The role of photobiomodulation therapy in the care of cancer patients: review of the literature

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SUMMARY

Photobiomodulation therapy is based on the application of visible and/or (near-)infrared light on the target tissue. We performed a review of 34 articles on the use of photobiomodulation therapy in the management of cancer related lymphoedema, oral mucositis, radiodermatitis, chemotherapy-induced peripheral neuropathy, osteonecrosis of the jaw, and xerostomia/hyposalivation. The findings suggest that photobiomodulation therapy is a promising option for the management of these cancer therapy-related side effects.

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INTRODUCTION

Cancer therapy ranging from surgery, chemotherapy (CTx), radiotherapy (RT) to targeted systemic therapies (e.g. hormone- and/or immunotherapy) can cause serious side effects. The severity of the side effects depends on the cancer type and site, the therapy characteristics, and the individual patient susceptibility. The patients' quality of life can seriously be affected by these side effects and therefore effective supportive care strategies are necessary.[1] The use of photobiomodulation therapy (PBMT), also known as low-level laser therapy (LLLT), was introduced in 1967 by Mester *et al.*[2] It's based on the application of visible and/or (near-)infrared light by laser diodes (LDs) and/or light-emitting diodes (LEDs) on target tissue.[3] Several studies have demonstrated that PBMT is able to stimulate the wound healing process, reduce inflammation, and relieve pain.[4] For the last twenty years, the use of PBMT for the management of cancer therapy-related side effects has been investigated in several clinical trials. However, for a lot of clinicians this new and emerging therapeutic option is still unknown.[5] The aim of this review was to summarise all the available clinical trials that examined the applicability of PBMT in the domain of cancer related lymphoedema (CRL), oral mucositis (OM), radiodermatitis (RD), chemotherapy-induced peripheral neuropathy (CIPN), osteonecrosis of the jaw (ONJ), and xerostomia/hyposalivation.

PBMT – CELLULAR AND TISSUE MECHANISM

The basic mechanism behind PBMT is quite complex and is still not completely clear. Several studies demonstrated that the light is absorbed by endogenous chromophores in the target cells. The main chromophore is cytochrome c ox-

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idase (CCO), located in the mitochondrial membrane. The absorbed light energy stimulates the electron transport chain in the mitochondria leading to an increased production of adenosine triphosphate (ATP). An increase in ATP will improve the cellular metabolism, leading to improved cellular functions.[4] Additionally, the nitric oxide (NO) production can be regulated by PBMT. NO causes vasodilatation, which will improve the transport of oxygen and immune cells into the tissue leading to enhanced cell repair.[4] Finally, PBMT can stimulate the production of a low level of reactive oxygen species (ROS). A low concentration of ROS can activate several transcription factors, leading to upregulation of various genes. These will generate proteins such as growth factors and inflammatory mediators that are involved in the wound healing process.[4]

Evidence of *in vitro* and *in vivo* studies show that PBMT is able to influence each phase of the wound healing process by enhancing phagocytosis and angiogenesis, by downregulating inflammatory mediators, by increasing the proliferation of keratinocytes and fibroblasts, and by stimulating the collagen synthesis.[6,7]

PBMT IN THE SUPPORTIVE CARE OF CANCER PATIENTS

Cancer-related lymphoedema (CRL)

Lymphoedema is a common side-effect in patients treated for breast cancer (BC) and head and neck cancer (HNC). In approximately 20% of BC patients, lymphoedema can develop in the upper extremity after BC treatment. Patients with breast cancer-related lymphoedema (BCRL) have to cope with pain and a diminished arm mobility leading to decreased daily functional activity.[8] Lymphoedema in HNC patients can develop externally, on the face and/or neck, or internally at the pharynx or larynx. A study by Deng *et al.* with 81 HNC patients, showed that 75 % of the patients developed CRL (10% external, 39% internal, and 51% both types). External CRL may affect the patient's body image, while internal CRL may cause breathing, swallowing, and speaking problems.[9]

The treatment of CRL is focused on preventing disease progression and reducing the symptoms. Complete decongestive therapy (CDT) is the main treatment option for CRL.[10]

