Clinical use of photobiomodulation as a supportive care during radiation therapy

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Introduction

Photobiomodulation (PBM), formerly called “low-level laser therapy (LLLT),” is a non-invasive therapy used, among other indications, as a preventive or curative treatment in the management of several radiotherapy side effects. The common definition of PBM is “a mechanism by which non-ionizing optical radiation in the visible or near-infrared spectral range is absorbed by endogenous chromophores to trigger photophysical and photochemical events without causing thermal damage, resulting in physiological changes and therapeutic benefits” [1]. The wavelengths used in PBM range from red light (600–700 nm (nm)) to infrared (700–1000 nm) and the therapeutic dose is the energy density measured in joules (J/cm²) [2]. Historically, PBM was developed by NASA using single low-intensity laser beams to accelerate the regeneration of astronauts’ muscle cells [3]. Since the first findings in the 1960s, lasers have been the most used and studied device as PBM modality. The advantages of laser beams are that they are highly concentrated, collimated, monochromatic electromagnetic wave beams and have a limited frequency range, long coherence length with the possibility of high-power densities [4]. Recent years have seen the development of devices using non-coherent light sources, such as light-emitting diodes (LEDs) or broadband

lamps. LED machines have become increasingly important in the scientific literature and are now common in clinical practice. The advantages of LEDs are mobility of the device, ability to treat a large area at once, safety, and being more economical with a lower cost per mW than lasers [4].

The biological rationale of PBM is the transfer of incident photon energy to an intracellular target which then affects cellular metabolism. The main target of PBM is the mitochondria. Absorption of red to infrared light waves by the mitochondria stimulates its role in the respiratory cycle chain of electron transport. This results in direct activation of cytochrome C, a direct increase in ATP and nitric oxide (NO) production, and expression and transcription of genes involved in cell replication signaling pathways [5]. NO is a vasodilator that increases the perfusion of tissues with oxygenated blood, but also of lymphatic vessels that become dilated and less porous. In addition, PBM induces increased production of pro-collagen and growth factors, including vascular endothelial growth factors and fibroblast growth factors [6].

Recently, the indications and modalities of PBM in the management of cancer treatment-induced toxicities were the subject of international recommendations at the 12th *World Association of Photobiomodulation Therapy (WALT) Conference* in 2018 [2, 7, 8]. Our objective is to describe and discuss the current and potential indications in clinical practice of PBM as a supportive care for patients treated by radiotherapy or chemoradiotherapy, based on our clinical experience and available guidelines and published literature.

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Acute oral mucositis

Oral mucositis is an extremely common side effect. The cause of oral mucositis may be multifactorial, involving chemotherapy, radiotherapy, molecular targeted therapy, or even immunotherapy. In addition to its functional impact and obvious impairment of quality of life, mucositis is a risk factor for bacteremia and sepsis or chronic mucositis [9]. Oral mucositis can also lead to a break or a dose reduction of radiotherapy or chemotherapy, and therefore loss of chance in overall survival for the patient.

The *Multinational Association of Supportive Care in Cancer and International Society for Oral Oncology* (MASCC/ISOO) Mucositis Study Group identified high-level evidence studies that supported the clinical use of PBM to prevent or treat radiation-induced acute oral mucositis [10–17]. Of the eight published placebo-controlled randomized trials, only one was negative on its primary endpoint, while the other seven were positive in favor of PBM in the management of radiation-induced acute mucositis. Consistent findings across these randomized trials were a decrease in the incidence of grade ≥ 3 acute mucositis, a decrease in pain intensity and opioid consumption, and an improvement in quality of life. Some publications also suggested a reduction in the intensity and duration of acute mucositis, a reduction in parenteral nutrition dependence, and a functional improvement, notably in salivary flow. From a methodological point of view, these eight trials were of heterogeneous quality. Indeed, the primary endpoint was not always clear or was not specified, the time at which the outcomes were assessed was not always specified or the measurements were repeated without adequate statistical methodology. Finally, the statistical tests were often multiple leading to inflation of the α -risk and thus limiting the power of the conclusions. In contrast, validated and consensus-based scales and scores were systematically used to assess the grade of mucositis, pain intensity, or quality of life. More recently, a systematic review of the literature followed by a meta-analysis including six of these eight trials suggested that PBM may reduce the risk of severe oral mucositis during radiotherapy by 64% (HR = 0.36, 95% CI [0.29–0.44]) and is also associated with favorable cost-effectiveness [18]. Another systematic review of the literature, which included ten placebo-controlled studies, found that nine of the ten studies favored the clinical use of PBM during radiotherapy to improve pain control and that five out of seven studies that compared analgesic drug requirements supported PBM to reduce opioid consumption [19].

