


The use of low-level light therapy in supportive care for patients with breast cancer: review of the literature

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Abstract Breast cancer is the most common cancer in women worldwide, with an incidence of 1.7 million in 2012. Breast cancer and its treatments can bring along serious side effects such as fatigue, skin toxicity, lymphedema, pain, nausea, etc. These can substantially affect the patients' quality of life. Therefore, supportive care for breast cancer patients is an essential mainstay in the treatment. Low-level light therapy (LLLT) also named photobiomodulation therapy (PBMT) has proven its efficiency in general medicine for already more than 40 years. It is a noninvasive treatment option used to stimulate wound healing and reduce inflammation, edema, and pain. LLLT is used in different medical settings ranging from dermatology, physiotherapy, and neurology to dentistry. Since the last twenty years, LLLT is becoming a new treatment modality in supportive care for breast cancer. For this review, all existing literature concerning the use of LLLT for breast cancer was used to provide evidence in the following domains: oral mucositis (OM), radiodermatitis (RD), lymphedema, chemotherapy-induced peripheral neuropathy (CIPN), and osteonecrosis of the jaw (ONJ). The findings of this review suggest that LLLT is a promising option for the management of breast cancer treatment-related side effects. However, it still remains important to define appropriate treatment and

irradiation parameters for each condition in order to ensure the effectiveness of LLLT.

Keywords Low-level light therapy · Photobiomodulation therapy · Breast cancer · Supportive care · Oncology

Introduction

Breast cancer is the second most common cancer worldwide, with an incidence of 1.7 million in 2012 [1]. Current breast cancer treatment options include surgery, chemotherapy (CTx), radiotherapy (RT), and/or adjuvant systemic therapies (e.g., endocrine therapy, trastuzumab) [2]. Some of the major side effects associated with breast cancer and its treatments are fatigue, skin toxicity, lymphedema, pain, nausea, etc. These can extensively lower the patients' quality of life. Consequently, management of these side effects is important in the supportive care of these patients [3].

Low-level light therapy (LLLT), recently named photobiomodulation therapy (PBMT), has gained its place in general medicine for already more than 40 years. It is a non-invasive treatment option used to stimulate wound healing and reduce inflammation, edema, and pain. LLLT is applied in a variety of medical domains ranging from dermatology, physiotherapy, neurology, to dentistry [4–8]. The use of LLLT in an oncologic setting has become an interesting study object in the recent years. Although there are different possibilities for using LLLT in the supportive care of breast cancer patients, many clinicians are still not familiar with this therapy.

The aim of the present article was to perform a review of the literature to demonstrate the available scientific evidence that supports or contraindicates the applicability of LLLT in the field of supportive care for breast cancer patients.

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Literature review

A search of the literature was performed by using the electronic database of PubMed, using the search terms “low-level light therapy” or “photobiomodulation therapy” alone or in combination with one or more of the following terms: “breast cancer,” “oral mucositis,” “radiodermatitis,” “lymphedema,” “osteonecrosis of the jaw,” and “chemotherapy-induced peripheral neuropathy.”

LLLT—mechanism of action on molecular level

LLLT is a noninvasive treatment option that is used to stimulate wound healing, reduce inflammation and edema, and relieve pain [4]. It uses nonionizing light sources such as laser diodes (LDs) and light-emitting diodes (LEDs) in the visible and near-infrared (NIR) spectrum (600–1000 nm) [5–7]. The term “level” refers to the reaction in the target cells that is caused by the light therapy. All the target cells of light therapy have a certain survival threshold. High-level light therapy (HLLT) used during surgery (e.g., tissue cutting or ablation, thermal coagulation) causes damage to the target cells by exceeding the survival threshold of the cells. In contrast, LLLT keeps the cellular reaction below this threshold and thereby it can modulate the activity of the target cells. Therefore, LLLT is a therapeutic modality [4, 8, 9].

The basic mechanism underlying LLLT is not yet fully elucidated and may vary among different cell types and tissue conditions. However, it can be stated that basic mechanism behind LLLT is based on the absorption of light by endogenous chromophores eliciting nonthermal, photophysical, and/or photochemical events at various biological scales leading to physiological changes [5, 7]. It needs to be mentioned that both visible (600–750 nm) and NIR light (750–1000 nm) follow the same basic working mechanism; however, their primary targets and photoreactions in the target cells differ. Visible light mainly targets cytochrome c oxidase (CCO) located in the mitochondrial membrane thereby causing a primary photochemical reaction. The absorbed energy leads to activation of the mitochondrial respiratory chain, which results into an accelerated electron transfer reactions. This leads to an increased production of ATP. On the other hand, NIR light induces a primary photophysical reaction by targeting the cell membrane, leading to the activation of Na^+/K^+ ATPase and Ca^{2+} pumps. As secondary reaction, the mitochondrial ATP production in the cell is upregulated. ATP regulates the production of cAMP, which is a second messenger. Furthermore, in both conditions, the mitochondrial membrane potential is altered, resulting into an increased activity of the Na^+/H^+ and $\text{Ca}^{2+}/\text{Na}^+$ antiporters and of all the ATP-driven carriers for ions, such as Na^+/K^+ ATPase and Ca^{2+} pumps. This eventually leads to an increase of the intracellular Ca^{2+}

level. Both Ca^{2+} and cAMP are very important second messengers [7, 10, 11]. These processes will increase the cellular activity and improve the intracellular signal transmission pathways. This will eventually lead to the synthesis of DNA and RNA, enzymes, and proteins, resulting in an enhanced cell proliferation, cell activation, and repair of injured/compromised cells [4, 7, 8].

