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BRIEF REPORT

Acneiform rash due to epidermal growth factor receptor inhibitors: high-level laser therapy as an innovative approach

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Abstract Acneiform rash associated with epidermal growth factor receptor inhibitors frequently presents facial manifestations. The treatment modality for such lesions still needs to be elucidated. The aim of this original report was to evaluate the effectiveness of high-level laser therapy in reducing the severity of facial acneiform rash induced by cetuximab, an epidermal growth factor receptor inhibitors. Four patients with metastatic colorectal cancer and two patients with head and neck cancer showing cetuximab-induced facial rash were treated by high-level laser therapy in two 8-min-long consecutive sessions/day over a 4-day treatment. Patients wore protective glasses to prevent eye damage related to laser light. Subsequently, patients were seen once a week for up to 21 days and after 180 days. During each day of treatment and each follow-up recall, patients were asked to complete a questionnaire about the onset and progression of their acneiform rash (for a total of eight sessions). Cetuximab-related toxicity and general discomfort visual analogue scales were also recorded in each of these eight sessions in the treated and control areas in each patient. After the fourth session of high-level laser therapy, the patients showed a noteworthy decrease in both cetuximab-related toxicity and visual analogue scales, up to a complete regression of the lesions at the end of the follow-up in all treated areas. The high-level laser therapy was effective in the healing of acneiform rash associated with epidermal growth factor receptor inhibitors with no side effects.

Keywords High-level laser therapy · Diode laser · Epidermal growth factor receptor inhibitors · Cetuximab · Acneiform rash

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Introduction

Epidermal growth factor receptor (EGFR) is a target of the monoclonal chimeric IgG-cetuximab (Erbitux®), which is used in both association with chemotherapy [1] or as a monotherapy in metastatic colorectal cancer expressing the EGFR and wild-type K-ras gene. Cetuximab is also effective in head and neck squamous cells carcinoma [2–4]. While EGFR Inhibitors lack many of the side-effects commonly observed with cytotoxic chemotherapy, they are associated with a set of unique dermatological toxicities [5].

The majority of patients treated with a monoclonal antibody (MoAb) EGFR inhibitor experience dermatological side-effects [6], most notably the papulopustular skin rash [7–12], which can impact quality of life and affect adherence to therapy [13]. Acneiform rash (AR) associated with EGFR inhibitors often presents different degrees of facial manifestations [14]. General indications to manage this side-effect [15–20] include using sun-protective measures and avoiding activities and products that are likely to dry the skin (long hot showers, alcohol-based/perfumed products, over-the-counter acne medications, etc.) [21]. Oatmeal baths and creams may provide symptomatic relief. Management should be individualized according to the type, severity, and location of the rash. In case of grade two

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(GII) skin toxicity, related to cetuximab-related toxicity (CRT) scale (Table 1), topical antibiotic treatment (clindamycin 1% gel, erythromycin 3% gel/cream or metronidazole 0.75–1% cream/gel) can be used twice per day until improvement to grade one (GI), without reducing cetuximab dose. Interestingly, evidence of beneficial effects of vitamin K1 cream on patients experiencing severe AR have been presented [22]. For dermatitis pustule prevalent type (GII), the use of oral semi-synthetic tetracycline is suggested. In case of grade three (GIII) toxicity (along with similar topic treatment) dose reduction (or drug interruption), systemic therapy with semi-synthetic tetracycline (minocycline, doxycycline) for at least 4 weeks and oral corticosteroids for up to 10 days are suggested until the rash became asymptomatic. For GIII, highly symptomatic/nonresponsive patients, treatment with oral retinoids, intravenous corticosteroids, intramuscular/intravenous antihistamines, intravenous antibiotics (amoxicillin/clavulanic acid, gentamicin) could be used. None of these treatments have proven to be completely successful to heal the cetuximab-associated AR. Moreover, all the above treatments could be toxic and expensive, and they have to be carried out for a long time before proving clinically significant results.

