

CLINICAL INVESTIGATION

Head and Neck Cancer

ORAL MUCOSITIS PREVENTION BY LOW-LEVEL LASER THERAPY IN HEAD-AND-NECK CANCER PATIENTS UNDERGOING CONCURRENT CHEMORADIO THERAPY: A PHASE III RANDOMIZED STUDY

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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/cm² 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. © 2012 Elsevier Inc.

Mucositis, Head-and-neck cancer, Low level laser, Chemoradiotherapy.

INTRODUCTION

Oral mucositis is a major treatment-related complication of concurrent chemoradiotherapy (CRT) for head-and-neck cancer (HNC). It affects patients' nutrition, pain control, quality of life, and adequate treatment delivery, because it can lead to unplanned radiotherapy (RT) breaks, compromising treatment efficacy (1, 2). HNC patients usually present with locally advanced disease and ideally are treated with concurrent cisplatin-based CRT whenever pos-

sible (3), either as definitive or adjuvant treatment. Thus, the early detection and grading of mucositis and the prompt treatment of this debilitating adverse effect are essential in the multidisciplinary supportive care of these patients.

Several measures have been studied to prevent or treat oral mucositis induced by chemotherapy or RT, but efficacy has not been consistently shown for any. A Cochrane's recent systematic review (4) of the prevention of oral mucositis in cancer patients concluded that the strength of the evidence

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was variable among the many interventions and that well-designed trials of this issue are needed.

Low level laser (LLL) therapy is a promising preventive therapy. It has been used in the prevention and treatment of oral mucositis in several clinical settings, including RT for HNC patients and high-dose chemotherapy with hematopoietic stem cell transplantation (5–11). These studies, in general, have shown that LLL treatment is safe and that LLL provides some benefit; however, high-quality evidence is missing, mostly for HNC patients receiving CRT (12, 13). In addition, the best LLL treatment schedule still needs to be defined.

Therefore, we performed a Phase III, randomized, double-blind study to evaluate the efficacy of LLL to prevent or delay the appearance of severe oral mucositis induced by CRT in HNC patients and its effect on unplanned RT interruptions and pain control.

METHODS AND MATERIALS

Subjects

The eligible patients were 18–75 years old, with previously untreated, histologically confirmed, head-and-neck squamous cell carcinoma of the oropharynx, hypopharynx, nasopharynx, larynx, or oral cavity, undifferentiated nasopharyngeal carcinoma, or cervical metastasis with an unknown primary site. All patients were candidates for adjuvant or definitive CRT, consisting of conventionally delivered 60–70 Gy (1.8–2.0 Gy/fraction, one daily fraction, from linear accelerator 6-MV photons and 6–9-MeV electrons, using standard three-dimensional or two-dimensional RT plans, with customized blocks), 5 d/wk (Monday to Friday), and concurrent cisplatin 100 mg/m² on Days 1, 22, and 43. Other platin-based chemotherapy regimens (*e.g.*, weekly cisplatin) were allowed. The patients presenting with Grade 3 or 4 dysphagia or odynophagia (National Cancer Institute Common Toxicity Criteria, version 2.0) were excluded.

Before study initiation, the institutional ethics committee approved the protocol. The trial was conducted at a single institution (Hospital das Clínicas da Faculdade de Medicina da USP, southeastern Brazil), in accordance with the applicable guidelines of Good Clinical Practices and the Declaration of Helsinki and Brazilian law. All patients provided written informed consent before undergoing any study procedure or receiving any study therapy.

Treatment plan

All patients underwent oral examination and preventive dental treatment before starting RT. Preventive dental treatment consisted of educating patients about oral hygiene; panoramic radiography; tooth and periodontal examination; removal of calculus; extraction of teeth with extended caries, coronary destruction, severe periodontal disease, or requiring endodontic treatment; and elimination of trauma sources.