Furthermore, nitric oxide (NO) release and/or production in the mitochondria appear to be upregulated by LLLT. There are two possible pathways linked to the release of NO by LLLT. First, it is possible that LLLT prevents the binding of NO to CCO. NO downregulates the cellular respiration by binding to CCO. LLLT prevents this process from taking place by dissociating NO from CCO, which results in an increased ATP production. Secondly, LLLT may cause an increase in the nitrite reductase activity of CCO (a one-electron reduction of nitrite gives NO), which leads to an increase in NO production. NO is known to cause vasodilatation by triggering the relaxation of smooth muscle associated with endothelium. This vasodilation increases the availability of oxygen to exposed cells and also allows for greater traffic of immune cells into tissue [8, 12].

Finally, LLLT is also able to increase the production of reactive oxygen species (ROS) in the mitochondria. ROS is involved in the redox-signalling pathway between the mitochondria and the nuclei. In the nuclei, ROS will activate several transcription factors, which will lead to the upregulation of various stimulatory and protective genes. This will result in the production of several proteins that trigger downstream effects such as an increase in cell proliferation and migration, a modulation in the levels of cytokines, growth factors, and inflammatory mediators, and an increase in tissue oxygenation [10, 13].

LLLT—mechanism of action on cellular and tissular level

Several *in vitro* studies with different cell types ranging from keratinocytes, endothelial cells, and fibroblasts have been conducted. Results of these studies have shown that LLLT is able to increase the cellular migration, proliferation, and metabolism. LLLT can also induce collagen synthesis and growth factor secretion. Furthermore, there is also a downregulation of the production of pro-inflammatory cytokines and cell apoptosis by LLLT [14–20].

Some of the animal studies investigating the effects of LLLT on wound healing have found similar results to the ones found in the *in vitro* studies, ranging from decreased inflammation and increased collagen and granulation tissue in the wound bed to increased tensile strength and faster epithelization [20–23].

LLLT in the supportive care of breast cancer patients

Different clinical trials investigated the use of LLLT for a variety of side effects related to breast cancer treatment, such as breast cancer-related lymphedema (BCRL), oral mucositis (OM), radiodermatitis (RD), chemotherapy-induced peripheral neuropathy (CIPN), and osteonecrosis of the jaw (ONJ) [24–26].

BCRL

Breast cancer treatment (e.g., surgery, lymph node dissection, and/or RT) can cause damage to the lymph vessels and nodes, which leads to an impaired lymph flow and accumulation of a protein-rich interstitial fluid in the upper extremity (UE) [27]. Approximately 20 % of the patients develop lymphedema after breast cancer treatment. The most important risk factors for developing BCRL include axillary-lymph-node dissection, mastectomy, the number of lymph nodes dissected, and a high body mass index (BMI). Furthermore, the presence of metastatic lymph nodes, undergoing CTx or RT, and a low regular physical activity seem to be moderate-risk factors for BCRL [28]. BCRL is a chronic condition, which is associated with pain, poorer arm mobility, a diminished quality of life, and restrictions in daily activities [29].

Up to now, the current standard of care for BCRL is complete decongestive therapy (CDT), which consists of four main parts: manual lymphatic drainage (MLD), compression bandaging, exercise, and skin care. However, this treatment option is not beneficial for all of the BCRL patients and therefore alternative treatment modalities need to be investigated [30, 31].

LLLT for the management of BCRL

Since 1995, the use of LLLT for the treatment of BCRL has been investigated in humans and the U.S. Food and Drug Administration (FDA) accepted it as treatment option for BCRL in 2006 [32]. The proposed underlying mechanism is that LLLT increases the lymphatic drainage by stimulating the formation of new lymph vessels, by improving the lymphatic motricity, and by preventing the formation of fibrotic tissue [33–36].

A recent meta-analysis of nine studies by Smoot et al. provided moderate evidence that LD-LLLT alone or combined with other treatments was able to reduce the arm swelling and pain in women with BCRL (Table 1). Reducing the limb volume improves the mobility and thereby the quality of life of the patient. Furthermore, LD-LLLT might also reduce the pain that is accompanied with lymphedema. In addition, the meta-analysis revealed that combination therapies that include LD-LLLT are more effective in reducing the arm volume than treatments without LD-LLLT. Concerning side effects, LD-

LLLT does not seem to increase the risk on cellulitis, an acute infection of the skin and the subcutaneous tissues, which is a known side effect in patients with lymphedema. There were no studies that investigated the risk on metastasis or relapse in the areas that were treated with LD-LLLT [36].

