DOI: 10.1111/ipd.12090

INTERNATIONAL JOURNAL OF PAEDIATRIC DENTISTRY

Class IV laser therapy as treatment for chemotherapy-induced oral mucositis in onco-haematological paediatric patients: a prospective study

MADDALENA CHERMETZ[1], MARGHERITA GOBBO[1], LUCA RONFANI[2], GIULIA OTTAVIANI[1], GIULIO A. ZANAZZO[2], FEDERICO VERZEGNASSI[2], NATHANIEL S. TREISTER[3], ROBERTO DI LENARDA[1], MATTEO BIASOTTO[1] & SERENA ZACCHIGNA[4]

[1]Division of Oral Medicine and Pathology, Department of Dental Science, University of Trieste, Trieste, Italy, [2]Institute for Maternal and Child Health, IRCCS Burlo Garofolo, Trieste, Italy, [3]Division of Oral Medicine & Dentistry, Brigham and Women's Hospital, Boston, MA, USA, and [4]International Center for Genetic Engineering and biotechnology (ICGEB), Trieste, Italy

International Journal of Paediatric Dentistry 2013;

Background. Oral mucositis is a debilitating side effect of chemotherapy. Laser therapy has recently demonstrated efficacy in the management of oral mucositis (OM).

Aim. This prospective study was conducted to evaluate the efficacy of class IV laser therapy in patients affected by OM.

Design. Eighteen onco-haematological paediatric patients receiving chemotherapy and/or haematopoietic stem cell transplantation, prior to total body irradiation, affected by OM, were enrolled in this study. Patients were treated with class IV laser therapy for four consecutive days; the assessment of OM was performed through WHO Oral Mucositis Grading Objective Scale, and pain was evaluated through visual analogue scale. Patients completed a validated questionnaire, and photographs of lesions were taken during each session. Patients were re-evaluated 11 days after the first day of laser therapy.

Results. All patients demonstrated improvement in pain sensation, and all mucositis was fully resolved at the 11-day follow-up visit, with no apparent side effects. Laser therapy was well tolerated with remarkable reduction in pain associated with oral mucositis after 1–2 days of laser therapy.

Conclusions. Given class IV laser therapy appears to be safe, non-invasive, and potentially effective, prospective, randomized, controlled trials are necessary to further assess efficacy and to determine optimal treatment parameters.

Introduction

Patients with cancer undergoing intensive chemotherapy (CT) regimens experience many side effects among which oral mucositis (OM) is one of the most debilitating. Usually, OM results in painful or hampered swallowing, chewing, and speaking, and in more severe cases, it can lead to unwanted hospitalization to allow enteral feeding[1].

In paediatric patients, many undesirable effects can be promoted by the onset of OM, such as increased loss of baseline body weight, higher probability of requiring fluid replacement, higher probability of fever, and ultimately risk of delays in chemotherapy. Interestingly, in paediatric and adolescent patients, no proportional correlation has been evidenced between OM' severity and entity of side effects, as well as between overall OM and number of possible side effects[2].

Despite the frequency and impact of OM, there is no consensus as to standard therapy for this affection. Many palliative strategies can be applied in patients suffering from OM, such as topical anaesthetics, mucosal coating agents, and cryotherapy. Treatment with low-power laser therapy (LPLT) has demonstrated efficacy both in reducing symptoms[3] and in preventing the onset of OM in adult cancer patients[4,5]. There are, however, no randomized controlled trials

Correspondence to:
Matteo Biasotto, Division of Oral Medicine and Pathology, Department of dental Science, University of Trieste, Piazza dell'Ospitale 2, 34100, Trieste, Italy.
E-mail: m.biasotto@fmc.units.it

(RCT) in paediatric cancer patients with a numerous sample.

Here, we present a pilot study, which aimed at demonstrating the efficacy of class IV laser therapy in the treatment for OM. The reassuring results obtained allowed us to start a multicentric, double-blind RCT in a haematological paediatric population coming from eight Italian paediatric hospitals.

The innovative protocol used, called 'high-power laser therapy' (HPLT), employs high power and high wavelength with several advantages as compared to traditional protocols.

