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Guest Editorial

Low-Level Laser Therapy in the Management of Mucositis and Dermatitis Induced by Cancer Therapy

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Low-level laser therapy (LLLT)/photobiomodulation (PBM) has been consistently shown in laboratory studies to have distinct biological effects, and has a dose-dependent mechanism of action at the cellular level.[1,2] Since the introduction of LLLT/PBM in 1967, >400 randomized, double-blinded (some placebo-controlled) clinical trials have been published for multiple applications.

Although the complex biological mechanisms underlying the therapeutic effects of LLLT/PBM have not been completely elucidated, and may vary among different cell types and tissue states (healthy versus stressed or hypoxic), laboratory and clinical studies suggest that LLLT/PBM significantly reduces inflammation and prevents fibrosis.[3–8] Moreover, LLLT/PBM, when delivered appropriately, reduces pain and improves optimal function of the whole organism.[1,9–11] In addition, *in vivo* studies show that LLLT/PBM is neuroprotective and may benefit neurodegenerative diseases and neurotrauma.[12,13]

Current data suggest that LLLT/PBM acts predominantly on cytochrome C oxidase (CcO) in the mitochondrial respiratory chain by facilitating electron transport, resulting in an increased transmembrane proton gradient that drives adenosine triphosphate (ATP) production.[14] ATP is the universal energy source in living cells essential for all biologic reactions, and even a small increase in ATP levels can enhance bioavailability to power the functions of cellular metabolism. In addition, the absorption of red or near-infrared (NIR) light may cause a short, transient burst of reactive oxygen species (ROS) that is followed by an adaptive reduction in oxidative stress.

A low concentration of ROS activates many cellular processes, because ROS activates transcription factors, including nuclear factor kappa B (NF-κB), resulting in the upregulation of stimulatory and protective genes.[15] These genes generate growth factors belonging to the fibroblast growth factor family, cytokines, and chemokines that are involved in tissue repair.

In hypoxic or otherwise stressed cells, mitochondria produce nitric oxide (mtNO), which binds to CcO and displaces oxygen.[16] This binding results in the inhibition of cellular respiration, decreased ATP production, and increased oxidative stress (a state that develops when the levels of ROS exceed the defense mechanisms), leading to the activation of intracellular signaling pathways, including several transcription factors.[17] These include redox factor-1 (Ref-1), activator protein-1 (AP-1), NF-κB, p53, activating transcription factor/cyclic adenosine monophosphate (cAMP)-response element–binding protein (ATF/CREB), hypoxia-inducible factor (HIF)-1, and HIF-like factor,[18] These transcription factors induce downstream production of both inflammatory mediators, such as tumor necrosis factor-alpha (TNF-α), interleukin [IL]-1 and IL-6, cyclooxygenase (COX)-2, and prostaglandin E2 (PGE-2),[17,19,20] and anti-inflammatory mediators (transforming growth factor-beta [TGF-β] IL10). There is evidence suggesting that when LLLT/PBM is administered with appropriate parameters to stressed cells, NO is dissociated from its competitive binding to CcO, ATP production is increased, and the balance between pro- and antioxidant mediators is restored, resulting in a reduction of oxidative stress.[21] For example, LLLT/PBM has been shown to attenuate the production of ROS by human neutrophils.[22] Silveira et al.[23] reported that LLLT/PBM reduced ROS in an animal model of traumatic tissue injury; whereas a study in a model of acute lung inflammation found LLLT/PBM to reduce the generation of TNF-α and to increase IL-10, an anti-inflammatory cytokine.[24] In addition, NO is a potent vasodilator[25] and can increase the blood supply to the illuminated tissue. LLLT-mediated vascular regulation increases tissue oxygenation and also allows for greater traffic of immune cells. These two effects may contribute to the promotion of wound repair and regeneration.[17]

Analgesic effects are probably induced by additional mechanisms rather than by the increased ATP/reduced oxidative stress model. LLLT/PBM with a relatively high power density (>300 mW/cm^2), when absorbed by nociceptors, has an inhibitory effect on A and C neuronal pain fibers. This slows neural conduction velocity, reduces amplitude of compound action potentials, and suppresses neurogenic inflammation.[11]

Virtually all conditions modulated by LLLT/PBM (e.g., ulceration, inflammation, edema, pain, fibrosis, and neurological and muscular injury) are thought to be involved in the pathogenesis of chemotherapy (CT) or radiotherapy (RT)-induced complications in patients treated for head and neck cancer (HNC). For example, in an animal model of oral mucositis (OM), it was demonstrated that LLLT/PBM

