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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

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Abstract 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) = energy (J/cm^2) × surface (cm^2)/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 occured 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.

Key words Low-energy laser · Mucositis · Radiotherapy · Head and neck cancer

Introduction

Acute oral complications are serious and disabling secondary effects for patients undergoing cancer therapy. The frequency of their appearance varies from 12% in patients receiving adjuvant chemotherapy to 100% in patients subjected to radiotherapy to the oral cavity when the total dose exceeds 50 Gy [15]. The mucosal lesions of the oral cavity and the functional problems they cause, grouped under the general term of "oral mucositis," result from a combination of different factors, linked either to the type of therapy or to patient susceptibilities [42]. Direct toxicity of chemotherapy or radiotherapy is the most important biological factor, but complications of salivary gland dysfunction, local trauma, and local or systemic infections can further modify the occurrence and evolution of mucositis [35, 45]. Mucositis can induce severe and debilitating pain, which can significantly increase the morbidity of cancer therapy and be sufficiently intense to necessitate the administration of high-dose opioid analgesics and enteral or parenteral nutrition. And finally, severe mucositis can lead to modifications of treatment planning and even to suspension of therapy, with an impact on patient's survival. It is frequently associated with nausea, vomiting, diarrhea, and pain, and considerably reduces comfort and the sensation of well-being of patients with sleep dysfunction, leading to anorexia and weight loss. The impact of oral mucositis on the cost of treatment has not been evaluated, but severe mucositis can certainly increase the duration of hospitalization and the need for special care [37].

Radiation-induced mucositis is the most important acute side effect in patients undergoing radiotherapy for head and neck neoplasms. It causes pain, which is aggravated by the patient's swallowing and normal oral functioning. In turn, mucositis and xerostomia together increase the risk of oral infection, which is caused mainly by opportunistic pathogens. With conventional fractionation (2 Gy/day, 5 fractions per week), patchy mucositis becomes evident during the third week of irradiation and progresses to confluent mucositis [23, 32]. Radiation-induced oral ulcers may appear after 3–4 weeks of treatment, and their evolution is progressive if radiation therapy is not stopped. With conventional fractionation, an incidence of 33–49% is described for confluent mucositis [22, 41].

The severity of mucositis is increased with the introduction of altered fractionations in head and neck radiotherapy. Horiot et al. [22] described a 66.5% incidence of diffuse mucositis with hyperfractionation (with no acceleration), as opposed to 49% with conventional fractionation, in patients being treated for oropharyngeal carcinoma. Geara et al. [18] reported an incidence of 53% of grade III and 22% of grade IV [Radiation Therapy Oncology Group (RTOG)] mucositis in 186 patients with head and neck neoplasms: 43% of them were treated with a concomitant boost regimen and 57% with hyperfractionation with no acceleration.

Oral ulcerations cause pain on swallowing and, as a consequence, a diminution of oral intake with loss of weight. The progression of oral lesions and their impact on the patient's general condition can require temporary discontinuation of the treatment or modification of the radiation treatment plan. The percentage of patients who need temporary discontinuation of the treatment varies substantially in the literature. It ranges from 4% to 43% for conventional irradiation [2, 16]. Factors associated with the incidence of suspension of treatment include the fractionation schedule, the concurrent use of chemotherapy [11], the size of the treatment fields, the use of individual field shaping, and the basic oral cavity care protocol (together with the dental and nutritional supportive care) [9]. At the Nice Cancer Center (Centre Antoine-Lacassagne), in a previous series of patients undergoing radiotherapy exclusively for head and neck neoplasms (1984–1992; unpublished data), 13.5% of the patients had a treatment gap lasting for over 5 days. Moreover, an interruption of radiotherapy and prolongation of the overall treatment time have been associated with a loss of local tumor control [21, 51]. Nishimura et al. [30], in T1 vocal cord carcinoma, referred to a decrease in the probability of local control from 89% to 74% with a 1-week gap in therapy. The consequences of such a loss of local control are well known: tumor progression, poor quality of life, decreased survival for the patient, and an increase in health service costs owing to the extended treatment of the illness.

