A Narrative Review on the Use of Photobiomodulation Therapy for the Prevention and Management of Acute Radiodermatitis: Proposed Mechanisms, Current Clinical Outcomes, and Preliminary Guidance for Clinical Studies

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A narrative review on the use of photobiomodulation therapy for the prevention and management of acute radiodermatitis: proposed mechanisms, current clinical outcomes and preliminary guidance for clinical studies

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Abstract

Objective

A narrative review of the available scientific evidence to identify the current proposals relating the use of photobiomodulation (PBM) to treat acute radiodermatitis (ARD), to guide future research.

Background data

A devastating side effect of radiotherapy is ARD, defined as an inflammatory skin reaction induced by radiotherapy. Currently, there is still no standard of care for ARD. PBM is a non-invasive light therapy, which is a growing modality in the field of supportive cancer care. There is a need for identifying the therapeutic irradiation windows in this field, based upon the available literature.

Method

An electronic search of original articles in the PubMed database was performed with the following keywords: "photobiomodulation therapy", "low-level light therapy", "low-level laser therapy", "acute radiodermatitis", and "radiotherapy" until December 2019. Randomized controlled trials (RCTs), prospective non-randomized, case report, cohort, cross-over, and retrospective studies were selected for this review.

Results

Nine clinical trials that investigated the use of PBMT in ARD were available for evaluation. Results demonstrate that PBMT could significantly reduce the severity of ARD and the accompanying discomfort and pain in patients with cancer.

Conclusion

Based on the available evidence of the narrative review, PBM might be an effective therapy for the prevention and management of ARD in patients with cancer. More research is needed to confirm this finding.

Keywords

Photobiomodulation therapy; Acute radiodermatitis; Radiotherapy; Supportive care; Light therapy; Cancer; Narrative review

Introduction

The use of light-therapy based applications for the management of cancer-therapy related adverse events has steadily increased in the last 40 years [1]. The most well-known and studied indication of photobiomodulation therapy (PBMT) in the field of supportive cancer care is oral mucositis (OM), which is an inflammation of the oral mucosal lining. A recent systematic review showed that based on the available evidence, PBMT is an effective therapy for the prevention of OM, using specific PBM parameters in specific patient populations [2]. Based on the wound healing and anti-inflammatory properties of PBMT, several studies have investigated the use of PBMT for the prevention and management of acute radiodermatitis (ARD) since the 1990s [3]. To date, there is no general consensus on the role of PBMT in the treatment of ARD. Therefore, in this narrative review, the appropriateness of PBM and ARD will be reviewed based on the current scientific evidence, in order to set up a proposal of a therapeutic protocol to use in future clinical research.

In this article, the clinical characteristics, pathogenesis, and management of ARD will be discussed in combination with a narrative review of the available scientific evidence regarding the use of PBMT for the prevention and treatment of ARD in a clinical setting.

Methods

This is a narrative review of the use of PBMT for the management and prevention of ARD. An electronic search in the PubMed database was performed until December 2019. The following keywords were used: “photobiomodulation therapy”, “low-level light therapy”, “low-level laser therapy”, “acute radiodermatitis”, and “radiotherapy”. Different combinations of the search terms were made by using the Boolean operators “AND,” “OR,” and “NOT”. Clinical study designs that were selected for this review were

randomized controlled trials (RCTs), prospective non-randomized, case report, cohort, cross-over, and retrospective studies written in English. No restrictions on the year of publications were set. Abstracts, book chapters, review articles, letters to editors, and newspaper articles were excluded.

Results

A total of nine clinical trials investigating the use of PBM for the management of ARD were selected (Table 1). The first case report study investigated the use of PBM in three patients with breast cancer post-mastectomy, who developed RT-induced skin ulcers. They underwent three weekly laser diode (LD)-based PBM sessions (632.8 nm, 3 mW/cm^2, 30 J/cm^2). Results demonstrated improved wound healing [4].

Following, two clinical trials focused on the use of light emitting diode [5]-based PBMT in patients with breast cancer undergoing RT post-lumpectomy or –mastectomy [6, 7]. In both trials, PBM was applied daily during the full course of RT (590 nm, 0.15 J/cm^2). A prospective intervention trial with a retrospective control group demonstrated that PBM significantly reduced the incidence of Radiation Therapy Oncology Group (RTOG) grade 2 ARD or higher in 47 patients with breast cancer [6]. However, a randomized control trial (RCT) of 33 patients with breast cancer was not able to confirm this result [7].