The patients were assigned to LLL or sham laser (placebo) treatment by computer-block randomization. The patients assigned to LLL therapy were treated with a 660-nm wavelength gallium-aluminum-arsenide, 10-mW laser, with a spot size of 4 mm² (Twin Flex, MMOptics, São Carlos, Brazil). The patients underwent LLL applications daily for 5 consecutive days (Monday to Friday), every week, immediately before each fraction and during all RT sessions. The average energy density delivered to the oral mu-

cosa was 2.5 J/cm², and the energy dose delivered to the treated surface was 0.1 J. LLL was delivered intraorally outside the malignant tumor-located area. During each LLL session, nine areas were treated to several points, for 10 s each, including the inferior and superior lips, right and left cheeks, dorsal and ventral tongue, hard and soft palates, right and left gums, and tongue frenulum, as previously described (5). During the sessions, the patients wore wavelength-specific, dark safety glasses. Those patients assigned to receive sham laser applications were treated with the same schedule.

Topical treatments (*e.g.*, oral lidocaine gel, oral aluminum hydroxide suspension) were administered to all patients after the appearance of mucositis. Analgesic agents (nonsteroidal anti-inflammatory drugs and/or opioids) and antifungal agents were prescribed at the physicians' discretion.

Baseline and follow-up assessments

The primary endpoints were the oral mucositis severity at Weeks 2, 4, and 6 (National Cancer Institute Common Toxicity Criteria, version 2.0) and the number of RT interruptions due to mucositis. The secondary endpoints included patient-reported pain scores. Oral mucositis and dysphagia were evaluated in accordance with the National Cancer Institute Common Toxicity Criteria, version 2.0. These toxicity evaluations were performed by trained radiation oncologists who were unaware of the subject's treatment arm assignment at Weeks 2, 4, and 6 of RT. Pain was assessed using a visual analog scale by patient self-evaluation, also at Weeks 2, 4, and 6 of RT. A score >7 was defined as severe pain. Weight loss and the placement of feeding tubes were monitored every 2 weeks.

Statistical analysis

To detect a decrease in the incidence of Grade 3 or 4 oral mucositis from 80% in the control arm (placebo/sham laser) to 50% in the experimental arm (LLL), we planned to enroll 74 patients, with a Type I and Type II error of 5% and 20%, respectively. The patient characteristics and mucositis scores were compared using the *t* test or Mann-Whitney *U* test, as appropriate. The chi-square test or Fisher's exact test was used to compare the proportions between categories. All reported *p* values were two-tailed and were considered statistically significant at *p* < .05. The analyses were done using the Statistical Package for Social Sciences statistical software, version 10.0 (SPSS, Chicago, IL).

RESULTS

Patient and tumor characteristics

A total of 75 patients were consecutively enrolled in the trial between March 2007 and December 2008. The patient characteristics are listed in Table 1. The median age was 55 years, and most patients were men. Most patients were diagnosed with squamous cell carcinoma, and the oropharynx was the most common primary site (44%). Most patients presented with locally advanced disease: 56 patients (75%) had Stage T3-T4 and 61 patients (81%) had Stage N+. The two arms were well balanced with respect to all patient and tumor characteristics.

RT and concurrent chemotherapy

The patients underwent conventionally fractionated RT (2-Gy daily fractions, 5 times weekly), with the exception of 1 patient. The patients also mostly underwent concurrent

Table 1. Patient and tumor characteristics

Characteristic	LLL	Placebo	<i>p</i>
Patients (<i>n</i>)	37 (49)	38 (51)	
Age (y)			.93
Mean ± SD	53.1 ± 9.4	53.2 ± 10.3	
Median	55	55.5	
Gender			.59
Male	27 (73)	30 (79)	
Female	10 (27)	8 (21)	
Histologic type			.33
Squamous cell carcinoma	33 (89)	37 (97)	
Undifferentiated carcinoma	3 (8)	—	
Neuroendocrine tumor (metastatic to neck)	—	1 (3)	
Clear cell carcinoma (metastatic to neck)	1 (3)	—	
Primary site			.80
Oropharynx	17 (46)	16 (42)	
Larynx	7 (19)	9 (24)	
Nasopharynx	6 (16)	4 (10)	
Oral cavity	3 (8)	4 (10)	
Hypopharynx	3 (8)	4 (10)	
Other (unknown primary site)	1 (3)	1 (3)	
T Stage			.20
T1-T2	10 (27)	6 (16)	
T3-T4	26 (70)	30 (79)	
N Stage			.61
N0	6 (16)	5 (13)	
N1-N2	25 (67)	26 (68)	
N3	5 (13)	5 (13)	
Unknown stage	1 (3)	2 (5)	

