Chemotherapy Side Effects

1. Magnetic resonance imaging (MRI) controlled outcome of side effects caused by ionizing radiation, treated with 780 nm-diode laser --preliminary results.

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J Photochem Photobiol B. 2000 Dec;59(1-3):1-8.

BACKGROUND and OBJECTIVE: Ionizing radiation therapy by way of various beams such as electron, photon and neutron is an established method in tumor treatment. The side effects caused by this treatment such as ulcer, painful mastitis and delay of wound healing are well known, too. Biomodulation by low level laser therapy (LLLT) has become popular as a therapeutic modality for the acceleration of wound healing and the treatment of inflammation. Evidence for this kind of application, however, is not fully understood yet. This study intends to demonstrate the response of biomodulative laser treatment on the side effects caused by ionizing radiation by means of magnetic resonance imaging (MRI).
STUDY DESIGN/PATIENTS and METHODS: Six female patients suffering from painful mastitis after breast ionizing irradiation and one man suffering from radiogenic ulcer were treated with lambda=780 nm diode laser irradiation at a fluence rate of 5 J/cm2. LLLT was performed for a period of 4-6 weeks (mean sessions: 25 per patient, range 19-35). The tissue response was determined by means of MRI after laser treatment in comparison to MRI prior to the beginning of the LLLT.
RESULTS: All patients showed complete clinical remission. The time-dependent contrast enhancement curve obtained by the evaluation of MR images demonstrated a significant decrease of enhancement features typical for inflammation in the affected area.
CONCLUSION: Biomodulation by LLLT seems to be a promising treatment modality for side effects induced by ionizing radiation.

[Nizkointensivnaia lazernaia terapiia v detskoi onkologii]

Balakirev S A, Gusev L I, Kazanova M B et al.

Voprosy onkologii. 2000; 46 (4): 459-461.

The study by Balakirev suggests that the application of laser therapy makes it possible to reduce the time needed for the management of radiation injury and chemotherapy complications in pediatric patients 1.5-2-fold. It was shown that exposure to laser caused mononuclear levels of donors' blood to rise, which in turn led to release, in higher concentrations, of IL-1 and FNO cytokins, major factors of immune response development.

[Low-intensity lasers in pediatric oncology].

Durnov L A, Gusev L I, Balakirev S A et al

Vestn Ross Akad Med Nauk. 2000; (6): 24-27.

The study by Durnov outlines the outcomes of treatment for complications associated with chemo- and radiation therapy in children with malignant neoplasms by using lowintensity laser radiation. The use of this therapy may reduce the duration of treatment of these complications by 1.5-2 times. The use of low-intensity laser radiation in the treatment of other complications that are common in pediatric oncological care is briefly described. J Photochem Photobiol B. 2000 Dec;59(1-3):1-8. Magnetic resonance imaging (MRI) controlled outcome of side effects caused by ionizing radiation, treated with 780 nm-diode laser -- preliminary results.

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[The correction of the subcellular postradiation changes in the hypothalamus and parathyroid gland by using low-intensity laser radiation. An experimental study].

Korolev Iu N, Panova L N, Geniatulina M S

Vopr Kurortol Fizioter Lech Fiz Kult. 2000; (3): 3-4.

The study by Korolev showed that exposure of the rat adrenals 30 days after radiation (1 Gy) to infrared laser radiation arrested the development of ultrastructural disorders in the cells of the hypothalamus and the parathyroid gland and enhanced subcellular manifestations of adaptation and rehabilitation processes. HeNe laser reduces mucositis a) Barasch B et al. Helium-neon laser effects on conditioning-induced mucositis in bone marrow transplantation patients. Cancer. 1995; 76 (12): 2550-2556. Oral mucositis is a common complication of bone marrow transplantation conditioning therapy. Different drugs are given in order to reduce rejection of the implant. These drugs induce an oral mucosits. The mucositis is painful and complicates nutrition. Sometimes the intake of the drug has to be stopped due to complications. In the study above 20 patients received HeNe to their oral mucosa, either right or left of midline. One side was sham irradiated. Laser treatment was well-tolerated and reduced the severity of oral mucositis. b) Cowen D et al. Low energy helium-neon laser in the prevention of oral mucositis in patients undergoing bone marrow transplant: results of a double blind randomized trial. Int J Radiat Oncol Biol Phys. 1997; 38 (4): 697-707. Significant reduction of oral mucositis using a 60 mW HeNe laser

Chemo-and radiation-induced mucositis : results of multicenter phase iii studies.