In 2016, the DERMIS trial, a prospective, quasi-experimental intervention trial investigated the therapeutic use of LD-based PBM in 79 patients with breast cancer post-lumpectomy treated with RT. PBM was applied twice weekly in a therapeutic manner (808+905 nm, 168mW/cm^2, 4 J/cm^2) starting at an RT dose 40 Gy. The study demonstrated that PBM significantly prevented the exacerbation of ARD [8]. Another prospective intervention trial with 70 patients with breast cancer undergoing RT showed

a comparable outcome when PBM was applied twice weekly from the first day of RT (660+850 nm, 44.6 mW/cm^2, 0.15 J/cm^2) [9]. The first large placebo-controlled RCT that investigated the use of LD-based PBM in a preventive manner was the TRANSDERMIS trial. In this study, 120 patients with breast cancer undergoing RT were treated with PBM (808+905 nm, 168mW/cm^2, 4 J/cm^2, continuous pulsed wave mode) twice weekly starting from the first day of RT. Both subjective and objective outcomes measures were collected. Results demonstrated that PBM significantly reduced the incidence of RTOG grade 2 ARD or higher [10]. Moreover, this decrease in the severity of ARD seemed to be associated with an improved patients' quality of life. PBM was able to effectively lower the degree of erythema and improve the skin barrier function based on objective outcome measures of skin discoloration and transepidermal water loss [11].

Concerning the use of PBMT for ARD in head and neck cancer (HNC) patients, the evidence is limited. In 2018, a prospective intervention trial demonstrated that PBMT twice daily during the full course of RT is beneficial in the management of ARD in HNC patients when compared with the institutional standard skincare [12]. A case report study describes two patients with HNC, who developed RTOG grade 3 ARD during their RT course. PBM was applied on a daily basis (660nm, 27.77-35.71 J/cm^2, 40-100 mW). For one patient, the skin reactions already improved after 48 hours towards a grade 2 ARD and six days after PBM initiation the patient presented a grade 1 ARD. For the second patient, four PBM sessions were needed to induce healing and after seven PBM treatments, the patient demonstrated complete healing [13]. A prospective, pilot trial studied the use of PBM in 33 patients with HNC or lung cancer. Patients were treated with PBM (3x/week, 590-830 nm, 60 J/cm^2, 100mW/cm^2) alongside the standard institutional skincare. Results showed that 33% of the patients presented moist desquamation one-week post-RT. As there was no control group, it is hard to evaluate the effectiveness of PBM in this study [14]. Currently, the first placebo-controlled, RCT is performed in which the efficacy of PBM (2x/week, 808+905 nm, 168mW/cm^2, 4 J/cm^2)

for the prevention of ARD in HNC is evaluated (ClinicalTrials.gov Identifier: NCT02738268). Preliminary results demonstrate that PBMT could significantly reduce the incidence of severe ARD (RTOG grade 2 or higher) [15].

General guidelines for PBM and ARD

Based on the available evidence regarding the use of PBMT in the management of ARD, some general guidelines for PBM parameters can be proposed for further research: 630-905 nm, 2-6 J/cm^2, 20-150 mW/cm^2, continuous and pulsed emission mode, external delivery, and daily treatment during the full course of RT or even post-RT (Table 2). There is a wide variation in application and treatment parameters as shown in the accompanying table. Therefore, it is not possible to make robust recommendations for clinical application before further study with larger study participant numbers.

Discussion

In 2018, 18.078.957 people were diagnosed with cancer worldwide. The number of cancer patients is still increasing. Based on the statistics of the International Agency for Research on Cancer (IARC), the number of new cancer cases is expected to rise to 23.6 million by 2030 [16]. Radiotherapy (RT) alone or in combination with other cancer therapies (e.g. surgery, chemotherapy, hormonal therapy, immunotherapy) is used in up to 50% of all newly diagnosed cancer patients. RT is a locoregional treatment that uses ionizing radiation to induce maximal damage to the tumor while minimally affecting normal tissue. Despite on-going improvements in RT techniques, patients still develop a wide array of quality of life (QOL)-impairing side effects, depending on both treatment- and patient-related risk factors [17]. One of the most frequent and devastating complications of RT is ARD, defined as an inflammatory skin reaction [18].