Materials and methods

Eighteen paediatric haematology oncology patients aged 10–17 (median age 13) that developed ≥2 grade were enrolled in this clinical trial from November 2011 through April 2013. All patients were receiving their cancer therapy at the Pediatric Hemato-Oncology Department at the Institute for Maternal and Child Health – IRCCS 'Burlo Garofolo' (Via dell'Istria, 65, 34137 Trieste), and the study was conducted in collaboration with the Dental Clinic Department, University of Trieste, 'Ospedale Maggiore' (Piazza Ospedale, 1, 34100, Trieste) between November 2011 and April 2013, after obtaining ethical approval. Twelve patients (67%) were males. Ten patients (55.4%) were affected by acute lymphoblastic leukaemia (ALL), 4 patients (22.2%) by non-Hodgkin lymphoma (NHL), one patient (5.6%) by Ewing's sarcoma, one patient (5.6%) by acute myeloid leukaemia (AML), one patient (5.6%) by aplastic anaemia, and one patient (5.6%) by osteosarcoma. All patients underwent CT with various drugs depending on their neoplasia, whereas six patients had also been subdued to HSCT prior to total body irradiation (TBI).

Patients could not have previously been treated with laser therapy and had to be able to open their mouth at least 20 mm. Patients were enrolled in the study as soon as haematologists asked a consultation with the oral pathologists. For this reason, severity of OM ranged from grade two to grade four, according to the scale used for evaluation (WHO).

Treatments were provided using a K-Cube3 diode GaAlAs laser (class IV, series number #00027 Treviso, Italy). The following HPLT protocol was performed twice a day during four consecutive days: 970 nm wavelength, 5W power, duty cycle 50%, 35–6000 Hz frequency, 230 s duration, and 1 cm^2 spot size. Laser application was performed all over the oral cavity, both in ulcerated and erythematous areas and in free of clinical signs' ones. Defocused modality was preferred to focused modality, and a rotatory motion was used all over the oral cavity. On average, HPLT was started 7.5 ± 3.0 days after the end of CT cycle. Patients and operators wore protective glasses to prevent eye damage during HPLT. Patients were seen 11 days after the beginning of laser therapy for re-evaluation.

Oral mucositis was evaluated using the WHO scale by an operator of the department of oral medicine and pathology with at least 2 years of experience in the field. Presence and severity of ulceration and/or erythema were registered according to nine areas in the oral cavity: upper lip, lower lip, right side of tongue, left side of tongue, right cheek, left cheek, hard palate, soft palate, and floor of the mouth (Table 1). The same operator performed assessment of pain through a linear 1–10 visual analogue scale (VAS).

A questionnaire about the onset and progression of OM was completed at each study visit. Questions asked about sensation of pain/alteration in swallowing, mucosal integrity, saliva, and oral hygiene (Table 2). Photographs of affected areas were taken at each session. This was a single-blind study. HPLT

Table 1. Ulcerations and erythema in oral cavity's areas.

Area	Ulcerations				Erythema			
Upper lip	0	1	2	3	0	1	2	3
Lower lip	0	1	2	3	0	1	2	3
Right cheek	0	1	2	3	0	1	2	3
Left cheek	0	1	2	3	0	1	2	3
Right side of tongue	0	1	2	3	0	1	2	3
Left side of tongue	0	1	2	3	0	1	2	3
Floor of the mouth	0	1	2	3	0	1	2	3
Soft palate	0	1	2	3	0	1	2	3
Hard palate	0	1	2	3	0	1	2	3

Ulcerations: 0 = none; 1 = <1 cm^2; 2 = 1–3 cm^2; 3 = >3 cm^2.
Erythema: 0 = none; 1 = mild; 2 = moderate; 3 = severe.

Table 2. Personal assessment of oral mucositis(OM).

Voice	Normal	Deep/hoarse	Difficulty in phonation/pain when speaking
Swallowing	Normal	Mild pain	Swallowing not possible
Lips	Smooth, rosy, moist	Dry and chapped	Ulcerated, bleeding
Saliva	aqueous	Thick	xerostomia
Tongue	Rosy, moist, with papillae	Plaques, absence of papillae, with/without erythema	Vesicles, chapped
Mucose	Rosy, moist	Red, plaques without ulcerations	Ulcerations with/without bleeding
Hygiene	Rosy, moist	Oedema with or without redness	Spontaneous bleeding or after pressure
Teeth/prosthesis	Cleaned	Calculus, localised remains	Calculus, generalised remains

was performed by the same operator during the 4-day protocol, in all patients. Evaluation of OM was performed by another operator at the end of laser sessions and after 11 days. In addition, neutrophils' count and white body cells' (WBC) count were recorded for each patient on Days 1, 4, and 11 (Figs 1 and 2).

