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COMMENTARY

Photobiomodulation therapy in the management of oral mucositis: search for the optimal clinical treatment parameters

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Abstract
This commentary attempts to clarify the setting of photobiomodulation (BPM) therapy in the management of oral mucositis. The suggested dose range balances efficacy data with our current understanding about PBM safety. The literature about the molecular basis of photobiomodulation and its controversial relationship to malignant transformation is briefly presented.

Keywords Cancer · Oral mucositis · Photobiomodulation · Laser therapy · Light · Low-level · Treatment

Commentary

Photobiomodulation (PBM) has become a recognized therapeutic modality for a range of pathologies, including oral conditions [1] and a variety of oral complications of cancer treatments [2]. A list of oral indications for PBM in cancer patients has been proposed; however, the quality of available data varies significantly. There is, however, sufficient evidence to support the use of PBM in the management of oral mucositis [3–6]. The MASCC/ISOO clinical practice guidelines for management of oral mucositis are worded specifically regarding PBM, since the treatment parameters are a crucial factor [6].

Our understanding of PBM therapy is increasing on multiple fronts. Briefly, the main clinical effects include analgesia, anti-inflammatory effect, and accelerated wound healing [1, 7]. Evidence suggests that PBM effects are mediated by interference with the redox status of the cell and are dependent on the initial redox at time of exposure. Although the complete biological mechanisms underlying the range of these effects have not been elucidated, there is robust evidence for two specific phases of light-tissue interaction. These include a primary, direct effect of the irradiant light on biological molecules and a secondary, indirect effector response. Whereas the primary event occurs immediately after the exposure, the secondary event will occur hours to days later. Two specific primary PBM mechanisms have been documented: an intracellular pathway involving direct absorption by cytochrome C oxidase, and an extracellular pathway involving activation of growth factor, TGF-β1 [8, 9]. There is a plethora of downstream secondary biological mediators associated with PBM treatments [10]. These include growth factors (BNF, GDNF, FGF, bFGF, IGF-1, KGF, PDGF, TGF-β, VEGF); anti-inflammatory cytokines (IL-2, IL-4, IL-8, IL10); pro-inflammatory cytokines (IL-1α, IL-1β, IL-6, TNF-α, PGE2, COX2); heat shock proteins (HSP70, HSP90); matrix metalloproteinases (MMP2, MMP9); and small molecules (ATP, GSH, ROS, Ca++, NO, H+) among others. These mediators are known to participate in proliferation, differentiation, angiogenesis, immune activation, anti- and pro-apoptosis, enhanced cell survival, and tumor growth. Of critical importance

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to optimization of desired effects is the concept of specific parameters based on the biphasic dose model (Arndt-Schultz curve) in which low-dose PBM stimulates, while higher doses inhibit [11] Thus, there is increased awareness of the clinical dosing for PBM therapy [12, 13].

While data on clinical benefits in mucositis are promising, questions remain on a potential risk for transformation of pre-malignant cells or stimulation/protection of malignant cells [7, 10]. There are several studies demonstrating equivocal data on safety at the molecular or cellular level, animal models and clinical trials [7, 10]. These inconsistencies could be attributed to several factors including lack of uniformity in treatment parameters; variations in patient population (mucosal surface pigmentation, genomic determinants); cell types and conditions used in studies (oral cancer, breast cancer, liver cancer, bone cancer, hematologic cancer); and possibly exogenous factors (smoking, chemotherapy/radiotherapy late effects). Moreover, several molecular pathways outlined in PBM therapy are also implicated in malignancies. Therefore, there appears to be no clear answer currently on level of risk and relative significance compared to benefit of the treatment.

In an attempt to develop standards of safe and effective practice, PBM application settings were suggested for oral complications of chemoradiation in head and neck cancer patients [2]. The recommended parameters for the management of oral mucositis in this population were wavelength between 633 and 685 nm or 780–830 nm, power output between 10 and 150 mW, and energy density of 2–3 J/cm^2 and no more than 6 J/cm^2. It is important to recognize that these parameter ranges were based upon clinical efficacy reported in the literature, rather than upon clinical safety data [4]. This was explicitly mentioned by the authors, noting that the suggested dose range was made as a precaution due to lack of specific safety evidence [2]. In fact, multiple studies with PBM therapy for oral mucositis have used energy density above 6 J/cm^2 (reviewed in Migliorati et al. [6]). No adverse effects were reported in the immediate timeframe [4]; thus, the safety question is limited to the long-term effect of PBM, mostly due to paucity of data. Nevertheless, a recent study following the long-term effects of PBM for oral mucositis suggested it may in fact improve survival among head and neck cancer patients treated with chemoradiotherapy [14]. Another recent paper in an animal model shows the precise cellular pathway that mediates upper dose threshold PBM involving cell stress orchestrated by ATF-4. This may be used as a molecular biomarker to define clinical safety [15]. It remains to be investigated if PBM may enhance cancer therapy or potentially interfere with cancer therapy, and well-designed future clinical studies are warranted.

