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Phase III randomised trial

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

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ABSTRACT

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 (660 nm–100 mW–1 J–4 J/cm^2) 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.

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Oral mucositis (OM) is a limiting factor in the treatment of patients suffering from head and neck squamous cell carcinoma (HNSCC) who undergo chemoradiotherapy. Its pathobiology is associated with injuries that occur in the epithelial and connective tissues as a response to a complex cascade of biological events [1–3]. Between 80% and 100% of all chemoradiotherapy-treated patients present OM [4–9] in different grades, starting from radiation doses between 15 and 20 Gy [2,3,9]. Severe OM (grades 3–4) is associated with increased morbidity (pain, dysphagia, weight loss, and reduced treatment compliance), poor quality of life, and higher hospital costs due to the need for medication, gastrostomy, and frequent appointments with the health-care team [2,8,10–13]. Besides severe OM may lead to treatment interruption, which may jeopardize the local control of the disease and patient survival [14]. Therefore strategies to prevent severe OM should be eagerly pursued.

Prospective placebo-controlled clinical trials, have shown that low-level laser therapy (LLLT) can be effective in the prevention of OM in patients undergoing hematopoietic stem cell transplantation [15–19]. However, in the setting of HNSCC patients treated with chemoradiotherapy a definitive trial is needed. Most of the initial trials included patients who underwent radiotherapy only [20–22] while in the only four chemoradiotherapy-based studies [23–26], a high incidence of OM was still observed.

Here we assessed the efficacy of LLLT in reducing the incidence of OM in HNSCC patients undergoing concurrent chemoradiotherapy and its impact on the patients' quality of life.

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Methods

Patients

From June 2007 to December 2010, a randomized, double-blind, prospective, placebo-controlled trial that included 94 HNSCC patients was carried out at the Brazilian National Cancer Institute in Rio de Janeiro. Patients were randomized into two groups of 47 patients each, which received either preventive LLLT or placebo.

To be included in the study patients had to be $\geqslant$18 years, have a histological diagnosis of squamous cell carcinoma (nasopharynx, oropharynx and hypopharynx), be ineligible candidates for surgery, be eligible to a combined treatment with radiotherapy and concurrent platinum-based chemotherapy, have a ECOG performance status (PS) [27], of 0 or 1 and have the oral mucosa intact. Patients who were receiving medication for the treatment and prevention of mucositis, and those incapable of complying with the treatment procedure or performing the oral hygiene protocol were not included.

Patients were evaluated by a dentist before starting the radiotherapy and any required dental treatment or the removal of teeth with uncertain prognosis, including teeth with active periodontal disease, teeth requiring endodontic treatment and teeth with cavities or extensive coronal destruction, was performed [28–31]. The study was approved by the institutional ethics committee under number MS-17/2007, in accordance with the guidelines of Good Clinical Practice and the Brazilian law, and all patients signed an informed consent form.

Study design

Patients were randomized in a non-stratified manner to study treatment and underwent the same protocol of chemoradiotherapy. The chemotherapy protocol was cisplatin (100 mg/m^2) on D1, D22 and D43. With the patients supine and immobilized by a thermoplastic mask, megavoltage RT was delivered by two or three-dimensional techniques. A total dose of 70.2 Gy (prescribed at midline) was delivered daily in 39 fractions on a 5 day-per-week schedule with a telecobalt unit and linear accelerator. Radiotherapy began on D1 and the posterior spinal cord was excluded from the treatment volume after 45 Gy. The primary tumor and the upper cervical lymph node regions were treated with two lateral fields. After spinal cord exclusion, additional electron fields (9–15 MeV) at 85–95% curves were used to boost the posterior lymph node chain. The lower neck was treated with an anterior field, to a given dose of 50.4 Gy in 28 fractions. Standard field limits were used for the primary site and the lymph node regions. Portals were verified at D1 and weekly to check positioning. All the recommendations listed at the ICRU report 29 for 2D planning [32] and at the ICRU reports 50 and 62 for 3D planning [33,34] were followed and achieved in 92.5% of the patients. In only 7 patients a gradient superior of −5% to +7% (13–20%) was documented. As a preventive measure for candida infection all patients were prescribed oral fluconazole (50 mg/day), starting at D6 until the end of radiotherapy [35–37]. In patients with a weight loss of 10% or more before or during treatment, with grade 4 OM or with pain on a visual analog scale (VAS) $\geqslant$6 (after opiod analgesic), a percutaneous gastrostomy or nasogastric feeding tube was done. All patients underwent oral hygiene with an extra-soft toothbrush and peroxidase-based system toothpaste after every meal and alcohol-free 0.12% chlorhexidine mouthwash [17] twice a day, from the first until the the last fraction of radiotherapy (Fig. 1).