Statistical methods/analysis

Categorical variables are presented as absolute frequencies and percentages; continuous data as medians and interquartile ranges (IQR). Differences between the evaluations carried out at the different study times were evaluated with the McNemar's test for paired categorical variable (i.e., difference in the presence of ulceration between Day 1 and Day 11) and with the Wilcoxon non-parametric tests for continuous variables (i.e., differences in VAS between Day 1 and Day 4). A P value <0.05 was considered statistically significant. The data were analysed using SPSS for Windows 11.0 (SPSS 2001; Chicago, IL, USA).

Results

CTC and VAS decreasing

At baseline, 61% of patients had WHO>2, with consequent difficulties in oral feeding. All patients showed a decrease in WHO from

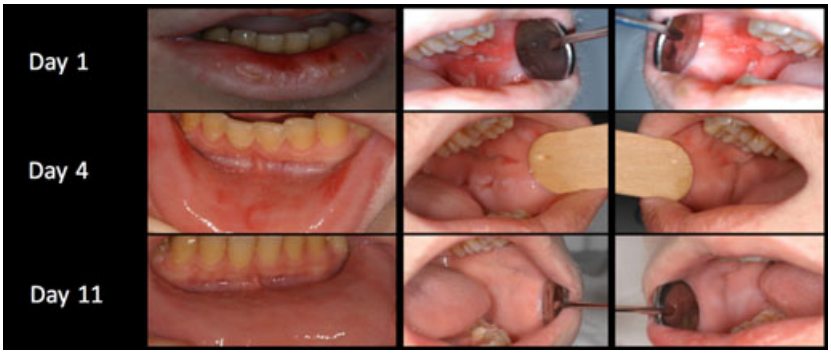

Fig. 1. Evolution on Day 1, Day 4, and Day 11 of oral mucositis on the lower lip and right and left cheeks.

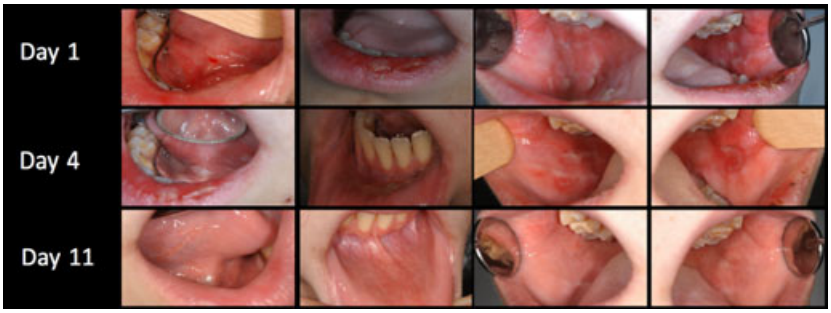

Fig. 2. Evolution on Day 1, Day 4, and Day 11 of oral mucositis on the floor of the mouth and lower lip and right and left cheeks.

a median of 3 (IQR 2–3.25) at Day 1 to a median of 2 (IQR 1–2) after 4 days of HPLT ($P = 0.001$), up to a complete healing (median WHO = 0, IQR = 0–1) at follow-up recall (Day 11, $P < 0.001$). Statistically significant decrease in WHO was already noticeable on Day 3 ($P < 0.05$) (Fig. 3).

At baseline, 61% of patients had a VAS≥ 5. A remarkable decreasing in median VAS scores was registered in all patients from Day 1 to Day 4: 5 (IQR 4–7) *vs* 2 (IQR 1–3), respectively ($P < 0.001$). Complete regression of VAS was registered on Day 11 in all patients ($P < 0.001$ *versus* median VAS evaluated at Day 1). To note, a noteworthy reduction in pain was already evident 1 day after the beginning of HPLT (4, IQR 3–6, $P = 0.05$) (Fig. 3).

Nine patients (50%) complained about a transient sensation of burning after laser therapy. Burning sensation used to start immediately after the end of laser therapy and to disappear in <1 h. It was generalized all over the oral cavity and was not associated with visible mucosal alterations.