OM

OM refers to inflammation of the oral mucosa caused by CTx and/or RT. It occurs in 20–40 % of the patients undergoing conventional CTx. It manifests as erythema and/or ulceration of the oral mucosal lining. OM is a very painful and distressing side effect of cancer therapy. It can lead to malnutrition as a result of inability to eat and swallow. Therefore, it significantly affects the patients' quality of life. When OM becomes severe, it might lead to a reduction in CTx dose or an interruption in RT treatment, which has a negative impact on the patients' prognosis [37, 38].

Current management options for the prevention and treatment of OM are diverse consisting of both pharmacological and nonpharmacological agents. However, there is only sufficient scientific evidence for a few of these treatments according to the guidelines of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO). They made a recommendation for some nonpharmacological treatments such as the use of cryotherapy and anti-inflammatory mouthwash to prevent OM. In addition, they suggested the use of oral care protocols to prevent OM. The panel made a recommendation for pharmacological agents that are mainly used for palliative care and pain relief. These agents include patient-controlled analgesia with morphine, transdermal fentanyl, and local anesthetics (morphine or doxepin mouthwash) [38].

LLLT in the prevention and management of OM

The use of LLLT for the management of OM has been included in the most recent guidelines of the MASCC/ISOO. They made a recommendation for the use of LLLT for the prevention of OM in patients receiving high-dose CTx in cases of hematopoietic stem cell transplantation (HSCT). In addition, the panel suggested the use of LLLT for the prevention of OM in head and neck cancer patients undergoing RT without concomitant CTx [38, 39]. Additionally, the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) made also the same suggestion to use LLLT in patients receiving high-dose CTx or chemoradiotherapy before HSCT in order to reduce the incidence of OM and its associated pain [37, 40].

Up to now, there were only five studies that investigated the effect of LD-LLLT on CTx-induced OM in breast cancer populations of varying size (Table 2). Kuhn et al. conducted a placebo-controlled study with 34 patients (three breast cancer

patients) to determine whether LD-LLLT applied every 24 h could reduce the duration of CTx-induced OM. They demonstrated that the duration of OM was reduced in the patients treated with LD-LLLT in addition to oral care [41]. In a study by Genot-Klastersky et al., they investigated the efficacy of LD-LLLT for the prevention of OM in a single arm study with patients with various solid tumors treated with CTx and who had experienced severe mucositis during a previous identical treatment (18 breast cancer patients). Results of the study showed that 81 % of the patients were considered to benefit from LD-LLLT, which indicates that LD-LLLT is effective for the prevention of CTx-induced OM [42]. In a case report study by Pires-Santos et al., they evaluated the efficacy of LD-LLLT for the prevention and management of CTx-induced OM in 12 breast cancer patients. They divided the patients into two groups: one group was treated with LD-LLLT in combination with the standard care protocol and the control group only received the standard care. Results of this study showed that LD-LLLT is able to reduce the pain and improve the oral tissue repair [43]. Arbabi-Kalati et al. performed a double-blind randomized controlled study (RCT) with 48 patients who underwent CTx (25 breast cancer patients) in order to investigate the efficacy of LD-LLLT in the prevention of OM. They showed that LD-LLLT was able to reduce the severity of OM and relieve the patients' pain [44]. Finally, in a retrospective study of our own research group, the effectiveness of LD-LLLT in the management of CTx-induced OM in 93 breast cancer patients was investigated. Results of this study showed that LD-LLLT significantly reduced the severity of CTx-induced OM and relieved pain [45].

RD

Up to 90–95 % of the patients undergoing RT will develop some degree of RD during the course of their therapy [46]. RD can be graded based on the criteria of the Radiation Therapy Oncology (RTOG) from red rashes and dry desquamation (grade 1), patchy/confluent moist desquamation (grade 2/3), to ulceration (grade 4). The severity of RD depends on different therapy- and patient-related factors [47]. Therapy-related factors include the irradiation dose delivered per fraction and the total dose, the duration of exposure, the volume of the treated area, and the combination with other therapies (e.g., chemotherapy). Patient-related factors include larger breast size, high BMI, overlapping skin folds, the sensitivity of the exposed skin region, smoking and nutritional status, preexisting skin conditions (e.g., psoriasis), and individual (genetic) susceptibility. However, there is still some controversy on which factors really determine the individual risk for developing severe skin reactions [48–50].

RD may be distressing and/or painful for the patient, which may affect their general quality of life. Furthermore, when the skin reactions evolve towards more severe forms, it might be

necessary to change the treatment protocol or even interrupt RT, hereby compromising treatment outcome. Therefore, preventing and managing RD is an important part of the patient care during RT. Current treatment options for RD include topical agents such as hydrophilic creams, gels, ointments, and wound dressings [50, 51]. The MASCC developed some clinical practice guidelines for the prevention and treatment of acute and late radiation skin reactions [52]. However, there is still insufficient evidence for a comprehensive consensus for the treatment of RD.

