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Systematic Review of Laser and Other Light Therapy for the Management of Oral Mucositis in Cancer Patients

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Systematic review of laser and other light therapy agents for the prevention and management of oral mucositis in cancer patients.

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Abstract

Background: The aim of this study was to review the available literature and define clinical practice guidelines for the use of laser and other light therapies for the prevention and treatment of oral mucositis.

Methods: A systematic review was conducted by the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer / International Society for Oral Oncology (MASCC/ISOO). The body of evidence for each intervention, in each cancer treatment setting, was assigned an evidence level. Based on the evidence level, one of the following three guideline determinations was possible: Recommendation, Suggestion, No guideline possible.

Results: A recommendation was made for low level laser (wavelength at 650 nm, power of 40 mW, and each cm2 treated with the required time to a tissue energy dose of 2J//cm2) for the prevention of oral mucositis in adult patients receiving hematopoietic stem cell transplantation conditioned with high-dose chemotherapy with or without total body irradiation. A suggestion was made for low level laser (wavelength around 632.8 nm, the power of 10-60 mW, and each cm2 treated with the required time to a tissue energy dose of 2j/cm2) for the prevention of oral mucositis in patients undergoing radiotherapy for head and neck cancer. No guideline was possible for other light sources such as infra-red LED and broad band visible light therapy, due to insufficient evidence.

Conclusions Best evidence available supports the use of GaAlAs at 650 nm wavelength at low intensity of 40 mW and each cm2 treated with the required time to a tissue energy dose of 2J/cm2 for the prevention of oral mucositis in HSCT patients. Additional lasers and other light sources were reported to be effective in similar wavelengths range and intensities. Well-designed research is needed to evaluate the oral mucositis prevention and treatment efficacy of other laser wavelengths and light therapy in other cancer treatment settings.

Keywords: oral mucositis, stomatitis, laser therapy, LLLT, LED, oral complications of cancer therapy, mucositis prevention, mucositis treatment

Introduction

This manuscript is part of a collaborative effort of the Multinational Association of Supportive Care in Cancer (MASCC) mucositis study group to update the existing guidelines for the prevention and treatment of oral mucositis in cancer patients. The original and last update of the guidelines in 2004 and 2007 respectively [1,2] reviewed the various therapies for mucositis, including the use of low level laser therapy (LLLT). [3]

LLLT is based on the interaction of light at low energy density, a few J/cm^2, with cells and tissues without the generation of thermal effects. This type of therapy is believed to promote photochemical, photophysical and photobiological effects in cells and tissues, without causing temperature rise above 98^o F. It is believed that the biomodulation effect over cells and tissues occurs due to the absorption of the laser light by endogenous photoreceptors.[4] In 1989, a review of several *in vitro* studies [5] revealed that primary phothoactivated receptors are components of the cellular respiratory chain. The activation of these receptors could lead to the stimulation or inhibition of the cellular metabolism, depending on the energy dose of light. Low energy doses could regulate the production of reactive oxygen species (ROS). It is known that the radiation wavelength can be beneficial to cells and tissues, [4] but there is uncertainty on how this happens. Visible light can lead to photochemical changes in the photoreceptors in the mitochondria, altering cell metabolism and producing a transduction effect in other cell components (biomodulation effect). [5] Others suggest that this effect is due to photo physical changes on the Ca++ channels in the cell membrane .[6]

At the time of the last MASCC/ISOO mucositis guidelines review,[3] studies testing laser therapy were few. Variable protocols for preventing and treating mucositis, the large

variation in the wavelength used, the technique used to deliver laser to tissues, and the use of diverse mucositis-grading tools did not allow for conclusive results making it impossible to standardize a particular protocol. Although the results were encouraging, no recommendation for the use of the LLLT was possible. As part of a comprehensive update of the MASCC/ISOO clinical practice guidelines for mucositis, the aim of this project was to systematically review the available literature and define evidence-based clinical practice guidelines for the use of laser and other light therapy devices for the prevention and treatment of oral mucositis.

Methods

The methods used in this systematic review are described in detail in Bowen et al. [[ref in this issue]] and Elad et al. [[ref in this issue]]. Briefly, a literature search for relevant papers indexed before 31st December 2010 was conducted using OVID/MEDLINE, with papers selected for review based on defined inclusion and exclusion criteria.