To summarize, the MASCC/ISOO endorses the clinical use of PBM for the prevention of radiation-induced acute mucositis [20, 21]. The main limit is the wide variety of PBM protocols available. As such, it is recommended that

the specific physical parameters of a published protocol be carefully followed to ensure optimal results (including the dose to the treated tissue over the entire area of interest). In other words, if the physical parameters of one protocol are combined with those of another, then the efficacy of the PBM will be random.

Epithelitis

Epithelitis or acute radiation dermatitis is the most common radiotherapy-related side effect. Prevention and management of acute radiodermatitis recommended by MASCC consist of daily hygiene measures and the application of topical steroids [22]. Several prospective controlled trials assessed the efficacy of PBM to reduce rates of severe epithelitis during adjuvant radiotherapy in breast cancer. The first double-blind placebo-controlled trial randomized 33 patients treated with adjuvant radiotherapy for breast cancer to either LED PBM (590 nm, 0.15 J/cm², 100 pulse, 250 ms/pulse, 2 cm from the breast skin) or a sham laser immediately before and after each radiotherapy session. The trial was negative, and no statistical difference was found between the groups [23]. More recently, the DERMIS pilot study prospectively compared two successive groups of patients treated with adjuvant radiotherapy for breast cancer. The first group received twice weekly laser PBM (808–905 nm, 0.168 W/cm², 4 J/cm², spot area 19.635 cm², 5 cm from the breast skin). The second group had routine supportive care without real or sham PBM. At the end of radiotherapy, the rate of grade ≥ 2 epithelitis was significantly decreased in the PBM group suggesting efficacy of PBM in this setting [24]. Following this publication, the randomized phase III TRANSDERMIS trial included 120 patients treated for a breast cancer to confirm efficacy of PBM following the same protocol with a more robust methodology. At the end of radiotherapy, the rate of epithelitis grade ≥ 2 as well as quality of life scores was significantly improved in the PBM group. The TRANSDERMIS trial was positive and thus confirmed PBM as an effective supportive care to prevent acute radiodermatitis in the setting of adjuvant breast cancer radiotherapy [25].

Regarding head and neck cancer, the prospective randomized DERMISHEAD trial evaluated efficacy of PBM to prevent acute epithelitis in this indication. The 46 patients included were randomized to either laser PBM (808–905 nm, 1.1–25 W, 4 J/cm², spot area 3.14 cm², 300–600 s, 2 cm from the skin) or a sham laser from day one of radiotherapy, twice a week. The use of PBM significantly reduced the rate of grade ≥ 2 epithelitis at the end of radiotherapy. Therefore, the DERMISHEAD trial supported the implementation of PBM in routine practice to prevent acute epithelitis for head and neck cancer [26].

In summary, the available data tend to show that PBM reduces the rate and severity of acute epithelitis in patients treated with radiotherapy [27]. Further randomized clinical trials are awaited to define the best PBM protocols that can be applied in clinical routine.

Acute dysphagia

Regarding head and neck cancer, dysphagia may be present at diagnosis in two-third of patients and may persist in the mid- and long terms. In the literature, dysphagia commonly caused or promoted serious complications such as inhalation pneumonitis in up to 20% of patients [28]. In addition to direct tumoral invasion, different mechanisms are involved in dysphagia. These may coexist, and there is a close relationship between acute mucositis, xerostomia, and dysphagia.

