Mar 4 84(5) 358-9

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?  
cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=1738189](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1738189)

## [Laser therapy in the prevention and treatment of mucositis caused by anticancer chemotherapy]

Ciais G, Namer M, Schneider M, Demard F, Pourreau-Schneider N, Martin PM, Soudry M, Franquin JC, Zattara H

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The appearance of mucositis is a frequent and painful secondary effect of anticancer chemotherapy. Patients who develop oral toxicity during the first course of treatment will almost assuredly show identical side effects during each subsequent course unless the drugs are changed or the doses are lowered. In the absence of an efficacious antidote or preventive prophylaxis for such lesions to date, this report presents the results of a preliminary retrospective non-randomized study of the effect of soft-laser treatments on mucositis in cancer patients receiving combination chemotherapy, including 5-fluorouracil. Iatrogenic mucositis was observed during 43% of 53 chemotherapy cycles in the case control population. Curative laser therapy reduced the time to repair lesions and the rate of therapeutic modifications. For patients who received soft-laser therapy as a preventive measure, the incidence of oral complications was reduced to 6% during 101 cycles of chemotherapy. All of these patients, even those who have encountered mucositis before receiving preventive laser therapy, terminated their cancer therapy as originally scheduled. Well designed and carefully controlled trials will be necessary to define the place of helium-neon laser therapy in the repair and prevention of oral complications due to cancer chemotherapy.

Bull Cancer 1992 79(2) 183-91

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=1392157](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1392157)

# Helium-Neon Laser Irradiation Is Not a Stressful Treatment: A Study on Heat-Shock Protein (HSP70) Level

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**Background and Objective:** Helium-neon (He-Ne) laser irradiation has been clinically used to reduce chemotherapy-induced mucositis. This work was designed to find out if this treatment is stressful at the cellular level by studying its effects on the level of the stress-inducible heat shock proteins.

**Study Design/Materials and Methods:** Human desmodontal and mouse L929 fibroblasts were irradiated using a 60 mW laser by a single application of 1.5 and 3J/cm<sup>2</sup> in continuous mode. Heat shock protein level was studied by gel electrophoresis and Western blotting using monoclonal antibodies.

**Results:** He-Ne laser treatment does not induce heat shock protein synthesis in human desmodontal nor in mouse fibroblasts at the energy densities used in this study.

**Conclusion:** These results indicate that the treatment is not stressful at the cellular level

Radiol Bras 2006;39(2):131 136

# Use of laser photomodulation in the evolution of oral mucositis associated to cyclophosphamide, methotrexate, 5-fluouracil - CMF in 5 fluouracil + adriamycin + cyclophosphamide - FAC chemotherapy protocols in patients with breast cancer

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The aim of this study was to evaluate the efficacy of the laser photobiomodulation (FBML) in prevention and treatment of oral mucositis induced by chemotherapy protocols CMF (cyclophosphamide, methotrexate, 5-Fluouracil) and FAC (5 Fluouracil + Adriamycin + Cyclophosphamide) in cancer patients breast. We selected 28 patients treated at the Center for High Complexity (CACON), who underwent 6 cycles of 21 days of treatment, with diagnosis of infiltrating ductal carcinoma (ICD C50.9). Were randomly divided into three groups: Group A - eight patients (Protocol FAC + Dental protocol of CACON + Laser), Group B - 6 patients (Protocol CMF + Dental protocol of CACON + Laser), Group C - was divided into two sub-groups: Group C1 with 8 patients (Control Group 1: FAC + Dental protocol of CACON) and group C2 with 6 patients (control group 2: Protocol CMF + Dental protocol of CACON). Patients in Group A and B were use of preventive FBML 24 hours before the start of chemotherapy cycle, then every 48 hours and was extended up to one week following completion of chemotherapy. The groups A and B, presented oral mucositis grade 0 (64.29%)  $p = 0.07$ , grade I (7.14%), grade II (14.29%), grade III (7.14%), grade IV (7.14%) compared to group C, who presented mucositis grade 0 (35.71%) in the initial evaluation with  $p = 0.10$ , grade I (21.43%), grade II (28.57%), grade III (14.29%), grade IV (0.00%), patients who used the FBML as a preventive and therapeutic showed a reduction and pain relief in 42.86%. It is concluded that the low power laser when used preventively or as therapy and showed immediate relief of pain and accelerate tissue repair.