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decreased COX-2 expression[26] and decreased the number of neutrophils in the inflammatory infiltrate.[27] Moreover, in the chronic sequelae of (C)RT, an excessive fibroblastic response is hypothesized to be related to acute oxidative injury, with resulting cell damage, ischemia, and an ongoing inflammatory response resulting in fibrosis.[28] The critical difference between normal wound healing and fibrosis development appears to be that in fibrosis, signalling pathways escape normal cellular regulation.[29] Reduction of fibrosis could be mediated by the beneficial effects of LLLT/PBM on the oxidant/antioxidant balance,[30] downregulation of the profibrotic TGF-β,[20] and inhibition of excessive fibroblast proliferation.[31]

Although most LLLT/PBM studies have demonstrated efficacy in management of both acutely and chronically affected tissues, not all LLLT/PBM investigations have yielded positive outcomes. As will be discussed, these divergent results may be attributed to several factors, including dosimetry. It has been observed that increasing the overall dose of LLLT/PBM may have a counterproductive effect compared with the benefits obtained with lower doses[32] Also it has been suggested that concurrent use of some medications that can inhibit healing (e.g., corticosteroids) may negatively affect the efficacy of LLLT/PBM.

Mucositis

Oral mucositis (OM) affects virtually all patients undergoing chemoradiation (CRT) for advanced HNC. Clinically, the manifestations of OM form a continuum, with erythematous mucosal changes when mild, and ulcerative lesions that expose the submucosa when severe. Its detrimental effects on quality of life (QoL) and functional status are significant.[33]

The current understanding of OM is largely based on animal models, which have shown the multifactorial nature of the condition and have implicated a cascade of interrelated events in multiple tissue regions. These observations congealed into the five-phase model of OM, based on the sequence of events following cytotoxic treatment.[34] The formation of excessive ROS and activation of NF-κB are the key factors in its pathobiology. Subsequent studies implicated microvascular injury, formation of proinflammatory cytokines, host–microbiome interactions, and extracellular matrix alterations in mucositis pathogenesis.[35] In addition, epidermal growth factor receptor (EGFR) inhibitors and tyrosine kinase receptor inhibitors (TKI) administered as single drugs or combined with CRT may enhance OM or cause additional symptoms. Effective management options for OM are still scarce,[36] and pain control is typically inadequate.[33]

A Cochrane meta-analysis concluded that LLLT/PBM may prevent severe OM.[37] A systematic review and meta-analysis of 11 CRTs in HNC patients treated with CT and/or RT concluded that there was consistent evidence that LLLT/PBM applied with doses of 1–6 J per point reduced OM prevalence, severity, and duration, and its associated pain.[38] Another meta-analysis including randomized controlled trials (RCTs) in various cancer treatment settings showed that LLLT/PBM reduced OM risk and decreased its severity and duration.[39] The efficacy appeared to be similar for red (630–670 nm) and NIR (780–830 nm) light, although the optimal doses seemed to vary between these wavelengths. The Clinical Practice Guidelines of the Multinational Association of Supportive Care in Cancer and International Society for Oral Oncology (MASCC/ISOO) Mucositis Study Group found evidence for LLLT/PBM prevention of OM in patients undergoing HSCT, and patients treated with RT for HNC.[36] Evidence was derived from high-quality studies using specific LLLT/PBM parameters, and the authors noted that there remains a need to identify optimal LLLT/PBM parameters including energy density, ideal timing of laser application, variations in cancer type, and cancer treatment regimens.

Based on this evidence and on our experience, we propose the following regimen for the management of OM (and mucositis affecting the oropharynx): wavelength of 633–685 nm, or 780–830 nm; power output of between 10 and 150 mW; energy density 2–3 J/cm^2 and $\leq$6 J/cm^2 on the tissue surface treated; frequency of two to three times a week up to daily; and successive applications on single spots on a lesion rather than a scanning motion over the entire lesion. Extraorally administered LLLT/PBM may be effective for the management of OM of the buccal mucosa, vestibule, and inner epithelial surfaces of the lips. This could be applied in combination with an intraoral device (Table 1).

Dermatitis

Radiation dermatitis occurs in the majority of patients treated with RT.