Laser therapy protocol

An InGaAlP (indium phosphide, gallium and aluminum) diode laser (DMC, São Carlos, São Paulo, Brazil), with 100 mW, 1 J, 4 J/cm2, a spot size of 0.24 cm^2, emitting continuous light at 660 nm, was used for laser therapy. The same energy and energy density was used for all the patients. The preventive LLLT was applied daily, for 5 consecutive days (Monday to Friday), every week, immediately before every single fraction of RT by a dentist and the tip touched the mucosa of the lips, right and left buccal mucosa, left and right lateral tongue border, buccal floor, and ventral tongue, totaling nine points per region. The application time per point was 10 s and the total application time was 12 min. Exactly the same protocol was applied to the placebo group except that the laser tip produced no light. All patients used blinded glasses and were unable to see the dental procedure. For ethical purposes, patients in the placebo group who had grade 3–4 OM or presented a 6 cm of ulcerated area in the oral cavity, were discontinued from the trial and received LLLT (660 nm, 100 mW, 2 J, 8 J/cm^2, per point) with therapeutic purposes.

The dentists who applied the LLLT (HSA and MPR) knew which patients were allocated to each study group, but the nurses (TGPS and EC) who evaluated the oral cavity of the patients daily were blinded.

Patient evaluation

With the purpose of minimizing interobserver variation and familiarizing the team with the measurement scales for mucositis, all professionals involved were submitted to a specific training and testing before the initiation of the trial. A CD-ROM containing the research protocol as well as photographic examples of normal and damaged oral mucosa (mucositis) was given to all professionals involved in the application of LLLT and in the evaluation of patients. Daily evaluation of the mucosa of the lips, right and left buccal mucosa, left and right lateral tongue border, buccal floor, ventral tongue and oropharynx was performed according to the World Health Organization (WHO) mucositis scale [38] and the OM Assessment Scale (OMAS) [39]. Every day adverse events were recorded following the Common Toxicity Criteria of the NCI version 3.0 [40]. A modified visual analog scale (VAS) for pain assessment was used [20]. The opioid use was assessed in accordance with WHO for oral or oropharyngeal pain (in morphine equivalents) [41]. Body weight (Body Mass Index) was measured weekly from the first day of treatment. All information related to complications occurring during the treatment (such as treatment interruption, treatment delay, patient weight loss, hospitalizations, requirement for nasogastric tube or gastrostomy, and use of opioid analgesic) were recorded. Quality of life (QoL) was assessed on the 1st, 20th and 39th RT fraction by EORTC questionnaires [42] QLQ-C30 (overall quality of life; version 3.0) and QLQ-H & N35 (specific quality of life for head and neck patients). Patients who missed consultation ($\geqslant$3, corresponding to 7.7% of applications) for the application of either LLLT or placebo were considered to be noncompliant and were discontinued from the trial. OM was not evaluated after it. Data related to the primary endpoint were handled in a per protocol treatment analysis. Yet, a strict follow up of every single patient was carried out for disease progression and overall survival data.

Statistical analysis

The primary end point of the study was the incidence of grade 3–4 OM according to the WHO scale. Assuming an $\alpha = 0.05$ and a $\beta = 0.20$, with the estimates of proportion being 0.40 [4] for placebo (P_0) and 0.15 [17] for LLLT (P_1) a total of 94 patients were evaluated. The chi-square test (χ^2) and the Fisher's exact test were applied to evaluate the incidence of mucositis according to the WHO scale, VAS for pain scores, interruption of treatment, hospitalization, tumor response, patient exclusion, the need for nasogastric tube or gastrostomy and baseline characteristics of the patients. Logistic regression modeling was undertaken to deter-