Some prospective trials have reported efficacy of PBM to prevent dysphagia in patients treated with (chemo)radiotherapy for head and neck cancer. It should be noted that dysphagia was systematically evaluated in secondary exploratory analyses, and to date, no prospective randomized trial has evaluated the efficacy of PBM with dysphagia as the primary endpoint. A first phase III double-blind trial randomized 75 patients between treatment with laser PBM (660 nm, 10 mW, 2.5 J/cm², spot area 4 mm², 10 s/spot, intra-oral) or a sham laser daily before each session and throughout the duration of radiotherapy. This trial found no improvement in acute dysphagia of grade ≥ 3 or feeding tube dependence in the PBM group [10]. A second phase III triple-blind trial randomized 221 patients between laser PBM (632.8 nm, 24 mW, 3.0 J/cm², spot area 1 cm², 15–20 min/session, intra-oral) and a sham laser daily before each session and for the duration of radiotherapy. In contrast to the previous study, PBM decreased the incidence of acute dysphagia, total parenteral nutrition, and opioid use [11]. Finally, a third phase III double-blind trial randomized 94 patients to either laser PBM (660 nm, 100 mW, 4 J/cm², spot area 0.24 cm², 10 s/spot, intra-oral) or a sham laser daily before each session and throughout the course of radiotherapy. This trial was positive and confirmed that PBM was associated with significantly lower gastrostomy need and opioid use [15]. To confirm these preliminary results, clinical trials assessing dysphagia as a primary outcome are required.

Xerostomia

Grade ≥ 2 xerostomia occurs in approximately 76% of patients 3 months after radiotherapy for a head and neck cancer and in 30% of patients at 2 years in the era of intensity-modulated conformal radiation therapy [29]. Saliva is

a key factor in maintaining mucosal integrity, oral wound healing, taste perception, bolus formation, swallowing, and speech [30].

Four randomized trials have evaluated efficacy of PBM in the prevention or treatment of xerostomia in patients treated with radiotherapy or chemoradiotherapy. A first trial randomized 30 patients treated with high-dose chemoradiotherapy prior to bone marrow autotransplantation to either preventive treatment with laser PBM (632.8 nm, 60 mW, 1.5 J/cm², 10 s/spot, intra-oral, daily from d-5 to d-1 prior to radiotherapy) or conventional care. Xerostomia of any grade was statistically improved in patients treated with PBM without any significant adverse effects [31]. A second trial randomized 60 patients undergoing radiotherapy for head and neck cancer to either laser PBM (685 nm, 35 mW, 2 J/cm², spot size 0.028 cm², 25 s/spot, intra-oral) or a sham laser daily. The outcomes were statistically in favor of PBM with significantly higher salivary flow after PBM therapy [14]. Finally, very recently, a third trial randomized 21 patients undergoing radiotherapy for head and neck cancer between laser PBM with intra-oral applications (660 nm, 40 mW, 10 J/cm², spot area 0.028 cm², 7 s/spot, contact) and extra-oral salivary gland applications (810 nm, 40 mW, 25 J/cm², spot area 0.028 cm², 17.5 s/spot, contact) three times a week for the duration of radiotherapy or sham laser. Up to 2 months after the end of radiotherapy, no statistical differences between the two groups were observed regarding salivary flow, saliva composition, xerostomia, or quality of life [32].

In the treatment of radiation-induced xerostomia sequelae of head and neck cancer, a pilot study randomized 23 patients with severe hyposalivation to laser PBM (830 nm, 100 mW, 71 J/cm², spot area 0.028 cm², 20 s/spot) twice weekly for 6 weeks for a total of 12 sessions at the major salivary glands or conventional care. The trial was negative; there was no statistically significant difference between the two groups on either stimulated or unstimulated salivary flow, xerostomia, or oral health-related quality of life [33].

Recently, a systematic review of the literature of 314 articles including five controlled trials underlined the wide diversity of PBM protocols (type of laser, extra-oral or intra-oral application, number of sites applied, power, time per spot, fluence) and the conflicting results published for both prevention and treatment of xerostomia induced by radiotherapy alone or in combination with chemotherapy [34]. In order to further assess the potential role of PBM in preventing radiation-induced xerostomia, a meta-analysis of summarized data from five controlled trials using PBM in this indication was conducted in 2020. The conclusion suggested an increase in unstimulated salivary flow and stimulated salivary flow after preventive treatment with PBM, suggesting to the authors that PBM could minimize the impact of radiation-induced xerostomia without any adverse event [35].