Selected papers were reviewed by two independent expert reviewers and data was extracted using a standard electronic form. Studies were scored for their Level of Evidence based on Somerfield criteria [7] and flaws were listed according to Hadorn criteria. [8] A well-designed study was defined as a study with no major flaws per the Hadorn criteria. [8]

Findings from the reviewed studies were integrated into guidelines based on the overall Level of Evidence for laser and other light therapy agents. Guidelines were classified into 3 types: recommendation, suggestion, and no guideline possible. Guidelines were separated based on 1) the aim of the intervention (prevention or treatment of mucositis); 2) the treatment modality (radiotherapy, chemotherapy, chemo-radiotherapy, or high dose conditioning therapy for hematopoietic stem cell transplant), and 3) the route of administration of the intervention, when applicable.

The list of intervention keywords used for the literature search of this section included oral mucositis or stomatitis AND lasers, laser, LLLT, low level laser therapy, light therapy, phototherapy, low-level laser, LED, light-emitting diode, diode, visible light, He-Ne, InGaAlP, GaAlAs, InGaAs, CO2, and infra-red.

Results

The literature search identified a total of 692 papers from which a total of 24 clinical trials were included for final review. [9-32] The literature review process can be seen in Figure 1.

HSCT induced oral mucositis

A recommendation was possible for laser therapy in the wavelength around 650 nm, the intensity of 40 mW, and each cm2 treated with the required time to a tissue energy dose of 2J/cm2 for the prevention of mucositis in HSCT. This guideline is based on the combination of one well-designed randomized clinical trial with no major flaws [11] together with a series of studies reporting positive results with laser in a similar range of wavelength which were classified as lower level of evidence.

The pivotal trial evaluated the efficacy of two different low level Gallium Aluminum Arsenide (GaAlAs) diode lasers, 650nm and 780nm wavelengths in the prevention of oral mucositis in Hematopoietic Stem Cell Transplantation (HSCT) patients conditioned with chemotherapy or chemoradiotherapy. [11] Patients with clinically normal oral mucosa received intra-oral laser irradiation in several areas of the mucosa, with energy densities of $2J/cm^2$. Because of the preventive nature of the study, laser treatment began on the first day of the conditioning and continued through day +2 post HSCT. It was observed that the severity of oral mucositis score in patients treated with the 650nm laser were reduced, compared with placebo, and the 780nm laser groups ($p=0.06$). Of importance is the fact that patients in the 650 nm group statistically significantly likely received total body irradiation (TBI) thus a more aggressive therapy protocol. An

adjusted statistical test for TBI showed that the difference in mucositis severity on day 11 post HSCT was statistically significant (p=0.03). Laser therapy was well-tolerated and no adverse events developed.

In contrast to the above mentioned guideline, no guideline was possible for laser as a treatment of oral mucositis in HSCT patients. A single study with mixed cancer population [17] was insufficient to allow for a stronger guideline.

Two non-laser light-therapy devices were reported in the literature for the prevention of oral mucositis in HSCT patient population: LED and broad band visible light therapy. [18,19] Since it is unclear at present whether these modalities have the same mechanism as laser therapy, each was referred separately. As to LED, there are accumulating data showing that there is no difference in the interaction of a laser and a LED with the human tissue. [33-37] These studies showed positive effects in prevention and treatment of oral mucositis but represent initial investigations of new light technologies and with the available information no guideline was possible.

Radiotherapy induced oral mucositis

A suggestion was possible for the laser therapy in the prevention of oral mucositis in patients undergoing radiotherapy for head and neck cancer. This guideline is based on 3 studies showing positive results with laser therapy in the wavelength of 632 nm. [21-23] However, all three studies had major and minor flaws which did not allow for a recommendation.

Radio-chemotherapy induced oral mucositis

No guideline was possible for laser therapy in the prevention and or treatment of oral mucositis in patients treated with combined protocol of radio-chemotherapy for head and neck cancer. Studies were inconsistent in demonstrating effectiveness of laser therapy. [24-26] In addition, major flaws in study design reduced the overall level of evidence to IV.

Chemotherapy induced oral mucositis

No guideline was possible for this category either for prevention of treatment of mucositis using laser therapy or LED.

Discussion

This systematic review confirmed that the number of clinical trials assessing the use of laser and other light therapies in the prevention and control of oral mucositis is growing. However, it is important to keep in mind that the data presented in this review results from the use of a variety of low level laser and other light devices that operate in different wavelengths and are applied to tissues using a variety of protocols. All devices were within the range considered to be low-level laser (10-200 mW) (Table 1). Laser application protocols vary greatly and, therefore, conclusions cannot be applied separately for each of the individual laser devices.