PBMT FOR THE MANAGEMENT OF CRL

The effectiveness of PBMT for the management of BCRL has already been demonstrated in several studies and in 2006 it was accepted as treatment option by the Food and Drug Administration (FDA).[11] The beneficial effect of PBMT on BCRL is explained by the fact that it is able to stimulate the lymph flow and increase the number of lymph vessels. In addition, PBMT can also prevent the formation of fibrotic tissue.[11]

A meta-analysis of nine studies by Smoot *et al.* demonstrated moderate evidence for the effectiveness of LD-PBMT in the reduction of arm swelling and pain in women with BCRL (*Table 1*). Additionally, these studies showed that the combination of PBMT with CDT is more effective in reducing the arm volume than with CDT alone.[11] A recent randomised, placebo-controlled clinical trial (RCT) with 40 BC patients confirmed the results of the meta-analysis.[12] Up to now, there was only one case-control study that showed a beneficial effect of LD-PBMT in the management of CRL in HNC patients.[13]

A task force consisting of an international multidisciplinary panel of clinicians and researchers with expertise in the area of supportive care in cancer and/or the use of PBMT, developed guidelines for the management of complications related to cancer therapy. They suggested using a LED- or LD-PBMT device (wavelength 750-830 nm, power density 20–80 mW/cm^2, fluence 3 J/cm^2) two to three times a week to treat CRL until symptoms improve. They suggested applying it on the edematous area and the regional lymphatic chain.[1]

Oral mucositis (OM)

OM occurs in 20-40% of patients undergoing conventional CTx and in almost all patients undergoing RT for HNC. It is characterised by erythematous mucosal changes, which can develop into ulceration of the oral mucosa. OM can seriously affect the patient's quality of life, as it can be very painful and lead to malnutrition. In severe cases of OM, parenteral nutrition or eventually hospitalisation is necessary to prevent underfeeding.[14]

The guidelines of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) recommend the use of cryotherapy, oral care protocols, pain medication, and anti-inflammatory mouthwash to prevent and manage OM.[14]

PBMT IN THE PREVENTION AND MANAGEMENT OF OM

The use of PBMT for the prevention and management in OM has already been extensively investigated (*Table 2*). A meta-analysis of eleven RCTs in HNC patients showed that LD-PBMT reduced the OM incidence, severity, duration, and the associated pain.[15] Oberoi *et al.* performed another systematic review with meta-analysis of eighteen RCTs in which they showed that prophylactic use of LD-PBMT reduced severe OM and its associated pain in patients treated for HNC or undergoing hematopoietic stem cell transplantation (HSCT).[16] In 2014, the MASCC/ISOO panel developed clinical practice guidelines in which they included the use of PBMT in the prevention and management of OM based

TABLE 1. Summary of clinical studies investigating the use of PBMT for the management of CRL.