Abbreviations: LLL = low-level laser; SD = standard deviation.

Data presented as numbers, with percentages in parentheses, unless otherwise noted.

cisplatin (Table 2). The median delivered radiation dose was 70 Gy in both treatment arms, with a slightly greater mean dose delivered in the LLL arm. The cisplatin dose intensity did not differ between the two groups. Other treatment variables that could determine the risk of mucositis were similar between the LLL and placebo arms.

Mucositis incidence

All patients presented with some grade of oral mucositis during the treatment period. However, the appearance of Grade 3 mucositis was delayed in the LLL-treated patients (Table 3). The incidence of Grade 3 mucositis in the second week of CRT was 11% (4 patients) in the LLL group and 13% (5 patients) in the placebo group (*p* = NS). In the fourth week, 11% (4 patients) and 32% (12 patients) in the LLL and placebo arms presented with Grade 3 mucositis, respectively (*p* = .08, after Bonferroni correction for multiple comparisons). Finally, in the sixth week of CRT, the incidence was 22% (8 patients) in the LLL-treated arm and 24% (9 patients) in placebo arm (*p* = NS). No Grade 4 mucositis was detected throughout the study period.

Pharyngeal dysphagia incidence

A similar pattern in terms of pharyngeal dysphagia incidence was observed between the two arms during CRT.

Table 2. Radiotherapy and concurrent chemotherapy

Variable	LLL	Placebo	<i>p</i>
Radiotherapy			.67
Photons and electrons	34 (92)	36 (95)	
Photons	3 (8)	2 (5)	
Daily radiation dose fraction (Gy)			.32
1.8	1 (3)	—	
2.0	36 (97)	38 (100)	
Delivered radiation dose (Gy)			.03
Mean ± SD	69.4 ± 0.4	67.9 ± 0.8	
Median	70	70	
Range	60–70	60–70	
Radiation fractions (<i>n</i>)			.01
Mean ± SD	34.8 ± 0.5	33.9 ± 0.8	
Median	35	35	
Range	30–39	30–35	
RT planning			.20
Two-dimensional	15 (41)	22 (58)	
Three-dimensional	22 (59)	16 (42)	
Irradiated areas in oral cavity* (<i>n</i>)			.42
1–3	3 (8)	2 (5)	
4–6	19 (51)	23 (61)	
7–9	15 (41)	13 (34)	
Chemotherapy			.31
Cisplatin	35 (95)	33 (87)	
Carboplatin	1 (3)	3 (8)	
Paclitaxel	1 (3)	2 (5)	
Cisplatin dose intensity (mg/m ² /wk)			.50
Mean ± SD	39.5 ± 10.9	39.2 ± 15.9	

Abbreviations as in Table 1.

Data presented as numbers, with percentages in parentheses, unless otherwise noted.

* During each LLL session, nine areas were treated, 10 seconds each, including inferior and superior lips, right and left cheeks, dorsal and ventral tongue, hard and soft palates, right and left gums, and tongue frenulum, as previously described (5); RT: radiation therapy.

The incidence of Grade 3 pharyngeal dysphagia in the second week of CRT was 19% (7 patients) in the LLL group and 18% (7 patients) in the placebo group (*p* = NS). During the fourth week of CRT, the incidence was 29% (11 patients) and 55% (21 patients) in the LLL and placebo groups, respectively (*p* = .14, after Bonferroni correction for multiple comparisons). The corresponding percentages were 51% (19 patients) and 52% (20 patients) in the sixth week of CRT (*p* = NS).