Med Oral Patol Oral Cir Bucal. 2012 May 1;17(Supplement1):S252

[http://www.researchgate.net/publication/257881682\\_Use\\_of\\_Laser\\_Photomodulation\\_in\\_the\\_Evolution\\_of\\_Oral\\_Mucositis\\_Associated\\_to\\_Cyclophosphamide\\_Methotrexate\\_5-Fluouracil\\_-CMF\\_in\\_5\\_Fluouracil\\_\\_Adriamycin\\_\\_Cyclophosphamide\\_-FAC\\_Chemotherapy\\_Protocols\\_in\\_Patients\\_with\\_Breast\\_Cancer\\_Mechanisms\\_for\\_Low-Light\\_Therapy\\_VIII\\_edited\\_by/file/9c96052609f337ff5a.pdf](http://www.researchgate.net/publication/257881682_Use_of_Laser_Photomodulation_in_the_Evolution_of_Oral_Mucositis_Associated_to_Cyclophosphamide_Methotrexate_5-Fluouracil_-CMF_in_5_Fluouracil__Adriamycin__Cyclophosphamide_-FAC_Chemotherapy_Protocols_in_Patients_with_Breast_Cancer_Mechanisms_for_Low-Light_Therapy_VIII_edited_by/file/9c96052609f337ff5a.pdf)

# Radiation-and chemotherapy-induced mucositis in oncology results of multicenter phase III studies

Bensadoun RJ, Ciais G

**Purpose:** Following several positive randomized trials in the field of chemotherapy-induced mucositis, a randomized multicenter trial was conducted to evaluate low-level He:Ne laser therapy (LLLT) for the prevention of acute radiation-induced oropharyngeal mucosal lesions. **Materials and Methods:** The trial was open to patients with carcinoma of the oropharynx, hypopharynx, and oral cavity being treated by external radiotherapy, with a total dose of 65 Gy at a rate of 1 fraction of 2 Gy/day, 5 days a week, from cobalt-60 or linear accelerator photons. Patients were assigned to either laser treatment (L+) or sham-treatment (L-) by computer blocked randomization. The protocol called for the inclusion of 30 patients, 15 in each arm. Analgesics could be prescribed, but not during the 2 days preceding each week evaluation. Patients received He:Ne laser applications daily for five consecutive days during the seven days of head and neck radiotherapy. The 9 treatment areas included: posterior third of buccal mucosa, soft palate, and anterior tonsillar pillars. The treatment time (t) for each application point was given by the equation:  $t \text{ (s)} = \text{energy (J/cm}^2) \times \text{surface (cm}^2) / \text{Power (W)}$ . The average energy density delivered to the treatment areas was 2 J/cm<sup>2</sup>. All laser illuminations were performed by the same individual in each center. Criteria for evaluation were the standard WHO scale for mucositis in the oropharynx and a segmented visual analogic scale for pain (patient self-evaluation). **Results:** Laser applications delayed time of onset, attenuated the peak severity, and shortened the duration of oral mucositis. The difference between L+ and L- patients was statistically significant from week 4 to week 7. During the 7 weeks of treatment, the mean grade of mucositis in L+ patients was significantly lower (p = 0.01) than the mean grade in L- patients. Results of decrease in pain intensity were also quite convincing. Laser applications reduced the incidence and duration of morphine administration. Ability to swallow was also improved. **Conclusion:** Low level He:Ne laser (LLL) seems to be a safe and efficient method for the prevention of radiation-induced stomatitis and chemo-induced mucositis, with a tremendous potential interest for combined modality treatment.