First author (ref.)	Year	Publication type	Study type	Sample size + cancer type	Treatment groups	PBMT device	Wavelength (nm)	Power (mW)	Energy density (J/cm²)	Laser schedule	Evaluation schedule	Results
Piller[11]	1998	Full article	Single group	10 BC	LD-PBMT	Scanning; Space Mid M3-UP LD	Scanning head: 632.8 IR lasers: 904 (x2)	10-14	NA	16 sessions over 10 weeks	Pre-treatment During treatment: biweekly Post-treatment: final treatment, 1, 3, 6, 30–36 months	42% reduction in arm volume after PBMT. The arm tissue (except the upper arm) softened. Subjective symptoms improved (e.g. pain, cramps, heaviness, mobility).
Carati[11]	2003	Full article	Double-blind, single crossover RCT	64 BC	-Sham laser and 1 cycle of LD-PBMT -2 cycles of LD-PBMT	Direct contact: Rian Corp LTU 904H LD	904	5	NA	3×/week for 3 weeks; two cycles (18 sessions) 8-weeks between -cycle washout period	Pre-treatment Post-treatment: final treatment and 4, 8, 12 weeks for each cycle	PBMT reduced effectively the arm volume, extracellular fluid and tissue stiffness in 33% of the patients.
Kaviani[11]	2006	Full article	Double-blinded RCT	11 BC	-LD-PBMT -Sham laser	Noncontact mode applied 1 cm above skin; Mustang-024 Ga-As LD	890	10	1.5	3×/week × 3 weeks 2 cycles with an 8 week inter-cycle washout period (18 sessions)	Pre-treatment Post-treatment cycle 1: Immediately (final treatment) and week 9 Post-treatment cycle 2: weeks 18 and 22	In both groups the arm circumference decreased, but no significant difference between the groups.
Maiya[11]	2008	Full article	Cycled RCT	20 BC	-LD-PBMT + UE exercise -UE exercise + CG	-Thor DD Laser; He-Ne laser -EC Laser Therapy; LD	632.8 850	NA	NA	Daily; 10 days (10 sessions)	Post-treatment: immediately (Final treatment)	Significantly higher reduction in arm volume and pain score in PBMT group.
Kozanoglu[11]	2009	Full article	RCT; blinded, alternating allocation	50 BC	-LD-PBMT + educ -IC + educ	Electronica Pagani IR27/4 Ga-As LD	904	NA	1.5	3×/week × 4 weeks (12 sessions) 4 weeks (20 sessions)	Pre-treatment Post-treatment: immediately , 3, 6, , and 12 months	Arm circumference and pain score reduced in both groups, but the long-term results were better in the PBMT group.
Lau[11]	2009	Full article	Single-blinded RCT	21 BC	-LD-PBMT + educ -Waitlist + educ	Scanning 50 cm above skin; Comby 3 Terza Serie, Model D LD	808 905x2	NA	2	3×/week × 4 weeks (12 sessions)	Pre-treatment Post-treatment: immediately	No significant difference in arm volume reductions between the two groups.
Dirican[11]	2011	Full article	Single group pretest-posttest	17 BC	LD-PBMT + 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)	Pre-treatment Post-treatment immediately for each cycle	Combination of PBMT with CB showed benefits in the reduction of arm volume, pain and scar mobility.
Omar[11]	2011	Full article	Double-blind RCT with placebo group	50 BC	-LD-PBMT + exercise + educ + CG -Sham laser + exercise + educ + CG	Direct contact; Rian-Corp Ga-As LD	904	5	1.5	3×/week × 12 weeks (36 sessions)	Pre-treatment During treatment: weeks 4 and 8 Post-treatment: immediately and 4 weeks	Significant reduction in arm volume. Significant increase in shoulder mobility and handgrip strength in 93% of patients.
Ridner[11]	2013	Full article	RCT	46 BC	-LD-PBMT -MLD -MLD + LD-PBMT All received CB	Direct contact: Rian Corp LTU 904H LD	904	5	NA	Average number of sessions: -PBMT: 10 -MLD: 8 -MLD + PBMT: 10	Pre-treatment Post-treatment: immediately	Arm volume reduced in all groups, but no significant difference between the groups. No differences in quality of life. Skin quality improved in all groups.
Lee[13]	2013	Full article	Case control study	1 HNC	-LD-PBMT	-104 Diode Cluster Probe (lymphatic pathways) -904-LTU (fibrotic areas)	NA	5-10	1.5 and 3	Daily over 3 weeks	Pre-treatment, weekly during PBMT and 3 month after the end of PBMT	Significant reduction in oedema and improvement in swallowing.
Storz[12]	2016	Full article	Double-blind RCT with placebo group	40 BC	-LD-PBMT group -Sham laser group	Cluster laser device, non-contact mode: "TIME-LAS Vital"	980	640	4.89	2x/week x 4 weeks	Pre-treatment Post-treatment: immediately, 1-3 months	50% reduction in median pain score. Increase in mean quality of life and grip strength in PBMT group. No statistically significant difference between the groups.

Partially adapted from Robijns et al. (2017)[5]

Abbreviations: BC, breast cancer; HNC, head and neck cancer; CRL, cancer-related lymphedema; RCT, randomised controlled trial; LD, laser diode; PBMT, photobiomodulation therapy; MLD, manual lymphatic drainage; CB, compression bandaging; educ, education; CG, compression garment; IC, intermittent compression; NA, not available; ref, reference; UE, upper extremity.

TABLE 2. Summary of reviews with meta-analysis investigating the use of PBMT for the prevention and management of OM in cancer patients.