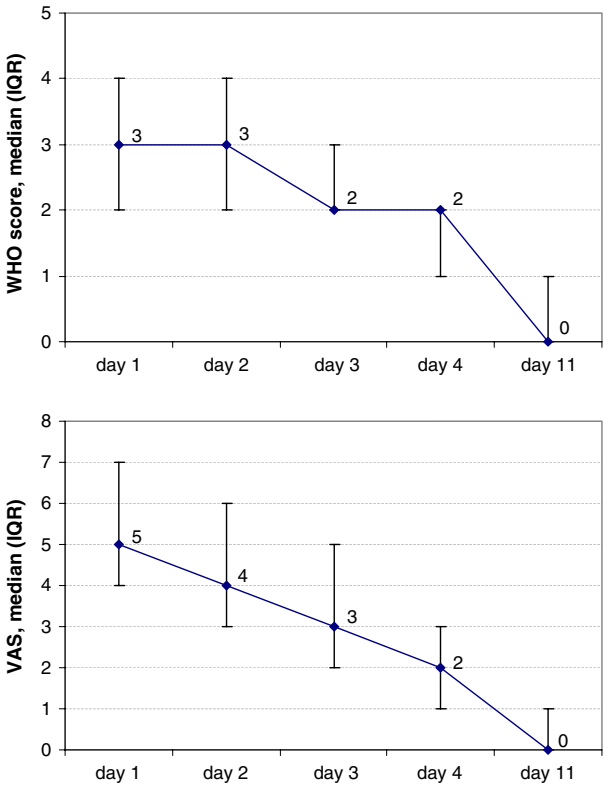

Fig. 3. CTC score and Visual analogue scaleVAS score progression between days 1 and 11.

Personal assessment of OM

As regards personal assessment of OM, a significant improvement was registered between Day 4 and Day 11 for swallowing difficulties, lesions of tongue, lips and cheek (Table 3). For example, 60% of patients referred difficulties in swallowing on Day 4, whereas only 20% had the same complaint on Day 11 ($P = 0.02$). Despite no significant differences were found for alteration of saliva or capacity of performing oral hygiene, 27% of patients complained about dry/thick saliva on Day 4 and 0% on Day 11, as well as 40% of patients had difficulties in performing oral hygiene on Day 4 and 13% on Day 11.

Ulcerations and erythema

According to area of ulcerations, the complete regression of lesions was evidenced in all patients in all examined areas, except for right cheek and left side of tongue. Differences between Day 1 and Day 11 were statistically significant for lower lip and right and left cheek (Table 4).

According to site of erythema, a significant healing was obtained on Day 11 on right and left cheek. Anyway, the majority of patients experienced a great improvement or disappearance of erythema in all examined areas on Day 11 (Table 4).

Neutrophils and WBC count

Table 5 shows results regarding neutrophils/WBC counts on Days 1, 4, and 11, expressed

Table 3. Personal assessment of oral mucositis before and after laser therapy.

Variable	Alteration day 4 (% patients)	Alteration day 11 (% patients)	*P**
Swallowing	60	20	**0.02**
Lips	47	27	**0.02**
Saliva	27	0	NS
Tongue	40	20	**0.03**
Mucosa	93	0	**0.001**
Oral hygiene	40	13	NS

Diff., significance of the differences between the groups; NS, difference not statistically significant; bold values state statistical significance.
*McNemar's test.

Table 4. Ulcerations and erythema before and after laser therapy: number of patients (%) presenting ulcerations or erythema in specific areas of oral cavity.

Site	Ulc day 1(%)	Ulc day 11(%)	*P**	Ery day 1(%)	Ery day 11(%)	*P**
Upper lip	27	0	NS	20	7	NS
Lower lip	40	0	**0.03**	53	0	NS
Right cheek	67	7	**0.04**	73	13	**0.002**
Left cheek	67	0	**0.02**	73	13	**0.002**
Right side of tongue	33	0	NS	40	13	NS
Left side of tongue	33	7	NS	33	20	NS
Floor of the mouth	33	0	NS	27	13	NS
Soft palate	13	0	NS	7	0	NS
Hard palate	20	0	NS	20	0	NS

Ulc, ulceration; Ery, erythema; Day 1 = first day of laser therapy; Day 11 = follow-up recall.
Diff., significance of the differences between the groups; NS, difference not statistically significant; bold values state statistical significance.
*McNemar's test.