Management of oral mucositis is currently directed primarily at palliation of the symptoms and prevention of infections. No therapy available today directly targets oral mucositis. Low-energy He-Ne laser (LEL), or "soft laser," has been reported to be effective in reducing the severity of oral mucositis lesions in a non-randomized trial initiated in Nice (France) by Ciais et al. [10, 34]. The efficacy of this method in the prevention of chemotherapy-induced oral mucositis was confirmed in two prospective, double-blind randomized trials in patients undergoing bone marrow transplantation [3, 12]. These initial findings and the high incidence of radiation-induced mucositis prompted a randomized multicenter trial to evaluate LEL 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 of at least 65 Gy at a rate of 1 fraction of 2 Gy/day

5 days a week, from cobalt-60 or linear accelerator photons without prior surgery or concomitant chemotherapy. Treatment fields were standardized: whatever the location of the primary tumor, all patients received bilaterally opposed symmetrical fields encompassing the whole of the oropharyngeal area. At 40 Gy (20 fractions of 2 Gy) the fields were reduced to exclude the spinal cord, with no modification of the oropharyngeal irradiation. At 56 Gy the opposed fields were reduced again, to focus on the primary and local extensions (the oropharynx had to be included) until the total dose of 65 Gy at mid-plane (Fig. 1). The estimated treatment volume at 65 Gy is indicated for each patient in Table 1.

Between September 1994 and March 1998, 30 patients entered this double-blind randomized study conforming to the Huriet law: since 1988, every clinical trial in France must have been approved by a certified board, and the patients must have given informed consent. The goal was to determine whether preventive He-Ne laser beam applications could reduce or prevent oral mucositis caused by radiotherapy.

Most of the patients (28) were treated at the Centre Antoine-Lacassagne, Nice (France), 1 at Marseilles (Institut Paoli-Calmettes) and 1 at Reims (Institut Jean-Godinot).

There were 26 men and 4 women. Their mean age was 60.4 years (range 36–78). On admission, all patients were requested to stop smoking tobacco and drinking alcohol, to prevent their potential worsening effect on oral mucositis. In accordance with literature data [9], oral examination and preventive dental management were performed prior to radiotherapy. Daily oral hygiene (cleaning of the teeth and any dental prosthesis) during treatment was recommended. 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. No associated anti-inflammatory or other mucositis treatment was authorized. Prescription of analgesics was allowed, but not during the 2 days before evaluation each week.

Patients received He-Ne laser applications daily for 5 consecutive days (Monday to Friday) each week during the 7 weeks of radiotherapy, before the radiation sessions. The malignant tumor had to be located outside the test zones selected for randomized preventive LEL application, The laser beam was applied to the tissues by means of a straight optical fiber with a 1.2-mm spot size. The nine laser treatment areas, each of which occupied 1 cm^2, included the posterior third of the internal surfaces of the cheeks, soft palate and anterior tonsillar pillars (Fig. 2). Laser illumination consisted of a continuous beam (wavelength: 632.8 nm; power: 60 mW in Nice and Marseilles, 25 mW in Reims), calibrated at the end of the optical fiber every day. The treatment time t for each application point was given by the equation: t (s) = energy (J/cm^2) × surface (cm^2)/power (W). The average energy density delivered to the oral mucosa was 2 J/cm^2 and it was applied at these nine points, equally distributed on the treated surfaces, for 33 s per point in Nice and Marseilles (each LEL session lasted approximately 5 min) and for 80 s in Reims (12 min for each specific LEL session). The 60-mW and 25-W medical lasers were designed and produced by Fradama (Geneva,

Table 1 Patient characteristics [*HY* hypopharynx, *OC* oral cavity, *OR* oropharynx, *L+* laser applied to the oropharyngeal areas (9 points), *L–* no laser applied to the oropharyngeal areas]