Based on the current scientific information, the panel was able to reach the following decision: "The panel recommends that, for centers able to support the necessary technology and training, LLLT be used to prevent oral mucositis, using a low level laser. Best evidence support the following protocol: 650nm, with the intensity of 40mW and each cm2 treated with the required time to a tissue energy dose of 2J//cm2 to the oral mucosa in HCT adult population receiving high-dose CT with or without TBI. [11] This represents an improvement from previous guidelines in which the use of laser therapy was only a suggestion and that new evidence from additional randomized trials was necessary before a recommendation could be made [1,2], reflecting the growing interest in the use of these devices in oral mucositis.

The recommendation above is supported by two Cochrane meta-analysis that evaluated prevention and treatment of oral mucositis with LLLT. The Cochrane *prevention* meta-analysis [38] found two studies [13,15] that were considered level III evidence showing 80% reduction in the incidence of severe mucositis in HSCT. However these

studies had major flaws by the Hadorn criteria and therefore, could not be considered for a recommendation by the panel. In addition, the Cochrane *treatment* meta-analysis [39] presented two additional studies [17,20] with statistically significant benefits for LLLT in oral mucositis but had major flaws by Hadorn criteria.

To emphasize the growing body of evidence in favor of LLLT in oral mucositis, several relevant late-breaking publications have been added to the laser-oral mucositis literature since the time we completed the literature search in December 2010. A systematic review with meta-analysis concluded that there is consistent evidence from small high-quality studies (mostly also included in the present review) that red and infrared LLLT can partly prevent development of cancer therapy-induced OM. LLLT significantly reduces pain, severity, and duration of symptoms in patients with OM. [40] Additional data from a trial with near-infrared light-emitting diodes applied extraorally in children and adults with hematological malignancies and solid tumors treated with HSCT demonstrated that the technology can significantly reduce patient-reported pain. [41] A recent randomized study in patients with malignancies treated with HSCT confirmed that oral mucositis incidence and severity can be reduced with LLLT. [42]

Late-breaking studies showed positive outcomes of prevention and treatment of oral mucositis in head and neck cancer populations being treated with radiation therapy [43], and in prevention of oral mucositis in head and neck cancer populations being treated with concurrent chemoradiation confirming that this technology seems to be effective in controlling the appearance and severity of oral mucositis, its associated pain, and it can also have beneficial effects on quality of life. [44,45] [42]

Indication	Laser type	Type of light therapy	Wave-length (nm)	Laser setting (power, energy, time; or intensity,, energy)	Route of Application (Intra/ Extra-oral)	Treatment Modality *(HSCT w/wo TBI, CT, H&N RT, or mixed)*	Patient population	Reference (author, year)	Effectiveness	Overall level of evidence	Guideline	Comments
P	HeNe	Laser	632.8	60mW; 1.5J/cm2, 10 sec	IO	HSCT w TBI	Adult	Cowen 1997[9]	Y - III	II	Recommendation	He-Ne Laser decreases severity but not incidence of OM
	HeNe	Laser	632.8	25mW; 1J/cm2, 40 sec	IO	HSCT w/wo TBI	Adult	Barasch 1995[10]	Y - III			He-Ne Laser decreases severity but not incidence of OM
	GaAlAs	Laser diode	650 / 780	40/60mW; 2J/cm2, [a]	IO	HSCT w/wo TBI	Adult	Schubert 2007[11]	Y - II			Diode 650 nm 2J / cm^2 LLLT reduces OM severity
	GaAlAs	Laser diode	660	10mW 2.5J/cm2, 10 sec	IO	HSCT w/wo TBI	Adult	Jaguar 2007[12]	Y - III			Laser increased time of OM appearance, reduced time of pain and morphine use
	GaAlAs	Laser diode	780	60mW; 4J/cm2, time-NS	IO	Mixed: HSCT* & CT	Pediatric	Cruz 2007[13]	N – III			No evidence of benefit from the prophylactic use of low energy laser in patients with cancer on chemotherapy who received optimal dental and oral care.
	InGaAlP	Laser diode	660	40mW; 4/6J/cm2, time-NS	IO	HSCT w/woTBI	Mixed	Eduardo 2009[14]	Y – IV			OM measured by WHO scale was maintained at grades I and II in 22/30 patients, grade III in 7 and IV in 1, in HSCT patients receiving high-dose CT
	InGaAlP	Laser diode	660	50mW; 4J/cm2, 16.7 sec	IO	HSCT w/woTBI	Adults	Antunes 2007[15]	Y - III			Preventive use of Laser in HSCT patients is a powerful instrument in reducing the incidence of OM
	InGaAlP / GaAlAs	Laser diode	660 / 780	25mW; 6.3J/cm2, 10 sec	IO	Mixed: HSCT w/wo TBI & CT	Adults	Khouri 2009[16]	Y - III			LLLT – lower frequency, progression, and severity of OM
T	GaAlAs	Laser diode	830	100mw; 4J/cm2, [b]	IO	Mixed: HSCT[d] & CT	Pediatric	Kuhn 2009[17]	Y - III	III	No guideline possible	encourage pediatric oncologists to use laser therapy as first-line option for children with

