Treatment with laser therapy of cutaneous damages induced by radiotherapy in breast cancer: our institutional experience.

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ABSTRACT

Background and aims.
Patients treated with radiotherapy on the entire breast may present an acute, subacute or chronic cutaneous damage of the healthy tissues involved in the radiation fields. The aim of the present study is the assessment, through a controlled clinical study, of the effectiveness of Low Level Laser Therapy in reducing pain and inflammation and in stimulating skin healing of radiotherapy ulcerations.

Material and methods.
From February 2009 to March 2010, 100 patients affected by breast cancer have been recruited, with an average age of 47 years. 47patients were treated with laser with an interval of 3-4 days between applications on the inflammation or ulcerations area meanwhile the rest 53 patients were treated with lenitive creams. All enrolled patients were subjected chemotherapy with various schemes combinated or not with hormonal treatment. We evaluated the cutaneous acute toxicity according to the RTOG scale either during radiotherapy and during follow-up (3 months after radiation treatment).

Results.
All patients completed the radiotherapy; 60% of patients presented G0-G1 cutaneous toxicity, 28% have developed G2 cutaneous toxicity, 12% have developed G3 toxicity; no patient presented G4 toxicity. Analysis of the data revealed a shorter time for the healing of the cutaneous toxicity after topical treatment with LLLT compared to the patients that had no LLLT treatment.

Conclusions.
This clinical trial showed that low level laser therapy was effective in stimulating wound healing and pain reduction, and strongly suggest that its application could be useful in treating radiotherapy (actinic) induced ulcerations. Further analysis on a larger number of patients is necessary for definitive results but our data as far indicates huge effect of the LLL treatment by decreasing the healing time of skin toxicity.

INTRODUCTION

External beam radiotherapy alone or in association with surgery and/or chemotherapy represents an integrating and irreplaceable part in the treatment of the breast cancer. In the last 30 years, technological improvements and greater precision in the delivery and in the dose distribution of radiotherapy have reduced the incidence of radio-induced complications [1]. However, a minimal part of patients may present an acute, subacute or chronic cutaneous damage of the healthy tissues involved in the radiation fields.

The treatment of acute effects on the skin and on the mucosae (cutaneous erythema, edema, pigmentation and/or mucositis) [2,3] is important. Despite topical treatments (creams, pastes or sprays) that are used on the radio-treated surfaces both during the radiation treatment, lasers provide low-energy stimulation of tissues that results in increased cellular activity during wound healing [4,5]. Lasers provide low-energy stimulation of tissues that results in increased cellular activity during wound healing [4,5]. Wound healing has three phases: first, a substrate is laid down, second, cells proliferate, and third, there is remodelling of tissue. The functions being stimulated

include both collagen production and angiogenesis [6,7]. So, the data published so far suggests the laser biostimulation produces its primary effect during the cell proliferation phase of the healing process, but also in the preliminary inflammation phase and in the final phases of tissue maturation [8,9].
At cellular level, it has been demonstrated that mitochondria are receptive to monochromatic near-infrared laser light which probably increases the respiratory metabolism of certain cells [10-12] with the enhancement of ATP production and the increase of the mitochondrial inner membrane potential.

Given the photobiological nature of low-power laser effects [13,14], some molecule (photoacceptor) must first absorb the light used for the irradiation and then, after promotion of electronically excited states, primary molecular events from these states can lead to a measurable biological effect at the cellular level. In 1988 [15] it was suggested that the mechanism of interaction between Laser and cell substrates was based on the absorption of monochromatic visible and near infrared radiation by components of the mitochondrial respiratory chain. Absorption and promotion of electronically excited states cause changes in redox properties of these molecules and the acceleration of electron transfer (primary reactions). Primary reactions in mitochondria of eukaryotic cells were supposed to be followed by a cascade of secondary reactions (photosignal transduction and amplification chain or cellular signalling) occurring in cell cytoplasm, membrane, and nucleus [15]. In 1995, an analysis of five action spectra suggested that the primary photoacceptor for the red-NIR range in mammalian cell is a mixed valence form of cytochrome c oxidase [16]. Further signalling pathways which follow IR Laser interaction with the cytochrome c oxidase have been recently discovered [11].
The results of various studies [17-19] gave finally the demonstration, through direct observation, that the suggested mechanism [15] of low power laser therapy at the cellular level is based on the increase of oxidative metabolism in mitochondria, which is caused by electronic excitation of components of the respiratory chain (e.g., cytochrome c oxidase). This causes an increase in the ATP production, the increase of the mitochondrial inner membrane potential, and the shift from a catabolic to an anabolic condition, i.e the recovery of the energetic homeostasis of the cell.
Other processes, that depend strictly on the availability of ATP, are prompted by Low Level Laser Therapy: fibroblast proliferation [20], DNA synthesis [21], attachment and synthesis of collagen and protocollagen growth factor production (including keratinocyte growth factor [KGF], transforming growth factor [TGF], and platelet-derived growth factor [PDGF], macrophage stimulation, lymphocyte stimulation (activation and ability to bind pathogens), and a greater rate of extra cellular matrix production have been reported with laser light treatment (for example the fostering of the formation of type I and type III protocollagen specific pools of mRNA) [22-30].