No.[a]	Age (years)	Gender	Primary tumor	Group (laser to OR or not)	Laser to skin of neck	65 Gy radiation volume (cm^3)	Mean mucositis score
1	59	M	OR	L–	Y	320	2.2
2	76	M	HY	L+	Y	350	1.8
3	61	M	OR	L+	Y	330	1.5
4	72	M	OC	L+	Y	380	1.9
5	47	M	HY	L–	N	360	2.5
6_M	36	F	OR	L+	N	320	2.0
7_R	69	M	OR	L+	N	340	1.7
8	64	F	OC	L–	N	376	1.9
9	64	M	OR	L–	N	310	2.1
10	61	M	OR	L–	Y	330	2.2
11	72	M	HY	L–	Y	350	2.0
12	62	M	HY	L+	Y	360	1.7
13	50	M	HY	L–	N	350	2.2
14	57	M	OR	L+	Y	324	1.8
15	75	M	OR	L–	Y	316	1.9
16	62	M	HY	L–	N	360	2.0
17	61	M	OC	L+	Y	378	2.0
18	50	M	OR	L–	N	324	2.1
19	53	M	OR	L+	Y	338	1.5
20	52	F	OC	L+	Y	356	1.6
21	67	M	OR	L–	Y	316	1.9
22	53	M	OR	L+	Y	324	1.4
23	42	M	HY	L+	Y	360	1.4
24	67	M	OR	L–	N	338	1.9
25	65	M	HY	L–	Y	354	2.1
26	69	M	OC	L–	N	354	2.3
27	57	F	OC	L+	Y	324	2.0
28	68	M	OC	L–	N	392	2.3
29	42	M	OC	L+	N	386	1.6
30	78	M	HY	L+	Y	342	1.2

[a] *M* Marseilles (60 mW), *R* Reims (25 mW), *all others* Nice (60 mW)