LLLT in the management of RD

The number of studies investigating the use of LLLT in the management of RD in breast cancer patients is limited (Table 3). In the late 1990s, Schindl et al. were the first to study the clinical effect of LD-LLLT on RD in patients. The study showed that LD-LLLT was effective in the induction of wound healing in RT-induced skin ulcers in a small group of post-mastectomy breast cancer patients. In another study of the same research group, they showed that LD-LLLT was able to significantly increase the dermal angiogenesis in the recalcitrant ulcers [24, 53, 54].

More recently, two studies evaluated the efficacy LED-LLLT in the prevention of RD [55, 56]. LEDs differ from LDs based on the fact that LEDs use noncoherent light and therefore they cannot produce a fully collimated monochromatic beam like a LD [7]. In the study conducted by DeLand et al., LED-LLLT treatment significantly reduced the incidence and the severity of RD in breast cancer patients treated with RT [55]. On the other hand, Fife et al. did not find a significantly reduced incidence or severity of RD after LED-LLLT in breast cancer patients [56]. These contrasting results may be attributed to a variety of factors (e.g., type radiation technique, nonblinded vs. blinded scoring of skin reactions, setup of the LED treatment).

From the abovementioned studies, no firm conclusions can be drawn on the beneficial effect of LLLT on RD. Schindl et al. only investigated the most severe form of acute RD (e.g., skin ulcers) in a small population. In addition, the LED studies showed contradictory results and LED also differs from LD.

In a recent pilot study of our research group [57], the efficacy of LD-LLLT as a treatment for RD in breast cancer patients was investigated. During this prospective study, two groups of breast cancer patients undergoing identical RT regime post-lumpectomy were compared. The control group (CTRL group, $N = 41$) received the institutional skin care protocol, while the experimental group (LLLT group, $N = 38$) was treated with this protocol plus biweekly with LD-LLLT (6 sessions) starting at fraction 20 of RT. LLLT was delivered to the patients by a diode laser in the infrared range (808–905 nm) with a fixed energy density (4 J/cm^2). The severity

Table 1 Summary of clinical studies investigating the use of LLLT for the management of BCRL

First author (ref.)	Year	Publication type	Study type	Sample size	Treatment groups	LLLT device	Wavelength (nm)	Power (mW)	Energy density (J/cm^2)	Laser schedule	Evaluation schedule	Results
Piller [84]	1998	Full article	Single group; pretest–posttest	10	LD-LLLT	Scanning; Space Mid M3-UP LD	Scanning head, 632.8 IR lasers, 904 ($\times 2$)	10–14	NA	16 sessions over 10 weeks	Pretreatment During treatment: biweekly Posttreatment: final treatment, 1, 3, 6, 30–36 months	Overall reductions in circumference in the proximal and distal upper arm, the elbow, and the wrist. Limb volume decreased with 100 ml at the end of treatment
Carati [32]	2003	Full article	Double-blind, single crossover RCT	64	•Sham laser and 1 cycle of LD-LLLT •2 cycles of LD-LLLT	Direct contact: Rian Corp LTU 904H LD	904	5	NA	3 \times /week for 3 weeks; 2 cycles (18 sessions) 8 weeks between cycle washout period	Pretreatment Posttreatment: final treatment and 4, 8, 12 weeks for each cycle	Two cycles of LLLT were effective in reducing the volume of the affected arm, extracellular fluid, and tissue hardness in approximately 33 % of patients (3 months after treatment)
Kaviani [85]	2006	Full article	Double-blinded RCT	11	•LD-LLLT •Sham laser	Noncontact mode applied 1 cm above skin; Mustang-024Ga-As LD	890	10	1.5	3 \times /week \times 3 weeks 2 cycles with an 8-week inter-cycle washout period (18 sessions)	Pretreatment Posttreatment cycle 1: immediately (final treatment) and week 9 Posttreatment cycle 2: weeks 18 and 22	Reduction in limb circumference and pain score was greater in the LLLT group than in the control group (not statistically significant)
Maiya [86]	2008	Full article	Cycled RCT	20	•LD-LLLT + UE exercise •UE exercise + CG	•Thor DD Laser; HeNe laser •EC Laser Therapy; LD	632.8 850	NA	NA	Daily; 10 days (10 sessions)	Posttreatment: immediately (final treatment)	Significantly greater reductions in arm circumference and in pain score in the LLLT group in comparison with the control group
Kozanoglu [87]	2009	Full article	RCT; blinded, alternating allocation	50	•LD-LLLT + educ •IC + educ	Electronica Pagani IR27/4 Ga-As LD	904	NA	1.5	-LD-LLLT; 3 \times /week \times 4 weeks (12 sessions) -IC; 4 weeks (20 sessions)	Pretreatment Posttreatment: immediately, 3, 6, and 12 months	Patients in both groups improved after the interventions (reduced limb circumference and pain score). LLLT group had better long-term results than the control group

Table 1 (continued)