Acute radiodermatitis

ARD occurs in up to 95% of the patients undergoing RT.. ARD can develop in several grades ranging from erythema, dry desquamation (grade 1), and moist desquamation (grade 2-3) to ulcerations (grade 4), as graded by the RTOG [19]. Moist desquamation arises in up to 30% of the patients undergoing RT [20]. ARD is accompanied by itchiness, pain, and a burning sensation, resulting in discomfort, which negatively affects patients' daily activities (e.g. household, washing practices, getting dressed, hobbies,) and QOL. In severe cases of ARD, RT needs to be interrupted, which limits the treatment outcome [21, 22].

Pathogenesis

The pathogenesis underlying the development of ARD is complex and comprises a few critical steps. Initially controlled by cytokines and chemokines produced by the irradiated skin cells, resident and circulating immune cells are recruited to the area of insult, hallmarked by an inflammatory skin reaction. Due to RT damage of the surrounding vessels, increased vascular permeability and vasodilation leads to an erythematous skin reaction. Alongside the inflammatory insult, RT also damages the DNA of the stem cells in the basal layer of the epidermis, leading to a disruption in the mitotic process, eventually impeding the self-renewing aspect of the skin. The skin tries to compensate for the damage by upregulating the proliferation of the stem cells. However, if the production of new cells is faster than the shedding of the old cells, dry desquamation arises. If the stem cell pool is depleted, skin repair is impossible, leading to moist, open wounds [23].

Treatment options

Many options for the management of ARD are currently being investigated in a wide variety of clinical trials. Yet there is still no comprehensive, evidence-based

consensus for the management of ARD. As such, each RT department uses its own management protocol based on practical experience [21, 24]. The most recent clinical guidelines were published in 2013 by the Multinational Association for Supportive Care in Cancer (MASCC) based on a systematic review. The MASCC strongly recommends daily hygiene practices and the application of potent topical steroids. Based on the available evidence, no recommendations or suggestions for other (topical) agents are made [25], and there is an urgent need for more evidence-based protocols for the management of ARD.

Photobiomodulation therapy (PBMT)

Since PBMT was discovered by Endre Mester in 1965, the number of medical applications has steadily increased, resulting in over 4000 scientific papers in various fields (e.g. dermatology, neurology, physiotherapy, oncology) [1]. PBMT can be applied by using both LD or LEDs [5] within the red and near-infrared (NIR) wavelength range of 600–1000 nm. In the past, scientists believed that the monochromaticity and coherence of an LD were essential characteristics to trigger the PBM effects. The negative aspect of LD-based PBMT is that these devices are expensive and can only be used by trained clinicians. Since the 1980s, non-coherent light sources such as LEDs have also made their introduction in the field of PBMT. LED devices are cheaper and easier to use, even by patients themselves. On both experimental and clinical levels, scientific evidence is available demonstrating that LD could be replaced by LED, but it remains a controversial topic in the field of PBMT [26, 27].

PBM parameters

PBM parameters are the critical factors that determine the efficacy of the therapy. These can be subdivided into irradiation and treatment parameters. Irradiation

parameters consist of the used wavelength (nm), energy density (J/cm^2), irradiance (W/cm^2), power (W), irradiation time (s), beam area (cm^2), energy (J), type of PBM device (LD vs. LED), and, the operating mode (continuous vs. pulsed). Treatment parameters, such as the physical relationship of the PBM device to the target tissue, the timing (i.e. before, during or after RT), treatment schedule, and the anatomical location are also crucial. Without these parameters, it is very hard to compare clinical trials to develop a specific PBM treatment protocol. Therefore, they need to be reported in detail [28, 29].

Biologic mechanism

The underlying mechanism of PBMT on the target cells depends on the cell type, tissue type, and the specific condition in which the target is treated (e.g. healthy or diseased state) and is still not fully understood. The proposed theory behind PBMT states that red and/or NIR light is absorbed by cytochrome c oxidase (CCO), a mitochondrial chromophore. Photon absorption causes dissociation of nitric oxide (NO) from CCO. NO is also released from intracellular stores (e.g. nitrosothiols) or from haemoglobin or myoglobin. NO is a potent vasodilator, leading to an increased blood flow [30, 31].

The dissociation of NO from CCO leads to an increase in the mitochondrial electron transport, which results in the upregulation of adenosine triphosphate production [32]. A short burst of reactive oxygen species (ROS) is also induced, causing changes in the cellular redox potential. Both ATP and ROS activate several transcription factors, such as nuclear factor kappa B (NF-kB) and activator-protein (AP-1). These transcription factors induce a photo signal transduction and amplification chain, leading to an increase in growth factor production, cell proliferation, cellular mobility, adhesion, and extracellular matrix deposition (ECM) [31].