												chemotherapy-induced OM.
P	LED	Light emitting diode	670	56mW/cm2 4J/cm2, 71 sec	EO	HSCT w/woTBI	Mixed	Whelan 2002[18]	Y – III	III	No guideline possible	Although more studies are needed, LED therapy appears useful in the prevention of OM in pediatric HSCT patients
P	Visible light	Visible light	400-1200	165-200mW/cm^2 9-18J/cm2, 45-90 sec	IO	HSCT [d]	Adult	Elad 2011[19]	Y - III	III	No guideline possible	Broad band visible light therapy is safe and effective in the prevention of oral mucositis in HSCT patients.
T	NS		NS	100mW for "laser"; 50, 250,500mW for "infra-red", 2 J/cm2, 33 sec	IO	HSCT w/wo TBI	Adult	Genot-Klastersky 2008[20]	Y - III	III	No guideline possible	Therapeutic laser therapy is beneficial for patients undergoing HSCT in delaying the development of OM grade 3. in reducing the
P	HeNe	Laser	632.8	60mW; 2J/cm2, 3 sec	IO	RT of H&N	Adult	Bensadoun 1999[21]	Y - III	III	suggestion	He-Ne effective in preventing RT OM
	HeNe	Laser	632.8	10mW; 1.8J/cm2, 3 min	IO	RT of H&N	Adult	Arun Maiya 2006[22]	Y -III			OM healing time reduced Effective for P & T
	HeNe	Laser	632.8	10mW; 1.8J/cm2, [b]	EO & IO	RT of H&N	Adult	Arora 2008[23]	Y - III			Significant reduction of OM grade in study group
P	InGaAlP	Laser diode	685	35mW; 1.1J/cm2, 32 sec	IO	CT/RT of H&N	Adult	Kelner 2007[24]	N - IV	IV	No guideline possible	LLLT and Chlorhexidine have similar effects
	InGaAlP	Laser diode	660	30mW, 2 J/cm2, time-NS	IO	CT/RT of H&N	Adult	Zanin 2010[25]	Y - IV			Improves quality of life and decreases incidence of OM in patients with H & N cancer treated with CT and RT
	NS		830	60mW; 12J/cm2, time-NS	IO	CT/RT of H&N	Adult	Lima 2010[26]	Y - IV			Delayed appearance of OM. Similar results for LLLT and Aluminun Hydroxide
T	GaAlAs / InGaAlP	Laser diode	808 / 660	40mW; 6J/cm2, 6 sec	IO	CT/RT of H&N	Mixed	Simoes 2009[27]	N - IV	IV	No guideline possible	Laser applied 3/week maintains oral mucositis to grades 1 and 2. Not enough information to allow for a conclusion