In summary, the evidence-based efficacy of PBM in the prevention and management of xerostomia associated with radiotherapy is mixed and based on a low to moderate level of evidence. The general trend suggests that PBM may be of value in preventing or treating salivary gland dysfunction. Randomized placebo-controlled trials and especially precise PBM protocols are needed to ensure preliminary positive results.

Lymphedema

Lymphedema of the upper limb affects approximately 20% of patients treated for breast cancer, resulting from alteration of lymphatic structures by surgery or radiotherapy or both [36]. The prevention of lymphedema is based on hygienic and dietary measures and the treatment on manual therapies of decongestion or lymphatic drainage [37].

A historical meta-analysis of nine studies, including seven randomized controlled trials, assessed efficacy of PBM in terms of upper limb volume and pain in the management of lymphedema in patients treated for breast cancer. PBM was associated with moderate level evidence of efficacy in terms of arm volume and pain [38]. It should be noted that the translation of this moderate reduction in arm volume and pain into a clinical benefit for patients was not investigated by the authors. In a randomized placebo-controlled trial including 40 women treated for breast cancer with upper limb lymphedema, the laser PBM protocol (980 nm, 640 mW, 4.89 J/cm², spot area 4.9 cm², 10 min/session, 8 sessions at the axillary level) did not show significant efficacy on quality of life, pain score, grip strength, and arm volume [39]. Recently, a randomized placebo-controlled pilot trial evaluated efficacy at 1 year of a protocol of laser PBM (904 nm, 1.5 J/cm², 1 min on each of 10 sites in the axilla and part of the homolateral chest wall, 8 to 16 sessions) in combination with manual decongestive therapies in the management of upper limb lymphedema in patients treated for breast cancer. At 1 year, the combination of PBM with decongestive therapies suggested a significant improvement in lymphedema-related symptoms, arm mobility, and emotional distress in these patients [40]. The most recent meta-analysis included seven randomized trials. The main limit was the lack of data regarding PBM parameters. However, the authors concluded that there was strong evidence (three high-quality trials) for the superiority of PBM against placebo in terms of arm circumference and volume reduction and moderate evidence (one high-quality trial) suggesting that PBM would be more effective than placebo for short-term pain relief [41].

In summary, the systematic review of the literature suggests that PBM is an attractive treatment approach for breast cancer treatment-related upper limb lymphedema. However,

due to the moderate level of evidence available, methodologically robust randomized trials are needed, particularly to determine the parameters of PBM.

Safety

There are no significant adverse events associated with PBM in the literature. However, there is controversy about the potential long-term risks of malignant transformation of healthy cells, or progression and recurrence of the primitive tumor, whose proliferation of tumor cells could be boosted when PBM is applied close to the tumor site [42]. Regarding this issue, in vitro data on the behavior of tumor cells exposed to PBM are conflicting, and clinical data on the long-term safety of PBM are scarce. A phase III trial with the primary objective of reducing the incidence of acute oral mucositis grade ≥ 3 randomized 94 patients to either laser PBM (660 nm, 100 mW, 4 J/cm², spot area 0.24 cm², 10 s/spot, intra-oral) or sham laser in the setting of chemo-radiotherapy for head and neck squamous cell carcinomas. After a relatively short median follow-up of 18 [10–43, 44–48] months, patients treated with PBM appeared to have better locoregional disease control, progression-free survival, and overall survival [15].

To conclude, until robust data are published on its long-term safety, especially on the theoretical risks of transformation into malignant cells or accelerated tumor growth, the clinical use of PBM near areas with known or potential tumor cells should be considered with caution. The patient should be informed of the theoretical benefits and risks of PBM in order to obtain informed consent before treatment.