While clinical data on PBM use in cancer patients appear to be reassuring, the crucial factor is to insure treatment safety. It is important to note that according to the current definition PBM is a non-thermal process, and any significant tissue heating should be explicitly avoided. We suggest that clinicians use the lowest PBM dose that is clinically effective, and use all recommended safety measures. It is also suggested that until we have more specific data on tumor effects, direct exposure of the tumor site during PBM treatment be avoided. At the same time, until adequate PBM safety data becomes available from both clinical and basic science studies, investigators have an obligation to explore and provide detailed information in their publications of different PBM device settings that provide the optimal risk: benefit ratio in their settings.

In summary, current evidence suggests that PBM with light in the red or near infrared spectrum is safe and effective for the management of oral mucositis in certain patient populations and certain light settings. The suggested energy density (1–6 J/cm^2) does not exclude other settings. It is recommended to avoid the tumor site and to follow good clinical practice. As research advances, more specific recommendations in this new and exciting field will become available.

Compliance with ethical standards

Conflict of interest The study is not funded. The following author disclosed relationship to commercial companies: PA (consultation to Lumitex, Philips Research Labs, RogerSciences International; patents at Harvard University; travel expenses covered by Lumithera, Thor lasers, Weber Medical). The following authors disclosed no conflict of interest: SE, R-JB, JE, JR-D, and AB. The authors have full control of all primary data and agree to allow the journal to review their data if requested.

References

1. Arany PR (2016) Craniofacial wound healing with photobiomodulation therapy: new insights and current challenges. J Dent Res 95:977–984
2. Zecha JA et al (2016) Low-level laser therapy/photobiomodulation in the management of side effects of chemoradiation therapy in head and neck cancer: part 2: proposed applications and treatment protocols. Support Care Cancer 24:2793–2805
3. Bensadoun RJ, Nair RG (2012) Low-level laser therapy in the prevention and treatment of cancer therapy-induced mucositis: 2012 state of the art based on literature review and meta-analysis. Curr Opin Oncol 24:363–370
4. Bjordal JM, Bensadoun RJ, Tunèr J, Frigo L, Gjerde K, Lopes-Martins RAB (2011) A systematic review with meta-analysis of the effect of low-level laser therapy (LLLT) in cancer therapy-induced oral mucositis. Support Care Cancer 19:1069–1077
5. Clarkson JE et al (2010) Interventions for treating oral mucositis for patients with cancer receiving treatment. Cochrane Database Syst Rev:CD001973
6. Migliorati C et al (2013) Systematic review of laser and other light therapy for the management of oral mucositis in cancer patients. Support Care Cancer 21:333–341
7. Zecha JA et al (2016) Low level laser therapy/photobiomodulation in the management of side effects of chemoradiation therapy in head and neck cancer: part 1: mechanisms of action, dosimetric, and safety considerations. Support Care Cancer 24:2781–2792
8. Arany, P.R., et al. Photoactivation of endogenous latent transforming growth factor-beta1 directs dental stem cell differentiation for regeneration. Sci Transl Med 6, 238ra269 (2014)

9. Karu TI, Pyatibrat LV, Afanasyeva NI (2004) A novel mitochondrial signaling pathway activated by visible-to-near infrared radiation. Photochem Photobiol 80:366–372
10. Sonis ST, Hashemi S, Epstein JB, Nair RG, Raber-Durlacher JE (2016) Could the biological robustness of low level laser therapy (Photobiomodulation) impact its use in the management of mucositis in head and neck cancer patients. Oral Oncol 54:7–14
11. Huang YY, Chen AC, Carroll JD, Hamblin MR (2009) Biphasic dose response in low level light therapy. Dose Response 7:358–383
12. Jenkins PA, Carroll JD (2011) How to report low-level laser therapy (LLLT)/photomedicine dose and beam parameters in clinical and laboratory studies. Photomed Laser Surg 29:785–787
13. Tuner J, Jenkins PA (2016) Parameter reproducibility in photobiomodulation. Photomed Laser Surg 34:91–92
14. Antunes HS, Herchenhorn D, Small IA, Araújo CMM, Viégas CMP, de Assis Ramos G, Dias FL, Ferreira CG (2017) Long-term survival of a randomized phase III trial of head and neck cancer patients receiving concurrent chemoradiation therapy with or without low-level laser therapy (LLLT) to prevent oral mucositis. Oral Oncol 71:11–15
15. Khan I, Tang E, Arany P (2015) Molecular pathway of near-infrared laser phototoxicity involves ATF-4 orchestrated ER stress. Sci Rep 5:10581