P	GaAlAs	Laser diode	685	35mW; 2J/point 70J/cm2, 54 sec	IO	CT	Mixed	Abramoff 2008[28]	Y - IV	IV	No guideline possible	LLLT has both a preventive and a therapeutic role in those prone to develop OM
	NS		NS	100mW for "laser"; 50, 250,500mW for "infra-red", 2 J/cm2, 33 sec	IO	CT	Adult	Genot-Klastersky 2008[20]	Y - III			Preventive laser therapy in beneficial in reducing the occurrence and intensity of OM in patients with solid tumors who have had previous mucositis
T	NS		830	45-50mW; 0.7-0.8J/cm2, 10-30 min [c]	IO	CT	Adult	Wong 2002[29]	Y - IV	IV	No guideline possible	Reduced incidence and severity of OM
	GaAlAs		685	35mW; 2J/point 70J/cm2, 54 sec	IO	CT	Mixed	Abramoff 2008[28]	Y - IV			pain relief and possible decrease in the severity of OM
	InGaAlP		660 / 830	100mW; 2J/cm2, time-NS	EO	CT	Pediatric	Moraes 2009[30]	Y – IV			Both 830 and 660nm lasers improved healing of oral mucositis with extra-oral application in pediatric patients with established oral mucositis
	AsGaAl	Laser diode	830	250mW; , 35 J/cm2, [e]	IE	CT	Adult	Nes 2007	Y-IV			Study aimed at the analgesic effect only
T	LED		645±15	7.8mW; 0.99J/cm2, 5 min [c]	IO	CT	Adult	Corti 2006[31]	Y – V	V	No guideline possible	The median healing time was 1.7 and in 7 L+ patients, was shorter than in the L- group. The healing rate increased
T	NS		660	30mW; 2J/cm2, 66 sec	IO	Mixed: RT of H&N & CT	Mixed	Sandoval 2003[32]	Y - IV			beneficial effects on the management of oral mucositis, improving the quality of life

NS – not specified, P – prevention, T – treatment, IO – intra-oral, EO – extra-oral, HSCT – hematopoietic stem cell transplantation, w – with, wo – without, TBI – total body irradiation, CT – chemotherapy, H&N – head and neck, RT – radiotherapy, Y – yes, N – no

[a] – the Methods refer to the formula to calculate the time for each application point (t[s]=energy [J/cm2] X surface area [cm2]/Power [W]); the surface area was measured per patient at baseline (numeric data are not reported in the source paper).

[b] – the Methods specify “The treatment time for each application point was given by the equation t(s)=energy (J/cm2) X surface area (cm2)/Power (W); however, the surface area was not reported neither stated it was measured.
[c] – time was specified per patient session and not per point of application.
[d] – it is not specified whether conditioning regimen included TBI or not.
[e] – time was not specified
Pediatric - <17 years old

Because of the variety of laser devices and the variation in individual protocols of laser and other light applications in oral mucositis, it is important to keep in mind that the results of each individual study apply exclusively to the cancer population studied, the wavelength of the laser device, and the settings utilized in that particular study. One additional issue that might play a role in the appearance and duration of oral mucositis is the absolute neutropenia observed in cancer populations treated with myelosuppressive therapies. [46] This confounder has not been evaluated in the majority of the trials and should be included in future investigations of the applicability of LLLT in oral mucositis prevention, treatment, and associated pain.

The mechanisms by which lasers promote beneficial effects in oral mucositis are still speculative and extrapolated from other experimental models. For instance, lasers are forms of coherent light emission. New technologies like LEDs and other non-coherent light waves can also be absorbed by tissue chromophores and promote biological effects. From the data available in the literature (Table 1) it seems that all effective light-therapy devices work in similar wavelength bands concentrating around picks in 650 nm, 780 nm and 830 nm. The 650 and 780 nm fall within the "red" range and the 830 nm fall within the "near infra-red" (NIR) range. It is uncertain to what extent the difference in the wavelength of the laser devices (for example 650 vs 632.8 nm) is meaningful in terms of light-tissue interaction, however, in terms of clinical outcomes there were differences in the effectiveness of certain wavelength and settings. It should be noted, there are no studies assessing the effectiveness of laser or other type of light source in non-red or NIR range. Thus, it may be possible that additional wavelength will be effective.

With the advancement of the technology, the early high pricing laser emitting devices has been reduced considerably, making the technology readily available. Education and training of staff is another factor that must be considered when using LLLT. Most of the protocols studied require daily and long applications. However, based on the evidence available we predict that LLLT will be soon incorporated as a routine practice in the prevention and treatment of oral mucositis and its associated pain. New studies should focus on the determination of the most effective source of light, the setting of theenergy to be delivered to the tissues, and the role of other confounders like cancer type, cancer therapy, and extent of myelosuppression. The newly available blue LED bring a new potential to the management of oral mucositis and research is warranted based on the known effects of this light therapy in wound healing. [47]

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Figure1. Literature search: Flow of papers from initial identification through final selection for review.