First author (ref.)	Year	Publication type	Study type	Sample size	Treatment groups	LLLT device	Wavelength (nm)	Power (mW)	Energy density (J/cm ²)	Laser schedule	Evaluation schedule	Results
Lau [88]	2009	Full article	Single-blinded RCT	21	<ul style="list-style-type: none"> •LD-LLLT + educ •Waitlist + educ 	Scanning 50 cm above skin; Comby 3 Terza Serie, Model D LD	808 905 × 2	NA	2	3×/week × 4 weeks (12 sessions)	Pretreatment Posttreatment: immediately	Reduction in limb volume in the LLLT group but no significant difference with the control group
Dirican [34]	2011	Full article	Single group pretest–posttest	17	LD-LLLT + CB/CG	Direct contact Rian Corp LTU 904H LD	904	5	NA	3×/week; two 3-week cycles; 8-week hiatus between cycles (18 sessions)	Pretreatment Posttreatment: immediately for each cycle	Reduction in limb circumference and in pain. Increase in range of motion and in scar mobility
Omar [89]	2011	Full article	Double-blind RCT with placebo group	50	<ul style="list-style-type: none"> •LD-LLLT + exercise + educ + CG •Sham laser + exercise + educ + CG 	Direct contact; RianCorp Ga-As LD	904	5	1.5	3×/week × 12 weeks (36 sessions)	Pretreatment During treatment: weeks 4 and 8 Posttreatment: immediately and 4 weeks	LLLT significantly reduced the limb volume, increased shoulder mobility, and hand grip strength in 93 % of patients
Ridher [33]	2013	Full article	RCT	46	<ul style="list-style-type: none"> •LD-LLLT •MLD •MLD + LD-LLLT All received CB	Direct contact; Rian Corp LTU 904H LD	904	5	NA	Average number of sessions: LLLT, 10 MLD, 8 MLD + LLLT, 10	Pretreatment Posttreatment: immediately	Significant reduction in volume in all groups but no significant difference between the groups. No significant difference between groups for pain score

BCRL breast cancer-related lymphedema, *RCT* randomized controlled trial, *LD* laser diode, *LLLT* low-level light therapy, *MLD* manual lymphatic drainage, *CB* compression bandaging, *educ* education, *CG* compression garment, *IC* intermittent compression, *NA* not available, *ref* reference

Table 2 Summary of clinical studies investigating the use of LLLT for the prevention and management of OM in breast cancer patients

First author (ref.)	Year	Publication type	Study type	Sample size	LLLT device	Wavelength (nm)	Power (mW)	Energy density (J/cm^2)	Laser schedule	Evaluation schedule	Assessment scale	Results
Kuhn [41]	2007	Full article	RCT with placebo group	Total = 34 LD-LLLT = 18 (2 BC) Sham = 16	GaAlAs LD	830	100	4	5 consecutive sessions	Daily until complete healing	NCI CTC	Mean OM duration (days) LLLT group, 6.6 Placebo group, 11.5
Genot-Klastersky [42]	2008	Full article	Single-arm prospective study	Total = 36 BC = 18	Scanning LD	650	100	2	3 sessions/week during CTx and/or RT	Weekly before and after the treatment	RTOG	Overall success rate, 81 %
Pres-Santos [43]	2012	Abstract	Case report study with 2 groups (control and LLLT)	Total = BC = 12 (6 in LLLT group and 6 in control group)	NA	NA	NA	NA	24 h before CTx, every 48 h during CTx and 1 week after CTx	NA	NA	More severe OM in control group. Reduction in pain (42.86 %) in LLLT group
Arbabi-Kalati [44]	2013	Full article	Double-blind RCT	BC = 25 Total = 48	Mustang-024 Ga-As LD	630	30	5	Prior to each CTx session	Two times/week	WHO	Statistically significant lower OM grade and intensity of pain in LLLT group
Mebis [45]	2014	Abstract	Retrospective study	Total = BC = 93	AsGA LD combined with an infrared LD	665	100/500	4	2 times/week until complete healing	Before the start and at the end of treatment	WHO	Statistically significant improvement in severity of OM and in pain

OM oral mucositis, CTx chemotherapy, RT radiotherapy, RCT randomized controlled trial, BC breast cancer, NCI CTC National Cancer Institute Common Toxicity Criteria, RTOG Radiation Therapy Oncology Group, NA not available, WHO World Health Organization, ref reference, LD laser diode, LLLT low-level light therapy

Table 3 Summary of clinical studies investigating the use of LLLT for the management of RD in breast cancer patients

First author (ref.)	Year	Publication type	Study type	Sample size	LLLT device	Wavelength (nm)	Power (mW)	Energy density (J/cm ²)	Laser schedule	Evaluation schedule	Assessment scale	Results
Schindl [24]	1999	Full article	Case report	3	HeNe LD	632.8	30	30	3 times/week until wound closure	Weekly and at 36 months follow-up	NA	Improved wound healing
DeLand [55]	2007	Full article	Prospective study with a retrospective control group	47	LED	590	NA	0.15	Daily after each RT session	Weekly	NCI CTC	Significantly reduced incidence of RD grade
Fife [56]	2010	Full article	Prospective, double-blind RCT with a placebo group	33	LED	590	NA	NA	Daily before and after each RT session + 7 additional daily treatments after the end of RT	Baseline, weekly during RT and 2–6 weeks after the end of RT	NCI CTC	No reduced incidence of RD grade
Censabella [57]	2016	Full article	Prospective quasi-experimental study with control and LLLT group	79	LD	808–905	60	4	2 times/week after the RT session starting at fraction 20 of RT	Baseline, fraction 20 of RT and at the end of RT	RTOG	Significantly less severe skin toxicity in LLLT group

RD radiodermatitis, HeNe helium neon, LED light-emitting diode, NA not available, RT radiotherapy, NCI CTC National Cancer Institute Common Toxicity Criteria, RTOG Radiation Therapy Oncology Group, ref reference, LD laser diode, LLLT low-level light therapy

of RD was evaluated by trained nurses before the start of LD-LLLT and at the end of RT according to the criteria of the RTOG [47].