Safety of PBM

Regarding the proliferative effect of PBM, the safety of the therapy in people with cancer needs to be investigated. *In vitro* studies examining the effect of PBMT on various cancer cell lines show disparate results: some show an increase in cell proliferation while others do not. Animal studies demonstrating that PBMT can stimulate tumor growth are very rare [33-35]. Clinical trials in patients with cancer have not demonstrated any adverse events regarding the use of PBMT [5]. There are even clinical trials that demonstrate an overall improved survival of patients with cancer after PBMT for OM [36]. Additionally, some studies suggest that PBMT can be used to (in)directly damage the cancer cells [37]. In order to elucidate the effect of PBMT on the tumor, and eventually the cancer treatment outcome, a follow-up period of at least five years must be included in clinical trials of PBM and RD.

PBM and wound healing: preclinical data

Numerous *in vitro* and *in vivo* studies have investigated the effect of PBMT on wound healing in general. They all demonstrate that PBMT can positively affect each phase of the wound healing process by up-regulating phagocytosis, enhancing angiogenesis, downregulating inflammatory mediators, and stimulating the proliferation and migration of keratinocytes and fibroblasts regulated by growth factors to eventually increase collagen synthesis [38-44]. PBMT positively affects the formation of collagen and granulation tissue, tensile strength, and epithelization of the wound bed [44-54].

An important factor in the wound healing process is transforming growth factor-beta (TGF-β), which can modulate hemostasis, inflammation and tissue remodeling. Recent studies have demonstrated that latent TGF-β can also be activated by PBMT, which could accelerate wound healing [55].

PBM and ARD: clinical data

This narrative review provides an overview of the clinical trials that have investigated the use of PBM in patients with RT-induced skin reactions. The available evidence shows that PBM could effectively reduce the severity of ARD. Still, no general recommendations can be made due to the fact the evidence is still scarce and the methodology of the trials is diverse. As such, there are a few points that need to be covered in future trials.

PBM parameters

One important limitation is that the PBM parameters are sometimes poorly reported in clinical trial reports. Future studies need to include these parameters in detail when developing a PBM treatment for a specific condition. To ensure that the exact PBM parameters are applied, device measurements of light output should be performed regularly before, during, and after a clinical trial [56].

Skincare for ARD

A wide range of topical skincare products is available on the market to prevent and manage ARD. However, the effectiveness of many of these products remains unclear due to a limited amount of scientific evidence. MASCC has published guidelines concerning the prevention and treatment of ARD, but these have not been updated since 2013 [25]. Many RT centers have developed their own protocols based on experience. Most of the previously described studies used a different skincare protocol, which makes it hard to compare the outcome measures between the various trials. Future trials of PBMT should describe their standard skincare protocol in detail.

Blinding

In all the described trials, the PBM device operator was not blinded, which could have led to the risk of bias. To implement double-blinded RCTs and reduce the risk of

the bias, an adjusted PBM device is necessary. The device needs to have an invisible light beam, a disguised glow, and a sealed randomization-coding system [57].

The future of PBM for ARD

To address the limitations of clinical trials and PBMT research on ARD in general, further research is needed.

Most studies to date have focused on the use of PBMT in patients with breast cancer. The number of trials in HNC is limited. As such, it would be interesting to also evaluate the effect of PBMT in other patients with cancer undergoing RT. Especially patients with gynecological or colorectal cancer who are prone to developing ARD in the genital and perianal area may benefit from an evidence-based and effective method for managing radiodermatitis [58].

Recent literature also suggests that PBMT can be used to precondition the skin before the true insult, such as UV-damage [59]. Preconditioning implies that the application of visible and NIR light to healthy skin cells can prepare them for future damage [59-61]. Pre-conditioning patients with PBMT before the actual start of the RT sessions may represent a new method to prevent ARD.

Conclusion

Based on this narrative review, PBMT could reduce the severity and duration of possible skin reactions in patients undergoing RT. Still, the number of clinical trials on

PBM and ARD is scarce and therefore more studies are needed. Future studies should focus on randomized controlled study designs with well-described and complete PBMT parameters in a larger and more diverse patient population. This would enable the implementation of PBM in the field of ARD, which would enhance the wound care management, improved the patient's performance status, and QOL.

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Conflicts of interest

The authors declare that they have no competing interests.

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