Unplanned RT interruptions

Unplanned RT interruptions due to severe mucositis were necessary for 6 patients (16%) in the placebo arm and none in the LLL arm (*p* = .02). These interruptions occurred at a mean number of fractions 19 ± 5 (mean ± SD), and the duration was 7 ± 2 days. In addition, 11 other interruptions were necessary, 6 in the LLL arm and 5 in placebo arm, mainly because of RT-related acute skin toxicity.

Table 3. Mucositis incidence and grading ($n = 75$)

Mucositis grade	Week 2 (n)		Week 4 (n)		Week 6 (n)	
	LLL	Placebo	LLL	Placebo	LLL	Placebo
0	1 (3)	2 (5)	1 (3)	–	2 (5)	–
1	10 (27)	11 (29)	14 (38)	12 (32)	13 (35)	12 (32)
2	22 (59)	20 (53)	18 (49)	14 (37)	14 (38)	17 (45)
3	4 (11)	5 (13)	4 (11)*	12 (32)*	8 (22)	9 (24)
4	–	–	–	–	–	–

Abbreviation: LLL = low level laser.

* $p = .08$, after Bonferroni correction for multiple comparisons.

Pain assessment

Severe pain (visual analog scale score >7) occurred in 5 of 37 patients in the LLL arm and 5 of 38 patients in the placebo arm during Week 2 of CRT. The proportion of patients presenting with severe pain remained similar between the LLL and placebo arms throughout Weeks 4 (8 of 37 and 8 of 38, respectively) and 6 (8 of 37 and 8 of 38, respectively) of CRT ($p = \text{NS}$). The use of concomitant analgesic medication was similar between the LLL and placebo arms (54% vs. 50% for nonsteroidal anti-inflammatory drugs and 8% vs. 8% for opioids, respectively).

Weight assessment and placement of nasoenteral feeding tubes

At randomization, the mean patient weight was similar between the two arms (61.1 ± 12.2 kg in the LLL arm and 61.1 ± 12.4 kg in the placebo arm; $p = \text{NS}$). No difference in the rate of weight loss was seen between the two arms. At the last week of CRT, the mean patient weight was 54.7 ± 9.6 kg and 55.2 ± 9.5 kg ($p = \text{NS}$) in the LLL and placebo arms, respectively. The placement of nasoenteral feeding tubes was necessary in 13 patients in the LLL arm (35%) and 11 patients in the placebo arm (29%; $p = \text{NS}$). This placement was done at a mean of five fractions later for the LLL patients (RT fraction number 22 vs. 17, $p = .01$).

Treatment safety, disease control, and survival

All patients have continued in follow-up to determine whether any differences occur in locoregional disease control, progression-free survival, and overall survival, which will be reported separately. At a median follow-up of 2 years, no difference was detected in either disease control or survival between the two arms.

DISCUSSION

We performed a prospective, randomized, double-blind study of oral mucositis prevention using LLL in HNC patients treated with concurrent CRT. Although more efficacious than RT alone, this combined treatment modality has been associated with a greater risk ($\leq 90\%$) of severe mucositis (14–17). The development of oral mucositis is associated with pain, nutritional compromise, and

infectious complications that can require the interruption of RT, with a resultant negative effect on tumor control (18). In addition, oral mucositis can have a devastating effect on patients' quality of life (2).

Our results were essentially negative, and LLL therapy as administered in the present study was not effective in reducing the incidence of Grade 3 or 4 oral mucositis; however, a marginal benefit could not be excluded. It reduced RT interruptions in these HNC patients treated with concurrent CRT. However, progressive weight loss was observed in both treatment arms. Our results are in agreement with those from randomized studies, which included patients treated with RT alone (5, 6) and noncontrolled studies of patients who had undergone RT and/or chemotherapy (19). However, the magnitude of the LLL effect, in terms of mucositis prevention, seemed smaller. As an example, a previous study showed a reduction in the incidence of severe mucositis from 35.2% to 7.6% during the whole RT duration (5). In the present study, an effort was made to control for the known factors associated with mucositis risk, including the RT and chemotherapy schedules, RT plans, and number of areas radiated in the oral cavity. The two treatment groups were equivalent concerning these variables, except for a slightly greater radiation dose delivered in the LLL-treated arm, which nevertheless reinforces the hypothesis that LLL therapy might be useful.