Before the start of LD-LLLT (i.e., at fraction 20), the distribution of the RTOG grades was comparable between both groups ($p = 0.690$), with most of the patients presenting RTOG grade 1. At the end of RT, the severity of RD was significantly different between the two groups ($p = 0.002$). More patients of the control group developed grade 2 RD as compared to those in the LD-LLLT treated group: There was an intensification of the skin reactions in the CTRL group ($p = 0.002$), while it remained stable ($p = 0.083$) in the LLLT group [57].

CIPN

CIPN is a known side effect of many neurotoxic chemotherapeutic agents (e.g., taxanes, platinum agents, and vinca alkaloids) in breast cancer patients. It occurs in approximately one third of the cancer patients undergoing CTx. CIPN is characterized by damage to the peripheral nervous system, which leads to a distorted communication between the central nervous system and the extremities. Most of the symptoms are sensory such as numbness, tingling and burning sensations, temperature sensitivity, and pain starting in the toes and fingers. In some cases, motor symptoms can occur, ranging from muscle weakness, decreased movement, and autonomic neuropathy. The type of chemotherapeutic agent, the administration time, and the cumulative dose determine the degree of neurotoxicity. Due to the distressing and painful symptoms of CIPN, it might substantially affect the patients' quality of life and reduce their function ability temporarily or permanent. In addition, CIPN can lead to reductions in CTx dose or treatment interruptions, which eventually affects the overall survival of the patients [58, 59].

Current management options for CIPN are focused on prevention, restoration of function, and on symptomatic treatment. For the prevention of CIPN, already different protective agents have been studied (e.g., vitamin E, acetyl-L-carnitine (ALC), leukemia inhibitory factor (LIF), erythropoietin, glutathione, and amifostine). However, there is not enough significant evidence to recommend these agents for general use. The main focus in the management of CIPN is supportive care

and symptom treatment. Some CIPN patients might benefit from physical and occupational therapy, especially in case of functional impairment. Pain management in CIPN patients is based on the use of antidepressants, antiepileptics, and opioids [60].

LLLT in the management of CIPN

Up to now, there was only one study investigating the effect of LD-LLLT for the management of CIPN (Table 4). In this study, 34 female breast cancer patients undergoing CTx were treated by LD-LLLT. The effect of LD-LLLT treatment was evaluated by using a 10-point scale Brief Pain Index (BPI) questionnaire before and after laser irradiation. After LD-LLLT the BPI score of the patients decreased with an average of 4 points [61]. Recently, Hsieh et al. investigated the effect of LD-LLLT on allodynia (pain from a stimulus that normally would not provoke pain) in a rat model of acute oxaliplatin-induced neuropathy. The results showed that repeated application of LD-LLLT significantly reduced the oxaliplatin-induced cold and mechanical allodynia. These findings indicate that LD-LLLT might be a potential treatment option for CIPN [62].

ONJ

The use of bisphosphonates or denosumab for the treatment of bone metastases in breast cancer patients has become standard of care. Bisphosphonates inhibit osteoclast-mediated bone resorption in vivo by several routes. They have a direct effect on bone resorption by impairing the osteoclast function and inducing osteoclast apoptosis [63]. Denosumab inhibits the osteoclast function by inhibiting the RANK-RANKL pathway [64]. Both therapies lead to a reduction in skeletal complications and associated pain. However, they may cause serious side effects of which medication-related osteonecrosis of the jaw (MRONJ) is the most frequent one [64–66].

The risk of developing MRONJ in cancer patients treated with bisphosphonates is approximately 1 %. In case of cancer patients undergoing denosumab treatment, the risk of developing MRONJ lies between 0.7 and 1.9 % [67]. The American Association of Oral and Maxillofacial Surgeons (AAOMS)

Table 4 Summary of clinical studies investigating the use of LLLT for the management of CIPN in breast cancer patients

First author (ref.)	Year	Publication type	Study type	Sample size	LLLT device	Wavelength (nm)	Power (mW)	Energy density (J/cm^2)	Laser schedule	Evaluation schedule	Results
Yamada [61]	2010	Abstract	Single group; pretest-post test	34	GaAlAs LD	830	NA	NA	NA	Before and after irradiation	BPI score decreased by an average of 4 points

CIPN chemotherapy-induced peripheral neuropathy, LLLT low-level light therapy, BPI Brief Pain Index, NA not available, ref reference, LD laser diode

defined MRONJ as an area of exposed bone in the maxillofacial region that does not heal within 8 weeks after identification by a health care provider, in a patient who was receiving or had been exposed to antiresorptive or antiangiogenic agents and who did not receive RT to the craniofacial region. Patients with MRONJ have to cope with nonhealing exposed bone areas, infections and swelling of the surrounding soft tissues, fistulas, and severe pain. Therefore, MRONJ can seriously affect the patients' quality of life [67, 68].