Low-level laser therapy (LLLT) has been demonstrated to be effective in wound healing through an anti-inflammatory and biostimulating mechanism. The effectiveness of laser therapy is due to responses induced by the cellular level photobiomodulation promoting acceleration of cellular metabolism, reducing inflammation, increasing local microcirculation, and the lymphatic system, leading to a decrease of the interstitial edema and an increase of the collagen synthesis. Both modulatory effects of LLLT over the inflammatory response might be the result of an important inhibitory role played by laser arrays, in a variety of cells, on the synthesis of prostaglandin, a chemical mediator widely supposed to provide chemotactic signals for leukocytes polymorphonuclear neutrophils, as well as on lymphocyte proliferation and maturation. This biological effect of laser therapy could make laser therapy itself an effective way of managing AR as it is a suppurative neutrophilic folliculitis characterized by perifollicular inflammatory infiltrate [23]. Since a biostimulating and anti-inflammatory effect can be obtained using wavelengths between 600 and 1,000 nm [24], we have decided to employ a wavelength of 970 nm, thus defining this therapy high-level laser therapy (HLLT) instead of LLLT. As the total dose administered is affected by the penetration of the beam and by phenomena like surface scattering and water, melanin, and hemoglobin absorption, we thought the choice of this parameter would improve the outcome of laser treatment, as the effect is concentrated on a more superficial area of damaged tissue.

Table 1 Cetuximab-related toxicities scale

Grading of most relevant cetuximab-related toxicities

National cancer institute toxicity criteria version 3.0 grading descriptive criteria					
Adverse event	Grade I	Grade II	Grade III	Grade IV	Grade V
Rash: desquamation	If macular or papular eruption or erythema is not associated with symptoms such as pain or itch, intervention is not indicated	Macular or papular eruption or erythema with pruritus or other associated symptoms covering<50% of body surface or localized desquamation or other lesions covering<50% of body surface area; intervention indicated	Symptomatic generalized erythroderma or macular, papular, or vascular eruption or desquamation covering>50% of body surface area	Generalized exfoliative, ulcerative, or bullous dermatitis	Death
Rash: acne/ acneiform	Intervention not indicated	Intervention indicated	Associated with pain, disfigurement, ulceration, or desquamation	-	Death
Allergic reaction - hypersensitivity	Transient flushing or rash: drug fever<38°C (<100,4°F)	Rash, flushing, urticaria, dyspnea, drug fever>38°C (>100.4°F)	Symptomatic, bronchospasm with or without urticaria; parenteral medication(s) indicated; allergy-related edema/ angioedema; hypotension	Anaphylaxis	Death

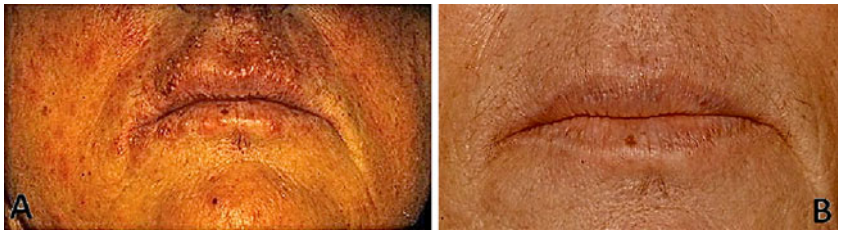

Fig. 1 **a** Before HLLT. **b** Fourth follow-up session

Materials and methods

Four patients with metastatic colorectal cancer and two patients with head and neck cancer, presenting cetuximab-induced AR, were treated. Before starting HLLT, all six patients showed GII AR (see Figs. 1a and 2a) according to the CRT scale (Table 1). Two patients had been presenting AR for 4 weeks, one of them for 21 weeks and one of them for 28 weeks, while the remaining two had been presenting AR for 40 weeks.

Before HLLT treatment, two patients had not been using any topic compound, while four patients had been spreading cream and gel on their skin lesions during the previous 10–12 months without clinical improvements. Dermatologists, oncologists, and GPs prescribed to the patients Aquacutis (emollient), vitamin K1, Hydracial™ Skin Vigor Cream (acetyl hexapeptide-8, acetyl octapeptide-3, hydroxyethyl urea, hexapeptide-11, sesamum indicum oil, additional natural oils) and Fissan cream (aqua, paraffinum liquidum, glycerin, cetyl alcohol, isopropyl palmitate, glyceryl stearate, Peg-100 stearate, polysorbate 60, sorbitan stearate, dimethicone, bisabolol, chamomilla recutita extract, parfum, carbomer, propylene glycol, tetrasodium EDTA, maltodextrin, silica, citric acid, sodium hydroxide, phenoxyethanol, methylparaben, ethylparaben) mingled with prometazina 2.00 g without success. All topical treatments were suspended before the beginning of HLLT not to interfere with the laser therapy itself.