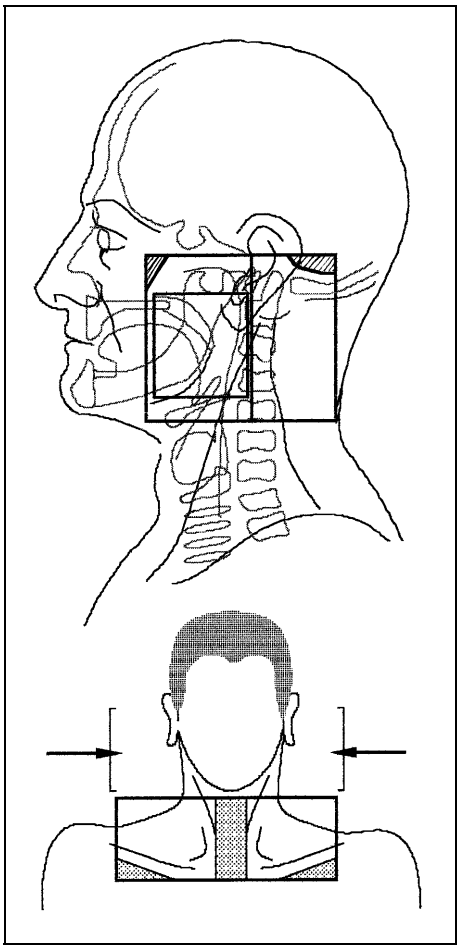

Fig. 1 Carcinoma of the oropharynx: fields of radiation

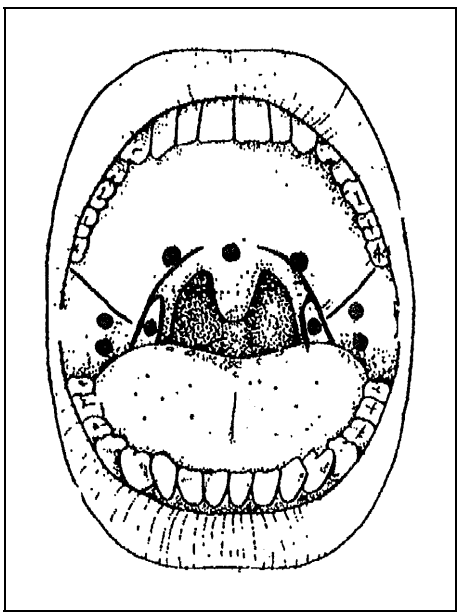

Fig. 2 Test zones : nine points in the oropharyngeal area

Switzerland). All laser illuminations were performed by the same individual in each center. This operator was the only person to know whether or not the patient was being sham-treated, and did not participate in the evaluation and scoring of mucositis. In the L+ group, 14 of the 15 patients also had a laser treatment before each fraction of radiation to the skin of the neck (Table 1). In the L– group, 7 of the 15 patients had laser treatment for the skin of the neck included in the fields of radiation (Table 1). Consequently the only difference between the two arms was the application (or not) of the LEL to the nine elective points chosen for test in the oropharynx. During the sessions, patients wore wavelength-specific dark glasses and were instructed to keep their eyes closed, to ensure that they did not know whether they were being sham-treated or receiving laser applications. The laser made the same noises, and the probe was held in the mouth in exactly the same way, whether control subjects or laser patients were being treated.

The whole irradiation field, the oral cavity and the visible oropharynx were inspected weekly during the 7 weeks by one specific physician (head and neck surgeon, or radiation oncologist), who was blinded to the result of randomization. The evaluation and scoring of mucositis and pain took account of the zone of interest of the study (oropharynx). The criteria used for evaluation were the standard WHO staging for mucositis (Table 2) and a modified visual analogue scale for pain (patient self-evaluation). Modifications of this visual scale were made for statistical analysis as follows: grades 1 and 2 were combined (=grade 1, or mild pain), as were grades 3–4 (=grade 2, or moderate pain), grades 5–7 (=grade 3, or severe pain), and grades 8–10 (=grade 4, or worst possible pain).

Concordance or differences in the frequency distribution between the two groups were tested by the Chi-square test and Student's *t*-test (significance level at $P=0.05$). The possible causes of different degrees of mucositis and pain were measured by variance analysis. Correlations were evaluated by Spearman's coefficient.

Results

All the patients completed the study: none were lost to follow-up or excluded for failure to complete the laser application protocol. Laser applications were well tolerated and there were no side effects attributable to the LEL treatment.

Laser treatment over the 7 weeks of the radiation treatment significantly reduced the mean intensity scores for oral mucositis in the laser treatment fields (Fig. 2). The mean grade of mucositis during radiotherapy was 2.1 ± 0.26 for the group without laser (L–) and 1.7 ± 0.26 for the group with laser (L+) ($P=0.01$). The mean for each patient is indicated in Table 1.

Except for the first week of treatment, the daily mean grade of mucositis was higher for the L– group

Table 2 Classification of oral mucositis

Grade	Symptoms
1	Soreness, erythema
2	Erythema, ulcers, can eat solids
3	Confluent ulcers, requires liquid diet only
4	Oral alimentation not possible, hemorrhagia

Table 3 Mean grade of mucositis per week, during 7 weeks of treatment [*L+* with low energy laser (15 patients), *L–* without low energy laser (15 patients)]

Week(s)	L–	L+	*P*-value
1	0.6 ± 0.63	0.8 ± 0.67	NS
2	1.8 ± 0.4	1.4 ± 0.63	NS
3	2.2 ± 0.52	1.8 ± 0.56	NS
4	2.66 ± 0.48	2.06 ± 0.25	0.01
5	2.86 ± 0.35	2.26 ± 0.59	0.01
6	2.4 ± 0.5	1.8 ± 0.35	0.0025
7	2.26 ± 0.45	1.66 ± 0.48	0.01
1–7	2.1 ± 0.26	1.7 ± 0.26	0.01

Table 5 Mean grade of pain intensity per week during the 7 weeks of treatment

Week(s)	L–	L+	*P*-value
1	0.13 ± 0.25	0.33 ± 0.7	NS
2	1.53 ± 0.63	1.06 ± 0.7	0.05
3	2.06 ± 0.59	1.2 ± 0.59	0.01
4	2.66 ± 0.48	1.73 ± 0.45	0.001
5	2.4 ± 0.51	1.66 ± 0.81	0.01
6	2.33 ± 0.49	1.26 ± 0.59	0.001
7	2 ± 0.0	1.13 ± 0.74	0.001
1–7	2.04 ± 0.22	1.8 ± 0.3	0.025

than for the L+ group, the difference being statistically significant for weeks 4, 5, 6 and 7 (Table 3).