Up to now, there is no standard treatment strategy for MRONJ and every case has to be treated individually. However, the AAOMS has made some recommendations depending on the stage of the disease ranging from pain management, use of antibiotics, antimicrobial mouth rinses, wound debridement, to surgical interventions (e.g., removal of sharp bone structures) [67–69].

LLLT for the treatment of MRONJ

LLLT is known to have a biostimulatory effect on soft oral tissues [70, 71]. In addition, LLLT seems to be able to stimulate the bone mineralization and production [72–76]. The efficiency of the use of LD-LLLT for the treatment of MRONJ has already been investigated in six prospective studies (Table 5). In the study by Angiero et al., ten MRONJ patients (one breast cancer patient) were treated with LD-LLLT after wound debridement. Six patients showed complete remission and four showed some improvements of symptoms [77]. Scoletta et al. treated 20 BRONJ patients with LD-LLLT (six breast cancer patients). The results of this study showed a significant reduction in pain score, clinical size, edema, and presence of pus and fistulas after LD-LLLT treatment [78].

The study by Romeo et al. evaluated the efficiency of LD-LLLT in the reduction of pain accompanied with MRONJ in seven patients (two breast cancer patients). Six patients showed a significant reduction in pain score [79]. Vescovi et al. treated 32 MRONJ patients with LD-LLLT and was able to show complete remission in nine patients and clinical improvement in 23 patients [80]. In the study by Martins et al. 14 patients underwent LD-LLLT in combination with platelet-rich plasma (PRP) treatment (seven breast cancer patients). Twelve patients showed complete remission and two some improvement [81]. In a final study by Altay et al., they treated 11 MRONJ patients with LD-LLLT in addition to medical and surgical treatment. Four patients showed full wound healing and seven patients partial recovery [82]. None of these studies showed any side effects linked to LD-LLLT treatment.

Laser parameters

Among the studies described above, the LLLT parameters (wavelength, power, energy density) that were used vary

greatly (Tables 1, 2, 3, 4, and 5). Appropriate LLLT parameters seem to be crucial in the effectiveness of this treatment method in the described disorders [8].

Wavelength

LLLT uses wavelengths that fall into an optical window of visible and NIR light (600–1000 nm). Tissue penetration is maximized in this range, as the principal tissue chromophores (hemoglobin and melanin) have high absorption bands at wavelengths shorter than 600 nm. Furthermore, at wavelengths above 1000 nm, water is absorbing many photons, reducing their availability for specific chromophores. Wavelengths between 600 and 750 nm (red light) are chosen for treating superficial tissue, and wavelengths between 750 and 1000 nm (NIR light) are chosen for deeper-seated tissues, because of their deeper penetration into tissue [8, 83].

The wavelengths most frequently used among the studies analyzed in this review ranged between red light and NIR spectral bands (639–904 nm). In the studies investigating the use of LLLT for the management of BCRL, NIR LDs were used and all appeared to be effective. The most common wavelength in seven of the nine BCRL studies was 904 nm. In three of the five OM studies, they use red light LDs with wavelengths between 630 and 665 nm and in one study they used a NIR LD (830 nm). Both types of wavelengths appeared to be effective for the prevention and treatment of OM. The studies investigating the use of LLLT for the management of RD used red light (632.8 nm), NIR (808–905 nm) LDs, or red LED light (590 nm). Thereby, the LED devices showed contrasting results. In the CIPN study, a NIR LD (830 nm) was used. The studies investigating the effectiveness of LLLT for the treatment MRONJ, mainly used LD in the red light or NIR range (650–910 nm). One out of six studies used a Nd:YAG (1064 nm) laser and one used an Er:YAG laser (2940 nm). However, these two LDs used light above the general optical window of LLLT, and they still showed beneficial results for the management of MRONJ.

Dosimetry

The dosimetry of LLLT is determined by several parameters, each affecting its efficacy. These parameters can be subdivided into two groups, i.e., the irradiation parameters (power density, the pulse structure, the coherence, and the polarization) and the energy density (“dose”). However, most of the selected articles in this review only described the power and energy density of the LLLT device. In literature, there is evidence that suggests that the effectiveness of LLLT treatments varies greatly on both the energy and power used. There seems to be an upper and lower threshold for both parameters between which LLLT is effective [4, 8].