Table 5. Neutrophils and white body cells' counts at different time points, presented as medians and interquartile ranges.

Neutr_day 1	Neutr_day 4	Neutr_day 11	Diff * day 1 *vs* day 4	Diff * day 4 *vs* day 11	Diff * day 1 *vs* day 11
50 (0–1625)	350 (0–2000)	1750 (500–3825)	NS	$P < 0.01$	$P < 0.01$
WBC_day 1	WBC_day 4	WBC_day 11	Diff * day 1 *vs* day 4	Diff * day 4 *vs* day 11	Diff * day 1 *vs* day 11
630 (88–2563)	1430 (85–3285)	2975 (1725–5568)	NS	$P < 0.01$	$P < 0.001$

neutr, neutrophils; WBC, white body cells; Diff., significance of the differences between time points.
* Wilcoxon. NS, difference not statistically significant.

as median and IQR, and differences between each couple of time points (Table 5).

Discussion

This prospective study was conducted to evaluate the efficacy of class IV laser therapy in 18 onco-haematological patients affected by OM.

The standard treatment for the most common haematological neoplasia in paediatric patients such as ALL, NHL, and solid tumours in general is CT with or without bone marrow transplant preceded by TBI. In the majority of cases, these treatments are associated with local and systemic complications.

Certainly, one of the most debilitating side effects of CT is OM[6], which occurs in more than 55% of children and adolescents suffering from ALL or lymphomas undergoing CT[7].

In general, OM begins 2–12 days after CT, and in an onco-haematological patient subjected to a high-dose CT, it can become very severe around 7–14 days after the beginning of therapy[8]. The average duration of oral lesions is 2–3 weeks, but it can last more in patients with severe neutropenia[9,10].

The pathogenesis of OM is divided into five stages, mediated by cytokines. In the first phase, antineoplastic agents provoke a direct damage to cellular DNA. In the following stages, the amplification of the transcription factors and the generation of signals induce a reduction in the cellular turnover with promotion of apoptosis and tissue damage. Despite the tissue integrity is still maintained in this phase, biological alterations can cause severe pain. This explains why clinical appearance of lesions is not always proportional to referred sensation of pain. Subsequently, 7–10 days after CT the ulcerative stage begins, and during this stage, there is a very high risk of bacterial or fungal superinfections. The healing phase is characterized by angiogenesis and cell proliferation[11]. In the present study, patients were treated through HPLT with OM of different grades regardless the dimensions of lesions, on average 7.5 $\pm$ 3 days after the end of CT. This is in accordance with the mean peak severity described in the literature[7].

Actually, there are many strategies to cure OM. They include topical palliative treatments, such as oral rinse solutions based on E vitamin

and aloe vera, cryotherapy, lidocaine or morphine-based rinse, and systemic treatments, such as administration of indomethacin, glutamine, or cytokines (granulocyte-macrophage colony stimulating factor)[12–14]. Anyway, approach to curative treatment is still not well established. Recently, laser therapy has proved successful in the prevention and treatment for CT-induced OM[15]. Laser light works through biostimulation: giving energy to mitochondria, photons are converted into adenosine triphosphate thus increasing DNA and RNA synthesis and cellular metabolism providing a reduction in symptoms and of the average healing time[16]. Laser light also stimulates vascular endothelial growth factor gene expression and neo-angiogenesis, collagen, serotonin, and cortisol production. All these effects accelerate healing time, cause reduction in pain and inflammation[17,18]. The efficacy of laser biostimulation in the treatment for OM is described in the literature in paediatric patients undergoing CT[19,20], but there is only one RCT about low-power laser therapy (LPLT) in paediatrics with a small number of patients, and no such studies have been conducted in Italy[21]. Moreover, the literature is conflicting with regard to laser devices and laser protocols that can be employed.

In the present study, high wavelength (970 nm) and high power (5 W, pulsed 50%) through a class IV laser device have been employed. According to the literature, analgesic and anti-inflammatory effects are obtained with wavelengths between 600 and 1000 nm[22], whereas biostimulatory effects of LPLT are obtained with less powerful protocols (<1W)[23]. High power has been used to provide a faster healing of lesions, as proved in previous works about inflammatory conditions[24,25]. Moreover, according to recent publication by Ottaviani *et al.*, HPLT induces better healing, reduced inflammation, and limited thermal damage along with maintained tissue integrity, as compared to traditional LPLT[26]. Anyway, this is the first study that experiments the use of a class IV laser device in paediatric patients affected by OM.