Discussion

PBM in the red or infrared spectrum has been shown in randomized controlled trials to be effective in the management of some radiotherapy-related complications, in particular acute mucositis, epithelitis, and upper limb lymphedema. These studies probably even underestimated the magnitude of the benefit of PBM due to incomplete assessment of the costs of these complications. Very recently, a systematic review of the literature concluded that there was evidence in favor of PBM in terms of cost-effectiveness for the prevention and management of cancer treatment-related toxicities, including acute oral mucositis and upper limb lymphedema [43]. Therefore, PBM could be considered as a full-fledged supportive care for patients treated in oncology. Indeed, well beyond the complications of radiotherapy, there is also consistent evidence supporting use of PBM to prevent and manage complications of chemotherapy. While strong evidence including placebo-controlled randomized trials has already

been published for *chemo-induced peripheral neuropathy*, convincing data exists for *hand-foot syndrome* or *chemo-induced alopecia*. In all cases, a major challenge is now to standardize practices through the publication of guidelines. Detailed protocols of PBM treatment are mandatory in order to optimize its efficacy and guarantee the reproducibility of its outcomes.

PBM is becoming a recognized treatment in many clinical situations when anti-inflammatory effect, analgesic effect, and/or tissue regeneration are expected.

WALT, in close collaboration with MASCC and ISOO, is defining optimal technical and dosimetric parameters in all indications, with collaborative guidelines and recommendations (especially for PBM using modern LED devices).

Regarding the different types of PBM applicators for cancer patients, we have the option of commercially available extra-oral devices and intra-oral devices, targeting structures such as cutaneous and oral mucosal surfaces, respectively. Also, we must remember the fact that, while using an extra-oral device for the application of PBM, to a certain extent (with wavelengths around 830 nm, not with 630–660 nm), we may be able to indirectly reach intra-oral surfaces such as (for head and neck region) the oral mucosa, vestibule, and inner epithelial surfaces of the lips in a dentate subject. This proves that a combination of the above two devices must be considered while managing the head and neck radiotherapy-induced side effects but not necessary in chemotherapy induced intra-oral effects.

Finally, we believe that the following parameters should become mandatory while considering PBM in all its indications. The parameters to be considered include wavelength (nm), power (mW), J/cm² per point (or “dose”), energy density, spot size, power density (mW/cm²), and laser machine calibration. Treatment characteristics should include the total number of J/cm² in any single laser session, the total number of sessions, the frequency of sessions (treatment protraction), the site(s) of treatment, and some precision regarding laser administration (contact pressure treatment, application over single area at one time than scanning motion, preparation of the mucosal or cutaneous surface) and most importantly a well-trained individual such as cancer specialist who could assess the region of interest, lesions to treat, and to grade them accordingly.

Regarding equipment required for an optimal PBM treatment, we have to choose companies that can certify PBM dose delivery and control this dose delivery in routine practice.

External LED devices are cheaper than laser diodes, with the same efficiency when high-quality LEDs are used (with unidirectional beam; monochromatic or polychromatic device, with one or a range of available wavelengths). More generally, external devices are more versatile than intra-oral

(or intra-cavitary) devices, and they are now totally validated in terms of calibration and clinical efficacy.

In all cases, maintenance of the machines, with regular controls, is needed.

WALT and other laser societies have to play a key role in the quality control of commercial devices.

Regarding PBM users, physicians have to *prescribe* PBM treatments, but they can delegate the realization of daily PBM delivery to the patient to a nurse or a radiotherapist.

Prescription is a medical task: knowing the target and the pathology that have to be treated conduct to the right choice in PBM device and in PBM parameters (wavelength, dose, etc.).

The first university diploma, which validate a 1-year training in “PBM in Cancer Supportive Care”, was created in France in 2020 (University of Paris-Saclay, Gustave Roussy Institute) with a great success.

Regarding cost-effectiveness of PBM compared with other supportive care treatments, we have few comparative data that include the use of modern PBM material and new quality control criteria (with a much better expected income and reliability compared with old devices). These comparative studies are now initiated in several countries and should confirm in the near future this cost-effectiveness: PBM material is not expensive, the main limiting factor being the cost of salaries (people using devices, 10 to 20 mn per patient). Moreover, reduction in the number and duration of hospitalizations, reduction of enteral or parenteral nutrition, and reduction of the use of morphinics, for example, were largely documented in several studies testing PBM for oral mucositis in cancer patients, with a significant decrease of treatment cost per patient.

Finally, with all this technical and clinical progress, PBM is entering a new era of maturity and evidence-based clinical use that should allow PBM to be fully considered as a part of “mainstream medicine”!

Declarations

Conflict of interest The authors declare no competing interests.

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