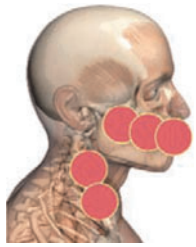
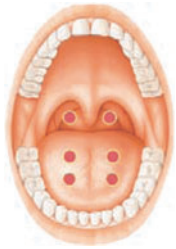
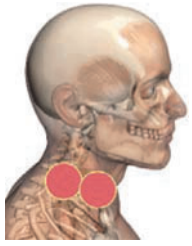
The pathobiology of acute radiation dermatitis is complex. Irradiation of the skin leads to direct tissue injury and inflammatory cell recruitment, involving damage to epidermal basal cells, endothelial cells, and vascular components. Radiation-induced generation of free radicals induces DNA injury and release of inflammatory cytokines (mainly IL-1 and IL-6). This process leads to development of erythema, edema, and possible ulceration. Late RT-induced changes in the skin are characterized by the disappearance of follicular structures, an increase in collagen and damage to elastic fibers in the dermis, and a fragile epidermal covering.[40] TGF-β is considered to play a central role in mediating RT-induced tissue fibrosis.[29,41,42]

The severity of skin reactions is dependent on the total radiation dose, the dose per fraction, the overall treatment time, beam type and energy, the surface area of the skin exposed to radiation, the use of combined chemoradiotherapy with or without targeted therapies, and individual risk factors. The severity of acute reactions has been shown to predict late effects. Radiation dermatitis impacts adversely on cosmesis and function, especially in patients with secondarily infected irradiated skin, and reduces QoL.

Patients with squamous cell carcinoma (SCC) of the head and neck treated with an EGFR inhibitor may develop an acneiform skin rash in addition to radiation dermatitis.[40]

Based on the effects of LLLT/PBM on the epidermis and dermis (reduced inflammation and improved wound healing), and on the shared similarities in pathobiology with OM, it seems reasonable to assume that LLLT/PBM may reduce the severity and/or prevalence of radiation dermatitis.[43,44] DeLand et al.[45] reported that LED treatments immediately after intensity-modulated radiation therapy (IMRT) reduced the incidence of radiation dermatitis in patients with breast cancer, but Fife et al.[46] were not able to reproduce these results, although they did not specify important parameters such as irradiation time and size of area treated.

TABLE 1. PROPOSED LLLT/PBM PROTOCOLS FOR ORAL MUCOSITIS AND RADIATION DERMATITIS

Complication	*Treatment protocol*	*Treatment area*	*LLLT/PBM device characteristics and application*	*Therapeutic LLLT/PBM dose*	*Optional target tissues*
Oral mucositis	*Prophylactic:* *Chemotherapy:* Protocols vary. Start treatment the 1st day of chemotherapy or prior to therapy and continue during all course of chemo		*Extraoral:* Mixed red and IR LED cluster 20–80 mW/cm^2	*Extraoral:* 3 J/cm^2 LED cluster	*Extraoral:* Lips, cutaneous surface corresponding to the buccal mucosae, bilateral cervical lymphatic chain
	Radiotherapy: Start treatment the 1st day of radiotherapy or prior to radiation, and continue all days of radiation (no requirement regarding the timing of laser sessions, before or after radiation session) *Therapeutic:* Continue treatment at least 3 times a week until symptoms improve Daily treatment is recommended in case of severe mucositis.		*Intraoral:* 630–830 nm 20–80 mW	*Intraoral:* *Prophylactic:* 2 J per point *Therapeutic:* 4 J per point until the whole area involved is covered (2 J for prophylactic use)	*Intraoral:* For prevention–treat each of the at-risk mucosal surfaces For therapy–sites vary, depending upon the site of mucositis
Radiation dermatitis	*Prophylactic:* Start daily treatment at the initiation of radiotherapy, or with a grade 1 radiation dermatitis *Therapeutic:* Continue treatment at least 3 times a week until symptoms improve		*Extraoral:* Red laser diodes cluster, 630–680 nm, 20–150 mW/cm^2 or Mixed red and IR LED cluster 20–80 mW/cm^2	*Extraoral:* *Prophylactic:* 2 J/cm^2 for laser diodes panel, 3 J/cm^2 for extraoral LED cluster *Therapeutic:* At least 4 J/cm^2	*Extraoral:* Cutaneous surfaces on the radiation field where dermatitis is anticipated (often erythematous after RT)

Courtesy of the iGLOB group. The other members of this group are: Judith A.E.M. Zecha, Judith E. Raber-Durlacher, Joel B. Epstein, Stephen T. Sonis, Sharon Elad, Michael R Hamblin, Andrei Barasch, Cesar A. Migliorati, Dan M.J. Milstein, Marie-Thérèse Genot, Liset Lansaat, Ron van der Brink, Josep Arnabat, Lisette van der Molen, Irene Jacobi, Judi van Diessen, Jan de Lange, Ludi E. Smeele, Mark M. Schubert, and James Carroll.

LLLT/PBM, low-level laser therapy/photobiomodulation; IR, infrared; RT, radiotherapy.

Hence, extraorally administered LLLT/PBM may be effective for the management of dermatitis induced by radiation therapy of various sites (breast, pelvis, head, and neck) (Table 1).

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