Class IV laser protocols are associated with several advantages. First of all, providing high power to tissues, a great amount of energy can be provided in a limited amount of time, which also copes with the necessity of being fast with paediatric patients that are not always compliant. Secondly, the effective amount of energy that reaches tissues after dispersion of it is higher. In fact, thanks to the characteristics of our device, a narrow divergence allows minimum dispersion of energy, even if irradiation is not perfectly orthogonal.

Also, a defocused mode was used. This means that a pre-determined amount of energy was given to the whole oral cavity for three different reasons: (i) both the preventive and the therapeutical strategies options were employed at the same time; (ii) the technique was less operator dependent; (iii) distal areas in the oral cavity (e.g., soft palate) could be reached although not orthogonally.

Unfortunately, OM is associated with painful complications such as difficulty in swallowing, chewing and phonation, as well as to superinfections and sepsis[27]. In the present study, the majority of patients (61%) suffered from difficulties in oral feeding and from pain due to the presence of ulcerations and erythema as well as from moderate to severe pain. All patients experienced a statistically significant decrease in pain sensation the day after the first laser application, both in case of high WHO values and in less severe OMs. On Day 11, complete healing and regression of pain were obtained (Fig. 3).

The transient sensation of burning referred by half of the patients was described as well tolerated and bearable thus we can affirm that class IV laser therapy was associated with no apparent side effects following the present protocol.

In the present study, all patients perceived a great improvement in all lesions and functional capacity (Table 3). This can be attributed to the anti-inflammatory effect provided by HPLT and by associated reduction in pain due to antalgic function. Alteration of saliva (described as 'dense and abundant' or as 'missing') was not statistically significantly influenced by HPLT. Anyway, this can be attributed to the small sample.

As regards improvement in oral hygiene performing, no significant differences between Days 1 and 11 were showed, but more than a

half patients referred an improvement in performing mouth cleaning. Considering the fact that the maintenance of a good oral status is associated with less frequent and less severe OMs, we believe that this result is withstanding[28].

Several risk factors related to the host organism such as age, gender, nutritional status, type of disease, xerostomia, previous damage to the oral cavity, poor oral hygiene, and genetic pre-disposition influence the development and severity of OM[29]. Particularly, toxic CT agents used to treat lymphomas and ALL are drugs acting at S-phase, such as methotrexate and cyclophosphamide[30]. The combination of these factors may trigger OM in any part of the oral cavity and oropharynx, although the most affected areas are floor of the mouth, buccal mucosa, and sides of tongue, due to the absence of keratinic coat. In the present study, ulcerations and erythema were reported in all examined areas (Table 4). The non-significant differences showed in some areas can be motivated by the reduced number of patients enrolled and by the reporting of a few ulcerations/areas of erythema for each area of the oral cavity. Undoubtedly, looking at percentages in Table 4, it is clear that HPLT has played an active and beneficial role in reducing/healing ulcerations/erythema in all sites examined. Probably, a larger sample would have reached the cut-off levels of significance. Consequently, laser therapy can be considered a valuable treatment strategy in all areas of oral cavity. Once again, this is in favour of the use of defocused mode and to employment of high amounts of energy.

Despite the present study shows encouraging results and is quite innovative, it undoubtedly has some limitations. First of all, it lacks of a control group; therefore, we cannot exclude the spontaneous improvement in lesions. Anyway, the literature shows spontaneous healing of CT-related OM in about 2–3 weeks, which is much longer than what we have evidenced in the present study[8,9]. Moreover, the possible role of neutropenia has to be hypothesized among factors influencing the spontaneous healing of OM. For this reason, we have evaluated patients' neutrophils/WBC count at each time point and gathered that although statistical significance was found between Day 1 and Day 11, as well as between Day 4 and Day 11, counts did not vary significantly between Days 1 and 4 (Table 5). This is in favour of the efficacy of laser therapy. Secondly, it would have been ideal to start HPLT on the exact day of OM's onset. This was not possible because patients were from different cities, sometimes far from Trieste, and were only referred to the oral pathologist when OM had become unbearable. Anyway, all patients were treated within 7.5 ± 3 days after the end of CT, which usually corresponds to the period of peak severity. Moreover, this is the first study about the use of HPLT in paediatric patients affected by OM, so further studies will be necessary to confirm our hypothesis. To mention, we have decided to evaluate the efficacy and safety of HPLT in a small sample of patients before starting a multicentric double-blind RCT that has currently been started in eight onco-haematology department all over Italy.