First author (ref.)	Year	Publication type	Type + number of studies included	Sample size	Wavelength (nm)	Power (mW)	Energy density (J/cm²)	Laser schedule	Results
Bjordal[15]	2011	Systematic review with meta-analysis	11 placebo-controlled RCTs	415	- Red (633–685) - Infrared (780–830)	-Red (10-60) -Infrared (50-100)	1-6 J/point	Minimum 3 sessions/week	Reduced OM prevalence, severity, duration, and associated pain.
Migliorati[17]	2012	Systematic review with meta-analysis	24 clinical trials	NA	400-1200	10-500	2-70	NA	Recommendation: - Prevention of OM in adult patients receiving HSCT (650 nm, 40 mW, and 2 J/cm²). Suggestion: - Prevention of OM in HNC patients undergoing RT without CTx(632.8 nm).
Oberoi[16]	2014	Systematic review with meta-analysis	18 RCTs and quasi-RCTs	1144	632.8-780	10-100	1.5-6.3	5 sessions/week - daily	Prophylactic PBMT reduced severe OM and pain in patients with cancer and HSCT recipients.

Partially adapted from Robijns et al. (2017)[5]

Abbreviations: OM, oral mucositis; CTx, chemotherapy; HNC, head and neck cancer; HSCT, hematopoietic stem cell transplantation; RCT, randomised controlled trial; NA, not available; ref, reference; PBMT, photobiomodulation therapy.

on a meta-analysis performed by Migliorati *et al.*[17] Following these guidelines, PBMT is recommended for the prevention of OM in patients receiving high-dose CTx in case of HSCT. In addition, they suggested using PBMT for the prevention of OM in HNC patients undergoing RT without concomitant CTx.[14,17] The European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) also recommend the use of LD-PBMT in patients receiving high-dose CTx or chemoradiotherapy (CRT) before HSCT.[18,19] The guidelines of Zecha *et al.* proposed to use PBMT both in a preventive and therapeutic manner (wavelength 630-830 nm, power density 20-80mW; energy density 2–4 J/cm²). The prophylactic use of PBMT can start before or on the first day of CTx/RT and continue during all days of the therapy on each site of the mucosal surface that is at risk. Once OM has developed PBMT is recommended two to three times a week up to daily until the symptoms improve.[1]

Radiodermatitis (RD)

RD affects up to 95% of the patients undergoing RT. RD is an inflammatory skin reaction that is characterised by red rashes, dry desquamation and in some cases moist desquamation. The severity of the skin reactions depends on different therapy- and patient-related factors. RD is a distressing and painful side effect of RT, which can lead to problems in the patients' daily life (e.g. washing practices, getting dressed, household activities, hobbies). Rarely, the skin reactions become too severe, leading to interruption of RT for a short period of time.[20] Existing treatment options for RD include different topical agents such as moisturising creams/gels and wound dressings. The MASCC panel developed clinical practice guidelines for the prevention and treatment of RD. However, the available evidence is still to weak to support a general consensus on the management of RD.[21]

PBMT FOR THE PREVENTION AND MANAGEMENT OF RD

The research on the use of PBMT for the prevention and management of RD in cancer patients is limited (*Table 3*).

Schindl *et al.* introduced it in the late 1990's, by performing a case report study in which they treated three breast patients with RT-induced skin ulcers after mastectomy. Re-