Furthermore there is a positive effect of laser treatment on well-known aspects of inflammation such as mast cell proliferation and degranulation [31].
At the clinical level, the final results of this cascade of events prompted by the application of low level laser therapy are the acceleration of the healing time and the increase in the biomechanical indices of tissue healing. Animal studies on the enhancement in wound healing prompted by low power density laser light have been performed in toads, mice, rats, guinea pigs, and swine [32-35].
Human studies showed that low power laser emissions were able to stimulate epithelialization during wound closure and healing skin grafts (see ref. 36 for a thorough meta-analysis on the clinical studies), together with a significant pain reduction.
The applications of low level laser therapy to counteract the side effects of chemotherapy and radiotherapy have been used, up to the present time, for the prevention and treatment of oral mucositis. Laser therapy was shown to significantly reduce the incidence and the severity of mucositis in chemotherapy, as far as both pain and healing are concerned [37,38].
This clinical trial showed low level laser therapy was effective in stimulating wound healing and pain reduction, and strongly suggest that its application could be useful in treating radiotherapy (actinic) induced ulcerations.

MATERIALS AND METHODS

From February 2009 to March 2010, in the Radiation Oncology Department of Padua, 100 patients affected by breast cancer were recruited. Of the 100 patients recruited, 47 patients who developed any grade of toxicity were treated with LLLT application twice on the week with an interval of 3-4 days between the applications.

The device used was a Diode laser with a wavelength of 980 nm and red (visible), 5W peak emission,4J/cm2 energy with

GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
No changes	Light and/or painless erythema Epilation Desquamation Dryness	Sensitive and/or intense erythema Desquamation Partial sweating Moderate edema	Desquamation Widespread sweating Marked edema	Ulceration Hemorrhages Necrosis

Table 1 - RTOG scale used

an application area of 225 - 400 cm2 . We used a 5000 Hz frequency. The treatment time depended by the skin extend of the wound.

The application mode consisted of point action in order to accelerate local cell stimulation for healing.

The remaining 53 patients were treated with daily application of lenitive skin creams. The topical treatment of irradiated skin began the first day of radiotherapy and lasted until 3 months after the end of radiation treatment. Patients had to repeat the application of the cream every day (2-3 times/day).

Radiotherapy was delivered with a 3D conformational technique, and the total dose was 60 Gy in 30 fractions (2 Gy/die). All patients were treated with tangential beams using 6 Mv photons both for whole breast therapy and electron bean for tumor bed boost. From the beginning of the treatment, every week each patient was submitted to skin examination to evaluate cutaneous toxicity [39]. The evaluation was carried out using the RTOG scale [40](table 1). Cutaneous toxicity caused by radiations was estimated also during the follow-up, which was conducted approximately after 2-3 months of the end radiation treatment in all patients. All the patients who reported a G3 skin toxicity were treated locally with steroid products.

RESULTS

Patients enrolled in our study and treated with external radiotherapy for breast cancer were 100. 47 of them were treated with LLLT twice at week with an interval of 3-4 days between applications. The average number of sessions of LLLT was 4, so the time of treatment was 15 days. 23 (49%) of these patients had G1 cutaneous toxicity,18 (38%) G2 and 6 (13%) G3.

As the treatment with LLLT proceeded we continued to evaluate the patients skin toxicity according to the RTOG toxicity scale.

Patients with G1 toxicity treated with LLLT had an average mean time of healing of 9-10 days. Those with G2 toxicity an average mean time of healing of 15-18 days and 4 of these patients still had a G1 toxicity after 2- 3 months of follow up. In the G3 skin toxicity group the average mean time of healing after LLLT treatment was about 25-30 days with a 50% of patients that still had G1 toxicity after 3 months of follow up. Three months after the end of radiotherapy, at the first follow-up visit, only 15% of the radiotherapy-treated patients(all groups) still showed G1 cutaneous toxicity.