Classification of mucositis grades in 1-week periods also showed a significant decrease for the L+ group (Table 4). In particular, the number of weeks in which patients had grade 3 mucositis was 37 (35.22%) for the L– group and 8 (7.62%) for the L+ group ($P = 0.001$). The decrease of grade 2 and 3 mucositis in the laser group was associated with an important increase in grade 1 mucositis, i.e. 11 weeks for the L– group (10.46%) and up to 31 weeks (29.5%) for the L+ group ($P = 0.001$).

Preventive use of laser application significantly ($P = 0.025$) reduced oral pain for the treatment area, as assessed by patients, over a 7-week period (Table 5). The mean grade of pain for the entire radiation treatment was 2.04 ± 0.22 for the L– group and 1.8 ± 0.3 for the L+ group. The decrease in pain intensity was significant during weeks 2–7 (Fig. 4). The ability to swallow was improved among L+ patients, with a median of 4.9 ± 1.33 weeks of swallowing difficulties, as opposed to 6 ± 0.84 weeks for L– patients ($P = 0.0$ 1).

Finally, we noted an important reduction in the incidence (expressed as a number of weeks for the whole population of patients) of grade 3 intensity of pain (Table 6), from 25 weeks (23.80%) for the L– group to 2 weeks (1.90%) for the L+ group ($P = 0.001$). This result is correlated with the observed number of patients taking morphine: 11 in the L– group and 5 in the L+ group.

Both mucositis and pain scores were maximal during the 5th week of treatment, then going slightly down in the two groups of patients, without any adjuvant therapeutic modality. This is a common observation during radiation treatment, in particular for head and neck cancer patients.

There was no significant differenced between the 2 arms for the incidence and duration of treatment gap during radiation. All patients received complete prescribed radiotherapy.

Table 4 Distribution of mucositis grades (in number of weeks) for the whole population followed for 7 weeks

Grade	L–		L+		*P*-value
0	7	6.66%	5	4.76%	NS
1	11	10.46%	31	29.52%	0.001
2	50	47.66%	61	58.10%	0.025
3	37	35.22%	8	7.62%	0.001
Total	105	100%	105	100%	

Discussion

Patients who undergo therapeutic oropharyngeal radiation invariably develop mucositis. This complication produces pain and sometimes interferes with food intake. About one-third of patients develop obvious mucositis when the total administered dose reaches 20 Gy over 2 weeks (2 Gy per fraction, 5 fractions per week). This increases to two-thirds of patients when the total radiation dose reaches 30 Gy. There has been a scarcity of available effective medication for local treatment, and systemic analgesics are relatively ineffective in relieving the pain of radiation-induced mucositis.

A new method of treatment of radiation mucositis is described here, and it was evaluated by means of a double-blind randomized trial. In this phase III study, no adverse effects were noted with the use of a 60-mW He-Ne laser. It is important, however, to emphasize the importance of preventing retinal damage by the use of wavelength-specific goggles. The results of this study are consistent with previous reports [3, 10, 12, 34]; furthermore, the higher energy of our laser beam than in some of the series cited [3, 10] allowed for the duration of treatment sessions to be shortened. This factor contributed to patients' abilities to complete the laser application protocol.

Laser applications delayed the time of onset, attenuated the peak severity and shortened the duration of oral mucositis, as shown in Fig. 3. The difference between L+ and L– patients was statistically significant from week 4 to week 7. With the total delivered dose of 65 Gy, conventionally fractionated, all L– patients de-