Table 5 Summary of clinical studies investigating the use of LLLT for the management of MRONJ in breast cancer patients

First author (ref.)	Year	Publication type	Study type	Sample size	Treatment	LLLT device	Wavelength (nm)	Power (mW)	Energy density (J/cm^2)	Laser schedule	Evaluation schedule	Results
Angiero [77]	2009	Full article	Three groups; pretest–posttest	Total = 49 BC = 8	<ul style="list-style-type: none"> •LD-LLLT ($N = 10$; BC = 1) •Surgical intervention ($N = 20$; BC = 4) •Conservative therapy ($N = 19$; BC = 3) 	Er:YAG laser	2940	NA	27–54	3 applications	12–80 months follow-up period	CR = 6; PR = 4
Scioletta [78]	2010	Full article	Single group; pretest–posttest	Total = 20 BC = 6	LD-LLLT	Pulsed LD	904	7	28.4	10 sessions over a period of 20 days	1 h before the laser procedure and 28 days after	Statistically significant decreased pain score, clinical size, edema, and presence of pus and fistulas
Romeo [79]	2011	Full article	Single group; pretest–posttest	Total = 7 BC = 2	LD-LLLT	Double LD	650 904–910	100–500	NA	Every 3 days for 2 weeks	Twice before each LLLT cycle, once before the initial laser application and 3 days after the last laser application	Statistically significant difference between the NRS rates before and after the protocol
Vescovi [80]	2012	Full article	Five groups; pretest–posttest	Total = 190 (BM = 85 MM = 62 OP = 43)	<ul style="list-style-type: none"> •Medical therapy •Medical therapy + LD-LLLT •Surgery •Surgery + LD-LLLT •Er:YAG laser surgery 	Nd:YAG Laser	1064	NA	14.37	Weekly during 2 months	NA	Combination of LLLT with medical therapy or surgery improved the severity and the healing of ONJ
Martins [81]	2012	Full article	Three groups; pretest–posttest	Total = 22 BC = 13	<ul style="list-style-type: none"> •Clinical protocol ($N = 3$) •Surgical protocol ($N = 5$) •PRP + LD-LLLT ($N = 14$; BC = 6) 	InGaAlP LD	660	40	6	Daily until mucosal healing	Followed until mucosal wound healing was clinically observed or weekly during the first month	CR = 12; PR = 2
Altay [82]	2014	Full article	Single group; pretest–posttest	Total = 11 BC = 3	LD-LLLT	GaAlAs LD	808	500	5	Five session on postoperative day 1, 3, 5, 7, and 10	Before the start of laser and follow-up (6–25 months)	CR = 4; PR = 7

MRONJ medication-related osteonecrosis of the jaw, *LLLT* low-level light therapy, *BC* breast cancer, *BM* bone metastasis, *MM* multiple myeloma, *OP* osteoporosis, *PRP* platelet-rich plasma, *CR* complete remission, *PR* partial remission, *MRS* numerical rating scale, *NA* not available, *ref*/reference, *LD* laser diode

Power

LLLT typically uses a power in the range from 1 to 1000 mW, and this varies widely depending on the type of medical application. Outside these thresholds, the light is either too weak to cause any effect or too strong as such it can cause damage to the tissue [8]. The power used in the studies that were described in this review ranged from 5 to 500 mW. The power that was used in most of the BCRL studies ranged from 5 to 15 mW. In general, the OM studies used higher power values. The most common power in these studies was 100 mW. Only one OM study used a power of 30 mW. In the RD studies, only two studies mentioned the power they used, which ranged from 30 to 60 mW. For the CIPN study, the power was not mentioned. In the MRONJ studies, the power used varied widely from 7 to 500 mW.

Energy density

As described in literature, there appears to be a biphasic dose response for LLLT. This means that an insufficient power density or too short irradiation time will have no effect on the irradiated tissue. Whereas, an inhibitory response in the tissue can be observed when LLLT is applied with a too high power density or a too high irradiation time. Therefore, selecting the correct dose of light (in terms of energy density) for any medical setting is difficult. The dose of light that is chosen depends on the pathology being treated and in particular upon how deep the light needs to penetrate into the tissue. For the treatment of superficial tissues, the most frequently used dose lays around 4 J/cm² with a range of 1–10 J/cm². For the treatment of deeper-seated tissue, the doses used range from 10 to 50 J/cm² [4]. By evaluating the energy density of the selected articles, it became clear that it varied widely, ranging from 0.15 to 54 J/cm². In the BCRL studies, they mostly used a low-energy density of 1.5 J/cm². In the OM studies, an energy density between 2 and 5 J/cm² was used. The energy density varied widely in the RD studies ranging from low (0.15 J/cm²) to high values (30 J/cm²). For the CIPN study, it was not described. The MRONJ studies used an energy density between 5 and 54 J/cm².

Conclusion

The studies analyzed in this review showed that LLLT has the potential to become a new treatment modality in the supportive care of breast cancer patients. These promising results need further confirmation in randomized double-blind control trials with larger (breast) cancer patient populations. These trials are needed to clear up some uncertainties regarding the lack of consistency between the laser parameters that are used. They need to investigate which type of laser protocol (e.g., LD

or LED, the dose, duration, frequency, power, number of laser sessions, etc.) leads to the most favorable outcome in clinical practice. Finally, it is necessary to investigate the safety of LLLT for the treatment of cancer patients. Therefore, studies need to include a longer follow-up phase of the patients in order to assess if LLLT does not impact tumor behavior directly and may cause tumor proliferation.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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