Regarding the Grade 3–4 mucositis rate, it was lower than expected in the placebo arm, which could explain our negative results. However, we consider this unlikely. The incidence of Grade 3–4 mucositis has mostly been $<50\%$ in patients treated with single-agent cisplatin CRT in previous clinical trials (14, 16, 17). Thus, we believe that a rate of 32% for Grade 3–4 mucositis at Week 4 could be acceptable for the placebo arm in our study, especially considering that 13 of 38 patients had primary tumors located either in the larynx or hypopharynx. Such patients usually present with a lower incidence of oral mucositis during RT. Another possible explanation for our low rate of oral mucositis could have been the elevated number of treatment interruptions in the placebo arm. In addition, the incidence of pharyngeal dysphagia at Week 6 (52%) was very similar to that reported by other investigators (14). In our study, no difference was found regarding the incidence of pharyngeal dysphagia between the two arms. Thus, our patients seemed to have the usual rate of complications. Regardless of the occurrence of mucositis among the patients, LLL might reduce the duration of mucositis in these patients; however, the median duration of mucositis was not different between the studied arms (data not shown).

Another important finding was the fewer unplanned RT interruptions due to mucositis in the LLL arm. This might translate in better treatment efficacy (20). Because clinicians might have different thresholds for deciding to interrupt RT, we acknowledge that a reproducibility issue exists (1). Our data, however, were consistent, because most interruptions occurred around the fourth week of CRT, when the mucositis grade was more severe. In addition, it was reassuring to find

that the interruptions due to RT-related skin toxicity occurred equally in both treatment arms, because laser treatment was not applied to the skin.

We found an unusually high number of unplanned RT breaks. This might reflect the perception, by the radiation oncologist, of serious complications, because most of our patients were underprivileged and might lack adequate social support to receive emergency care within an appropriate period.

Preventive therapy with LLL did not improve pain control in our study, in contrast to other studies (5, 6). We propose three explanations. First, pain medication was indicated at the physician's discretion and it was probably underused, because few patients (8%) were taking opioids, considering the observed pain scores (21% recorded their pain as severe). Second, most patients had advanced disease at presentation, which might be associated with more intense pain at baseline and not amenable to improvement using LLL therapy (including locally advanced laryngeal tumors and transglottic and/or oropharyngeal involvement). Finally, LLL might be effective in controlling the macroscopic mucosal lesions caused by RT. However, it might not normalize the complex mucosal inflammatory response induced by CRT (21, 22) or the resulting pain. The mechanisms underlying the anti-inflammatory and analgesic properties of LLL remain

unknown. Scavenging of reactive oxygen species, the stimulus of fibroblast proliferation, and collagen synthesis might be involved (6).

CONCLUSIONS

In the present study, LLL therapy was not effective in reducing Grade 3 or 4 oral mucositis, although a marginal benefit could not be excluded in terms of reducing RT interruptions, which might translate into improved CRT efficacy. For LLL therapy, the most efficient schedule of LLL application (dose and timing) and a standardization of LLL parameters (wavelength and power) must be established. Greater administered dosages (*e.g.*, 1–4 J) might be more effective, as suggested by the World Association of Laser Therapy for musculoskeletal pain and disorders (23). Skin LLL therapy also merits additional study in this context. Additional interventions to prevent and/or treat mucositis are urgently needed. Special attention to RT planning, the use of intensity-modulated RT, and adequate oral care are essential in preventing mucositis and dysphagia (24, 25). Analgesics, including opioids, close monitoring of nutrition and hydration, and the early diagnosis and treatment of secondary infections remain the only established measures to relieve and treat mucositis complications.

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