Conclusions

CT-related OM can affect patients' feeding capacity and impoverish their life quality. In fact, it is considered the most debilitating side effect of CT. The great evidence provided in the literature of the efficacy of laser therapy in the treatment for OM, in association with the characteristics of such therapy – easiness, atraumaticity, and safety – allow you to consider laser therapy an effective approach to curative treatment. Although the present study enrolled a reduced number of patients, to our knowledge, no studies have ever considered a larger sample in a paediatric population before. Moreover, the great results obtained both in objective healing of OM and above all in reduction in pain pave the way to account HPLT as a possible standard treatment for CT-induced OM.

The striking importance of laser therapy lies not only in its efficacy in healing lesions, but above all in the possibility of eliminating pain and reducing complications related to OM also

accompanied by the great advantages provided by its safety and easiness. The absence of side effects and the wide variety of beneficial effects of therapy – biostimulation, antiinflammation, antimicrobic, and antalgic – strongly encourage to consider HPLT part of everyday practise in the management of oncological paediatric patients affected by OM.

Why this paper is relevant

- M represents painful side effects of cancer therapy that can interfere with therapy schedule and effectiveness. Nowadays, no recommendations over a standard treatment have been provided;
- The present paper describes a safe, non-invasive, and predictable technique to manage OM;
- The therapy described is beneficial not only in reducing the dimension of lesions but also above all in relieving pain.

Conflict of interest

We certify that there is no conflict of interest, nor financial support with any organisation regarding the material discussed in the manuscript.

Written informed consent and ethical principles

Experiments were undertaken with the understanding and written consent of each subject and in full accordance with ethical principles.

The study has been independently reviewed and approved by an ethical board.

References

1 Cheng KK, Lee V, Li CH *et al.* Oral mucositis in pediatric and adolescent patients undergoing chemotherapy: the impact of symptoms on quality of life. *Support Care Cancer* 2012; **20**: 2335–2342.

2 AIRTUM Working Group; CCM; AIEOP Working Group. Italian cancer figures, report 2012: cancer in children and adolescents. *Epidemiol Prev* 2013; **37** (Suppl. 1): 1–225.

3 Cauwels RG, Martens LC. Low level laser therapy in oral mucositis: a pilot study. *Eur Arch Paediatr Dent* 2011; **12**: 118–123.

4 Worthington HV, Clarkson JE, Bryan G *et al.* Interventions for preventing oral mucositis for patients with cancer receiving treatment. *Cochrane Database Syst Rev* 2011; **13**:CD000978.

5 Clarkson JE, Worthington HV, Furness S *et al.* Interventions for treating oral mucositis for patients with cancer receiving treatment. *Cochrane Database Syst Rev* 2010; **4**: CD001973.

6 Scardina GA, Pisano T, Messina P. Oral mucositis. review of literature. *N Y State Dent J* 2010; **76**: 34–38.

7 Otmani N, Alami R, Hessissen L *et al.* Determinants of severe oral mucositis in paediatric cancer patients: a prospective study. *Int J Paediatr Dent* 2011; **21**: 210–216.

8 Cheng KK, Lee V, Li CH *et al.* Incidence and risk factors of oral mucositis in paediatric and adolescent patients undergoing chemotherapy. *Oral Oncol* 2011; **47**: 153–162.

9 Lopez M, Gebbia N, Cascinu S *et al.* Oncologia Medica Pratica. 3a edizione, Società Editrice Universo, parte XIII, chapter. 117, 3196–3201.

10 Miller MM, Donald DV, Hagemann TM. Prevention and treatment of oral mucositis in children with cancer. *J Pediatr Pharmacol Ther* 2012; **17**: 340–350.

11 Sonis ST. The pathobiology of mucositis. *Nat Rev Cancer* 2004; **4**: 277–284.

12 Peterson DE, Ohrn K, Bowen J *et al.* Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). Systematic review of oral cryotherapy for management of oral mucositis caused by cancer therapy. *Support Care Cancer* 2013; **21**: 327–332.