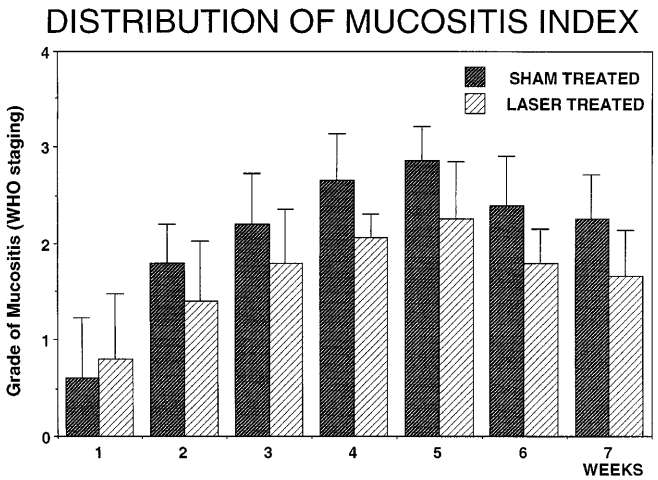

Fig. 3 Distribution of mucositis index

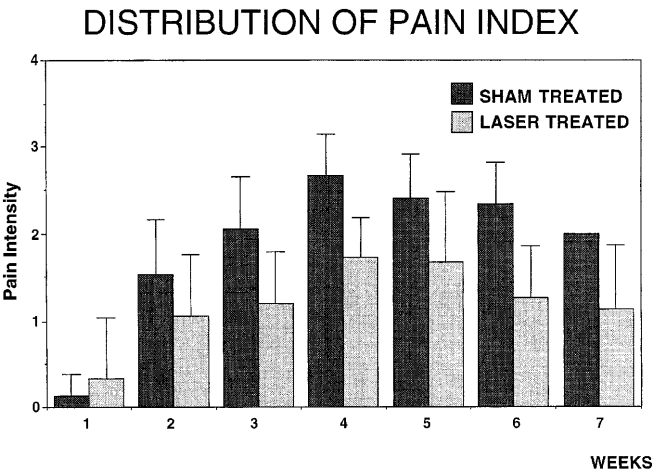

Fig. 4 Distribution of pain index

veloped mucositis at week 2, with a peak at week 5 (5 with grade 3 mucositis, 9 with grade 2, mucositis). All L+ patients also had mucositis at week 2, with a peak at week 5 (5 with grade 3 mucositis, 9 with grade 2, 1 with grade 1). During the 7 weeks of treatment, the mean grade of mucositis in L+ patients (1.7 ± 0.26) was significantly lower ($P = 0.01$) than the mean grade in L– patients (2.1 ± 0.26). Results relating to decrease in pain intensity were also quite convincing. Laser applications reduced the incidence and duration of morphine administration. Ability to swallow was also improved.

In our series, we cannot eliminate the role of a presumed "distant laser effect," since most of our patients (see Table 1), even in the L– group, were treated with LEL applied to the skin of the neck to prevent radiation-induced dermatitis in radiation treatment fields. The fact that our results were highly significant in spite of this could reinforce the validity of LEL's effect on mucositis prevention.

These results appear to confirm results from bone marrow transplant (BMT) studies that similarly utilized LEL treatment methods. In a prospective study, Barasch et al. [3] used a 25-mW laser one side of the mouth only (opposite side receiving placebo treatment) and reported a statistically significant reduction in oral mucositis on the treated side. In the Barasch study, each patient was his or her own control, which could be of importance, since mucosal damage on the sham-treated side could also have benefited from a distant systemic laser effect. Cowen et al. [12], using a 60-mW He-Ne laser performed a double-blind randomized phase III trial in which laser was administered to the treatment group during conditioning for transplant, before stem cell infusion. This study showed a 33% reduction of grades 3 and 4 mucositis in L+ patients. In this trial, mucositis was scored according to an oral examination guide, with a 16-item scale, 4 of which were assessed by the patients themselves [47]. The daily mucositis index was significantly lower in L+ patients ($P < 0.05$) from day +2 to day +7 after BMT. The duration of grade 3 stomatitis was also reduced in L+ patients ($P = 0.01$). Oral pain was lower ($P = 0.05$), and L+ patients required less morphinomimetics ($P = 0.05$). Finally, xerostomia and the ability to swallow were improved among L+ patients ($P = 0.05$ and $P = 0.01$, respectively). All these results were in keeping with previous observations, suggesting the efficacy of the method (retrospective studies [10] or phase I and II trials [38]). Schubert et al. [38], for example, identified a trend towards lower oral mucositis scores on all examination days in an interim results report of a phase I/II study in which laser application was performed prophylactically before BMT.