J Oral Laser Applications 2 (2002), No. 2 (15.07.2002)

<http://jola.quintessenz.de/index.php?doc=abstract&abstractID=7801>

# Cost-effectiveness of low-level laser therapy (LLLT) in head and neck cancer patients submitted to concurrent chemoradiation

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**Brazil** Introduction: Oral mucositis is a main factor for increasing treatment costs in head and neck squamous cell carcinoma (HNSCC) patients treated with chemoradiation (CRT)

**Objectives:** This study was designed to estimate the cost-effectiveness of LLLT to prevent oral mucositis in HNSCC patients submitted to CRT. **Methods:** From June 2007 to Dec 2010, 94 patients with HNSCC of nasopharynx, oropharynx and hypopharynx entered a prospective, randomized, double blind, placebo-controlled, phase III trial (47 LLLT (LG) and 47 placebo (PG)). CRT consisted of conventional RT 70.2 Gy (1.8Gy/d, 5 times/week) + concurrent cisplatin 100 mg/m<sup>2</sup> every 3 week. The LLLT used daily was a diode InGaAlP (660 nm- 100 mW-4 J/cm<sup>2</sup>). The cost per laser session was US\$ 34.00 for the baseline analysis. Hospitalization rates associated with the treatment of oropharyngeal or oral mucositis were not documented in the study and were estimated according to previously published data.

**Results:** Under the perspective of the Brazilian public healthcare system (SUS), total costs were higher in PG than LG on opioide use (LG = US\$ 29.45; PG = US\$143.72, gastrostomy (LG = US\$ 41.69; PG = US\$107.22) and hospitalization (PG = US\$ 63.59). In LG costs were higher with laser therapy (US\$ 1.549,50). The total incremental cost associated with the use of LLLT was US\$ 1.306,61 per patient. The incremental cost-effectiveness ratio (ICER) was US\$ 3.838,16 per case of grade 3–4 mucositis avoided when compared with no treatment.

**Conclusions:** Our results indicate that laser group had a smaller morbidity during treatment and LLLT is cost-effective when compared to placebo under a threshold of at least US\$ 4,000 per avoided mucositis case.

Support Care Cancer. 2013 Jun;21

<http://www.ncbi.nlm.nih.gov/pubmed?Db=pubmed&Cmd=DetailsSearch&Term=23604519>

# Use of Laser photobiomodulation in the evolution of oral mucositis associated with CMF chemotherapy protocol in patients with breast cancer- Case Report.

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Brazil The aim of this study was to evaluate the effectiveness of using a laser photobiomodulation on prevention and treatment of oral mucositis induced by chemotherapy protocol CMF (cyclophosphamide, methotrexate, 5-Fluouracil) in patients with breast cancer. Patients and Methods: We selected 12 patients who underwent 6 cycles of 21 days of treatment, with diagnosis of infiltrating ductal carcinoma (ICD C50.9). Were randomly divided into two groups: Group A with 6 patients (Protocol CMF + + Laser Protocol of stomatological CACON) Group B (Group C1 6 patients) were the control patients who received CMF hospital protocol established by CACON. The patients in Group A received the preventive use of FBML 24 hours before the start of chemotherapy cycle, then every 48 hours and was extended to one week after completion of chemotherapy. Results: In groups of oral mucositis grade 0 (64.29%), grade I (7.14%), grade II (14.29%), grade III (7.14%), grade IV (14.29 %) compared to group B, had mucositis grade 0 (35.71%), grade I (21.43%), grade II (28.57%), grade III (14.29%), grade IV (14.29%), patients who made use of FBML and as preventive therapy showed a reduction and pain relief in 42.86%. Conclusion: The low-power laser when used preventively or as therapeutic and showed immediate relief of pain and accelerate tissue repair.

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