13 Ryan AJ, Lin F, Atayee RS. Ketamine mouthwash for mucositis pain. *J Palliat Med* 2009; **12**: 989–991.

14 Feller L, Essop R, Wood NH *et al.* Chemotherapy- and radiotherapy-induced oral mucositis: pathobiology, epidemiology and management. *SADJ* 2010; **65**: 372–374.

15 Cunha CB, Eduardo FP, Zezell DM *et al.* Effect of irradiation with red and infrared laser in the treatment of oral mucositis: a pilot study with patients undergoing chemotherapy with 5-FU. *Lasers Med Sci* 2012; **27**: 1233–1240.

16 Bjordal JM, Bensadoun RJ, Tunèr J *et al.* A systematic review with meta-analysis of the effect of low--level laser therapy (LLLT) in cancer therapy-induced oral mucositis. *Support Care Cancer* 2011; **19**: 1069–1077.

17 Basso FG, Oliveira CF, Kurachi C *et al.* Biostimulatory effect of low-level laser therapy on keratinocytes in vitro. *Lasers Med Sci* 2013; **28**; 367–374.

18 Kujawa J, Zavodnik L, Zavodnik I *et al.* Effect of low-intensity (3.75-25 J/cm2) near-infrared (810 nm) laser radiation on red blood cell ATPase activities and membrane structure. *J Clin Laser Med Surg* 2004; **22**: 111–117.

19 Rimulo AL, Ferreira MC, Abreu MH *et al.* Chemotherapy-induced oral mucositis in a patient with acute lymphoblastic leukaemia. *Eur Arch Paediatr Dent* 2011; **12**: 124–127.

20 Abramoff MM, Lopes NN, Lopes LA *et al.* Low-level laser therapy in the prevention and treatment of

chemotherapy-induced oral mucositis in young patients. *Photomed Laser Surg* 2008; **26**: 393–400.
21 Kuhn A, Porto FA, Miraglia P *et al.* Low-level infrared laser therapy in chemotherapy-induced oral mucositis: a randomized placebo-controlled trial in children. *J Pediatr Hematol Oncol* 2009; **31**: 33–37.
22 Karu TI, Afanas'eva NI. Cytochrome c oxidase as the primary photoacceptor upon laser exposure of cultured cells to visible and near IR-range light. *Dokl Akad Nauk* 1995; **342**: 693–695.
23 Chung H, Dai T, Sharma SK *et al*. The nuts and bolts of low-level laser (Light) therapy. *Ann Biomed Eng* 2012; **40**: 516–533.
24 Gobbo M, Ottaviani G, Mustacchi G *et al.* Acneiform rash due to epidermal growth factor receptor inhibitors: high-level laser therapy as an innovative approach. *Lasers Med Sci* 2012; **27**: 1085–1090.
25 Gobbo M, Ottaviani G, Bussani R *et al.* Methotrexate-induced oral mucositis in rheumatoid arthritis disease: therapeutic strategy in a case report. *Photonics Lasers Med* 2013; **2**: 71–76.
26 Ottaviani G, Gobbo M, Sturnega M *et al.* Effect of Class IV laser therapy on chemotherapy-induced oral mucositis: a clinical and experimental study. *Am J Pathol* 2013; **183**: 1747–1757.
27 Markiewicz M, Dzierzak-Mietla M, Frankiewicz A *et al.* Treating oral mucositis with a supersaturated calcium phosphate rinse: comparison with control in patients undergoing allogeneic hematopoietic stem cell transplantation. *Support Care Cancer* 2012; **20**: 2223–2229.
28 Kashiwazaki H, Matsushita T, Sugita J *et al.* Professional oral health care reduces oral mucositis and febrile neutropenia in patients treated with allogeneic bone marrow transplantation. *Support Care Cancer* 2012; **20**: 367–373.
29 Anthony L, Bowen J, Garden A *et al.* New thoughts on the pathobiology of regimen- related mucosal injury. *Support Care Cancer* 2006; **14**: 516–518.
30 Maddireddy U, Rao N, Gogula VR *et al.* Chemotherapy-induced and/or radiation therapy–induced oral mucositis—complicating the treatment of cancer. *Neoplasia* 2004; **6**: 423–431.