A diode laser K1200 by Eltech S.r.l. (Via Castagnole, 20/H– 31100 Treviso, number K-1200-00149) was used to treat the AR. Four patients had only perioral lesions (Fig. 2a), while the remaining two patients had widespread lesions all over the face (Fig. 1a). All affected areas were irradiated except for the areas protected by protective glasses. Patients were treated with two 8-min consecutive session/day over a 4-day treatment (laser parameters were: wavelength 970 nm, power 5.0 W, 10 J/cm^2, duty cycle/pulsed mode 50%, frequency 10–1,000 Hz, spot size diameter between 0.8 and 2.5 cm). Daily laser applications were repeated twice at a 5-min interval. Total duration of treatment was 21 min. Both the patient and the operator used protective glasses to prevent the risk of eye damage. During the 4 days of active treatment and in each of four follow-up recalls (the first one on day 7, the second one on day 14, the third one on day 21, and the fourth one on day 180, starting from the last day of active treatment), patients were asked to complete a questionnaire in order to record the evolution of general discomfort through the visual analogue scale (VAS, Table 2). Operators also evaluated the severity of lesions through the CRT scale (Table 1).

Results

An evident decrease in the dimension of skin lesions was registered after the first two laser sessions for two patients and after the third one for the remaining four individuals. Complete regression of AR was recorded in all six patients at the second follow-up. The benefit was maintained up to the last follow-up despite that the patients carried on their cancer therapy (Table 3).

Patients' discomfort was grade eight for three of them and grade seven for three of them according to general discomfort VAS (Table 2). Despite the discomfort caused by lesions, patients were more worried about the aesthetic damage than about their symptoms (pain, itching, scabs, and desquamative lesions).

At the end of the treatment, all six patients showed complete healing of AR lesions (see Figs. 1b and 2b) and referred a total remission of pain (VAS = 0) and itch (Table 3).

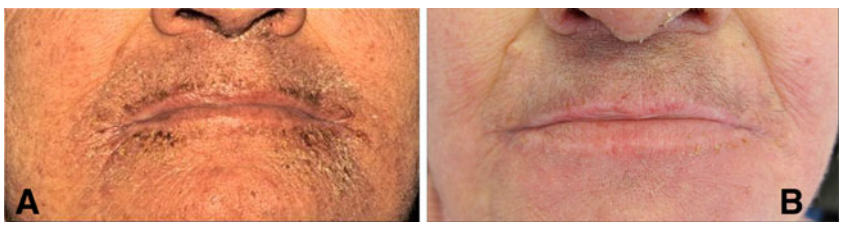

Fig. 2 **a** Before HLLT. **b** Fourth follow-up session

Table 2 General discomfort visual analogue scale

VAS = 0	VAS = 10
Not hurting	Hurting a whole lot
No itching	Severe itching
No aesthetic concern	Aesthetic concern

Discussion

Cetuximab binds to EGFR five to ten fold more than endogen ligands. EGFR is expressed in the basal layer of the epidermis and contributes to epidermal growth stimulation, differentiation inhibition, and wound healing acceleration [25]. Inhibition of EGFR results in impaired growth and migration of keratinocytes and inflammatory chemokine expression by these cells. The resulting inflammatory cell recruitment and subsequent cutaneous injury account for the majority of dermatological symptoms associated with anti-EGFR therapy including AR and papulopustular eruption, hair growth disorders, periungual and nail plate abnormalities, xerosis, telangiectasias, and itching. Disruptions of this barrier may also promote bacterial overgrowth further exacerbating injury to the cutaneous tissue [26].