We compared the previous LLLT treated group of patients with another group treated with external radiotherapy for breast cancer that had only daily cutaneous applications of lenitive creams for the healing of cutaneous toxicity.37 (74%) patients of these group had G1 cutaneous toxicity,10 (20%) G2 and 6 G3.All patients who manifested G2 toxicity stopped the first topical treatment and were treated with cortisone creams [41], which determined a reduction in toxicity grade in 70% of the cases. The mean average time of complete healing in the G1 group was 18-20 days, in the G2 group 30 days and in the G3 group about 50 days. Patients who manifested G3 cutaneous toxicity were treated with cortisone and healing creams. Three months after the end of radiotherapy, at the first follow-up visit, 29% of the radiotherapy-treated patients still showed G1 cutaneous toxicity. Our results are summarized on table 2

DISCUSSION

The breast cutaneous damage induced by radiation treatment on patients affected by breast cancer have been often evaluated. Some studies tried to evaluate the best topical treatment and the correlation between systemic therapy and skin radio-induced damage [42].

Macmillan et al. [39] added to the knowledge on the risk factors for skin

Grade of toxicity	Number of patients	Patients treated with LLLT	Patients treated with lenitive creams	Average total time of treatment with LLLT	Average total time of treatment with LLLT
G1	60	23	37	9 days	20 days
G2	28	18	10	18 days	30 days
G3	12	6	6	30 days	50 days

Table 2 - Patients and results.

breakdown. These include concurrent chemotherapy, the use of a bolus, and smoking. Porock and Kristjanson [43] noted that a lot of the current research on radiation-induced skin reactions has focused on patients with breast cancer.
There are many factors that probably influence the appearance of side effects on irradiated breasts. Bentzen et al. [40] found increased acute skin toxicity when patients received chemotherapy. Anthracyclines, paclitaxel and docetaxel are involved with growing possibility in skin side effects [44,45].

Turessonand Notter [46] found the peak acute reaction to be correlated with age, menopausal status, bilateral treatment and the type of radiation. The reasons for such variability in risk factors for acute skin reactions are not clear but could be related to differences in the study population or the small number of patients analyzed in the actual trial.

In our study 97 patients treated with external radiotherapy for breast cancer in our department 47 of them were treated with LLLT with an interval of 3-4 days between applications with mean time of treatment of about 23 days. 23 (49%) of these patients had G1 cutaneous toxicity, 18 (38%) G2 and 6 (13%) G3.The average number of applications of LLLT was 7.
As the treatment with LLLT proceeded we continued to evaluate the patients skin toxicity according to the RTOG toxicity scale (table1).

Patients with G1 toxicity treated with LLL had an average mean time of healing of about 9-10 days. Those with G2 toxicity an average mean time of healing of about 18-20 days and 4 of these patients still had a G1 toxicity after 2- 3 months of follow up. In the G3 skin toxicity group the average mean time of healing after LLLT treatment was about 30-40 days with a 50% of patients that still had G1 toxicity after 3 months of follow up. Three months after the end of radiotherapy, at the first follow-up visit, only 15% of the radiotherapy-treated patients(all groups) still showed G1 cutaneous toxicity (table 2).

We compared the previous LLLT treated group of patients with another group treated with external radiotherapy for breast cancer that had only daily cutanous applications of lenitive creams for the healing of cutanous toxicity.

We found that comparing the two groups we had a decrease of 50% of the mean average time of healing (10 vs 20 days) in rhe G1 patients,a 21% of decrease in the G2 group and a 25% of decrease in the G3 one.

Further analysis on a larger number of patients is necessary for definitive results but our data as far indicates huge effect of the LLLT treatment by decreasing the healing time of skin toxicity.

CONCLUSIONS

Today there is growing interest in the treatment of cutaneous side effects of radiotherapy. Particularly women treated for breast cancer ask us not only the clinical resolution of their oncologic story but also a satisfactory esthetic condition. Patients are also concerned about the most effective and faster way of decreasing the side effects of the radiotherapy.
In our study we confirmed the capacity of the LLLT treatment to decrease the time of skin toxicity induced by radiation therapy on patients treated in our institute for breast cancer. Further analysis on a larger number of patients is necessary for definitive results.

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