Considerable work has been directed towards determining the biological effects of He-Ne laser that would account for its observed wound healing and pain relief effects [1, 25]. Wound healing is one of the most studied aspects of low-energy lasers [6]. In studies of fibroblast responses to lasers, increased cell division and increased collagen production have been reported [31, 50] as well as stimulation of mitochondrial cytochromes. In gingival tissues, He-Ne laser applications could stimulate DNA synthesis of myofibroblasts, with-

Table 6 Distribution of pain intensity (in number of weeks) for the whole population followed for 7 weeks

Grade	L–		L+		*P*-value
0	14	13.34%	22	20.96%	NS
1	9	8.56%	42	40.0%	0.001
2	57	54.30%	39	37.14%	0.025
3	25	23.80%	2	1.90%	0.001
Total	105	100%	105	100%	

out any degenerative changes, and could transform fibroblasts into myofibroblasts, which may promote wound healing [33, 44]. Concerning pain relief, one mechanism that has been proposed is modulation of pain perception by modification of nerve conduction via the release of endorphins and eukephalins (J. Dejou et al., Marseilles, unpublished data).

At molecular level, the effect of He/Ne laser may be explained by the neutralization of free radicals induced by chemo- and/or radiotherapy (B. Rossi et al., Nice, unpublished data).

Numerous agents and methods have been tested in attempts to prevent or modulate cancer therapy-induced mucositis. Investigations have included various strategies of mucositis prophylaxis: (1) administration of direct cytoprotectants, such as sucralfate [28]), prostaglandin E_2, silver nitrate, beta carotene, and amifostine; (2) administration of indirect cytoprotectants, such as vitamin E, KGF-1 and -2, and pentoxifylline [52]; pharmacological manipulation of cytotoxic drug metabolism, such as modulation of 5-FU metabolism with allopurinol, or TGF-B3 [43]; modulation of 5-FU by a pharmacokinetically based adaptation of dose [48]; (4) infection prophylaxis with such topical antimicrobials as chlorhexidine [14] or nonsteroidal anti-inflammatory agents (e.g., benzydamine); and (5) nonpharmacological methods, including oral cryotherapy. Clinical trials with these modalities have yielded inconsistent results, so that none of them has become a standard adjunct with proven efficacy in modern cancer therapy.

Colony-stimulating factors (CSF) have shown some promise for mucositis prevention when used to enhance engraftment in patients undergoing BMT. Gordon et al. [20], in a trial study of oral mucositis, found a shorter duration of mucositis in patients receiving GM-CSF by continuous intravenous infusion, although the severity of mucositis was unaffected by the GM-CSF treatment [24]. Preventive and routine GM-CSF mouthwashes have also been used in patients undergoing head and neck radiotherapy [13, 36], apparently with beneficial effects, which still need to be confirmed by prospective randomized multicenter studies [8, 20]. The benefit may be realized through an improvement of local immunity, which reduces the damage associated with the influence of local flora. Similarly controversial effects have been obtained with G-CSF [17, 27, 39]; immunoglobulins [29]; epidermal growth factor [19]; and prostaglandin E_2 [26], both in therapeutic and in prophylactic use. A concern in most of these studies is whether adequate dosing or delivery systems were tested.

In comparison with these tested methods, our data appear very promising, and they are consistent with significant efficacy of this complementary treatment.

In conclusion, low-energy He/Ne laser (LEL) seems to be a safe and efficient method for the prevention of radiation-induced stomatitis, as demonstrated for chemotherapy-induced mucositis [3, 12], with a tremendous potential interest for combined-modality treatment. The concomitant use of chemo- and radiotherapy is becoming the new standard of care in advanced head and neck cancer, with very encouraging results even in nonresectable cases. Since the main limiting factor of these combined protocols is the acute mucositis [4, 7, 11, 40], this complementary treatment option with low-energy He/Ne laser could be important in enhancing the feasibility of such regimens, and especially in the conservation of dose-intensity effect. In Nice, where the method is now used routinely during head and neck irradiation, we are planning a new study testing LEL in patients being treated with contomitant chemo- and radiotherapy for advanced head and neck cancer. Even more than the improvement in patient comfort, the therapeutic index of combined specific treatment should be increased by the use of LEL, besides standard supportive care, oral care [5, 46, 49] and enteral nutrition. During this study, other laser wavelengths and powers may be tested and compared with the 60-mW He/Ne laser.

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