In the last months, we routinely used HLLT to treat chemotherapy-induced periodontal inflammations with excellent clinical results [27]. This preliminary study reports on the efficacy of HLLT in the management of cetuximab-induced facial dermatitis. High-level laser works through the emission of light. A primary response to laser light is achieved when chromophores and cell membranes (particularly of fibroblasts) are reached by photons. Afterwards, light is transformed into kinetic and chemical energy inside cells. Laser light induces a series of metabolic effects causing physiological cell mutations such as cellular membrane permeability [28]. The mitochondria calcium release triggers a change in the intercellular calcium level thus stimulating cellular metabolism [29] and regulating various processes involved in wound healing (such as cell migration, RNA and DNA synthesis, cellular mitosis, protein secretion, and cellular proliferation). Once stimulated by the light, cells can communicate together with both irradiated and non-irradiated cells through cytokines and growth factors. This increases the immune-inflammatory response by the activation of T-lymphocytes, macrophages and mast cells [30, 31]. The increase of endorphin production and the decrease in bradykinin production may reduce pain sensation. Anti-inflammatory effects are obtained through three main mechanisms: increase in leucocytes activity, stimulation of lymphocytes response, and temperature modulation. These derive from cytochromes activation, vasodilatation, prostaglandins synthesis, and IL-1 inhibition, due to cellular metabolism activation [32–34].

Table 3 Detailed parameters about VAS and CRT scale

VAS (Visual analogue scale)																																CRT (cetuximab-related toxicities) scale (grade I–IV)		
								Pain (0–10)							Itch (0–10)							Aesthetic concern (0–10)												
Patient #1																																		
D1	D2	D3	D4	FU7	FU14	FU21	FU180	7	5	5	4	2	0	0	0	10	5	0	0	0	0	0	0	10	7	7	6	5	0	0	0	II	II	I	I	I	CR	CR	0
Patient #2																																		
D1	D2	D3	D4	FU7	FU14	FU21	FU180	7	4	0	0	0	0	0	0	6	5	2	2	1	0	0	0	9	9	7	4	2	0	0	0	II	II	II	I	I	CR	CR	0
Patient #3																																		
D1	D2	D3	D4	FU7	FU14	FU21	FU180	8	8	7	7	5	3	0	0	10	9	8	7	5	3	0	0	8	6	5	3	1	0	0	0	II	II	I	I	I	CR	CR	0
Patient #4																																		
D1	D2	D3	D4	FU7	FU14	FU21	FU180	8	4	5	5	5	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	II	II	II	I	I	CR	CR	0
Patient #5																																		
D1	D2	D3	D4	FU7	FU14	FU21	FU180	8	9	8	7	5	0	0	0	8	8	7	7	5	2	0	0	10	9	8	5	2	0	0	0	II	II	II	I	I	CR	CR	0
Patient #6																																		
D1	D2	D3	D4	FU7	FU14	FU21	FU180	7	4	4	3	2	2	0	0	9	10	9	6	4	1	0	0	9	9	9	6	3	0	0	0	II	II	II	I	I	CR	CR	0

D1 = first laser application

D2 = second laser application

D3 = third laser application

D4 = four laser application

FU7 = first follow-up

FU14 = second follow-up

FU21 = third follow-up

FU180 = fourth follow-up

CR = complete regression

Considering the targets and the side-effects of cetuximab and the physiological and biological benefits induced by HLLT on cutaneous tissues, it can be hypothesized that HLLT can be effective and helpful in the healing of cetuximab-induced AR. We have decided to employ such wavelength, even if there is no evidence in the literature. In fact, studies usually report wavelengths in the near-infrared spectrum, up to 904 nm. Due to this fact, we decided to call the therapy "high" instead of "low", but with the same objective (antinflammation, biostimulation). Being that this a preliminary report, further studies are needed to support our results.

Conclusions

This is the first report in which the possibility of a complete regression and healing of cetuximab-induced AR can be obtained using HLLT treatment. Since laser applications are completely safe, non-invasive, quick, and easy, without contraindications and limited side-effects, they can be routinely used in the treatment of this dermatitis.

Despite the limited number of treated patients, we hypothesized that HLLT is an effective and innovative approach for the management of AR due to epidermal growth factor receptor inhibitors.

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Conflict of interest Statement The authors declare that there are no conflicts of interest.

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