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Considerable buccal toxicity of radiotherapy and/or chemotherapy in patients with cancer can cause patients to become discouraged and can alter their quality of life. In addition, such toxicity often necessitates alterations of treatment planning, with grave consequences in term of tumor response and even survival (concept of dose-intensity). With 5-fluorouracil and head and neck radiotherapy for example, acute mucosal toxic effect is the main limiting factor for which no clinically appropriate prophylaxis or efficacious antidote has been found to date. Management of oral mucositis is currently primarily directed at palliation of the symptoms, and prevention of infections. Low Level Laser Therapy (LLLT) has been reported effective in reducing the severity of oral mucositis lesions in a non-randomized trial, initiated in Nice (France) by Ciais et al. (1). The efficacy of this method in the prevention of chemotherapy induced oral mucositis has been subsequently confirmed in two prospective, double-blind randomized trials, in patients undergoing bone marrow transplant (2 ; 3). These initial findings and the high incidence of radiation-induced mucositis prompted a randomized multicenter trial to evaluate LLLT for the prevention of acute radiation-induced oropharyngeal mucosal lesions. 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, without prior surgery or concomitant chemotherapy. Between September 1994 and March 1998, thirty patients entered this double-blind randomized study conforming to theb Huriet law. The goal was to determine whether preventive HeNe laser beam applications could reduce or prevent oropharyngeal mucositis caused by radiotherapy. Patients characteristics: There were 26 men and 4 women. Mean age was 60.4 years (range 36 - 78). Oral examination and preventive dental management were performed prior to radiotherapy. Daily oral hygiene (cleaning of the teeth and 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 treatment was authorized. Analgesics could be prescribed, but not during the 2 days preceding each week evaluation. Patients received HeNe laser applications daily for five consecutive days (Monday to Friday) each week, during the seven weeks of radiotherapy. The malignant tumor had to be located outside the areas selected for randomized preventive LLL application. Laser was delivered to the tissues by a straight optical fiber with a 1.2 mm spot size. The 9 treatment areas included : posterior third of buccal mucosa, soft palate and anterior tonsillar pillars. Laser illumination consisted of a continuous beam (wavelength: 632.8 nm; power: 60 mW), calibrated at the end of the optical fiber every day. The treatment time (t) for each application point was given by the equation : t (sec) = energy (J/cm2) x surface (cm2)/ Power (W). The average energy density delivered to the treatment areas was 2 J/cm2, and was applied on these nine points, equally distributed on the treated surfaces, for 33 s per point (each specific LLL session lasted approximately 5 minutes). The 60 mW lasers were designed and produced by Fradama S.A. (Geneva, 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 sham-treated, and did not participate in the evaluation and scoring mucositis. During the sessions, patients wore wavelength-specific dark glasses and were instructed to keep their eyes closed, to assure that they did not know whether they were sham-treated or whether they received laser applications. The laser made the same noises, and the probe was held in the mouth exactly the same way, when treating control subjects and when treating laser patients. The whole irradiation field, the oral cavity and the visible oropharynx were inspected weekly during seven weeks by the same physician (head and neck surgeon, or radiation oncologist), blinded to the result of randomization. The evaluation of

mucositis and pain was performed on the oropharyngeal areas (9 points). Criteria for evaluation were the standard WHO scale for mucositis in the oropharynx; and a segmented visual analogic scale for pain (patient self evaluation). In this phase III study, no adverse effect was noted with the use of a 60-mW HeNe laser, though it is important to emphasize the importance of preventing retinal damage by the use of wavelength-specific goggles. This is consistent with previous reports. 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. With the total delivered dose of 65Gy, conventionally fractionated, all L- patients developed mucositis at week 2, with a peak at week 5 (13 with grade 3 mucositis, and 2 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 was significantly lower (p=0.01) than the mean grade in L- patients. Results on decrease in pain intensity were also quite convincing. Laser applications reduced the incidence and duration of morphine administration. Ability to swallow was also improved. These results confirm previous data collected with this method, especially for patients undergoing bone marrow transplant (BMT). In a prospective study, Barasch et al. (2) used a 25- mW laser on one side of the mouth only and reported a statistically significant reduction in oral mucositis on that side, according to the scoring system they used. 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 have benefited also from a distant systemic laser effect. Cowen et al. (3), using a 60 mW HeNe laser, performed a double-blind randomized phase III trial, in which laser was administered to the treatment group during conditioning, prior to the day of transplant. 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 items scale, of which 4 were assessed by the patients themselves. Daily mucositis index was significantly lower in L+ patients ($p < 0.05$) from d+2 to d+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 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 (1, 4). Schubert et al. for example (4), 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 during conditioning before BMT. In conclusion, LLLT seems to be a safe and efficient method for the prevention of chemo- and radiation-induced mucositis, 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, this complementary treatment option with low level HeNe laser could be important in enhancing the feasibility of such regimens, and especially in the conservation of dose-intensity effect. At Nice, where the method is now used routinely during head and neck radiation, we project a new study testing LLL in patients being treated with concomitant chemo- and radiotherapy for advanced head and neck cancer. Even more than the improvement of patient comfort, the therapeutic index of combined specific treatment should be increased by the use of LLLT, besides standard supportive care, oral care and enteral nutrition (5). During this study, other laser wavelengths and powers could be tested, and compared to 60-mW HeNe laser.

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