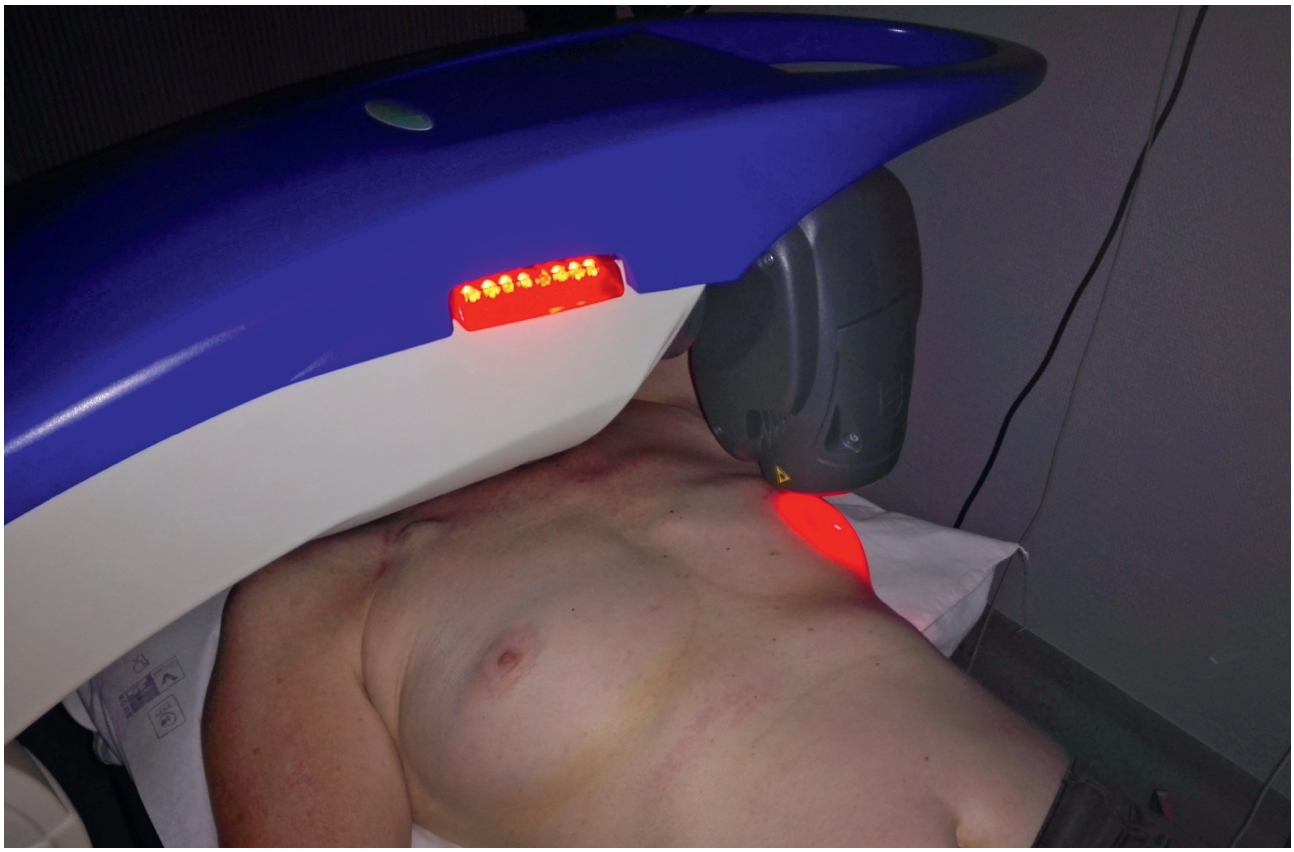

FIGURE 1. The application of PBMT to an irradiated breast of a breast cancer patient to treat acute radiodermatitis.

sults showed that LD-PBMT was able to improve the wound healing process of the skin ulcers.[22] Furthermore, there were two studies that investigated the use of LED-PBMT for the prevention of RD.[23,24] A study by Deland *et al.* showed that LED treatments reduced the incidence of RD in breast cancer patients.[23] In contrast, Fife *et al.* was not able to replicate these results in a RCT.[24] A possible explanation for the different results is the use of different treatment and assessment parameters in both studies. A more recent study by our research group showed that LD-PBMT is an effective treatment for acute RD in breast cancer patients. PBMT prevented the aggravation of acute RD and reduced the impact of it on the patients' quality of life.[25]

Zecha *et al.* suggested using LED- or LD-PBMT (wavelength 630–680 nm; power density 20-150mW/cm^2; energy density 2–4 J/cm^2) in a prophylactic (daily from the first day of RT) or a therapeutic regime (minimum three times a week) on the cutaneous surfaces of the irradiated area (*Figure 1*).[1]

Chemotherapy-induced peripheral neuropathy (CIPN)

Neurotoxic chemotherapeutic substances (e.g. platinum agents, taxanes, vinca alkaloids, thalidomide, and bortezomib) can lead to chemotherapy-induced peripheral neuropathy (CIPN). It affects approximately 68.1% of the patients when measured in the first month after CTx, 60.0% at three months and 30.0% at six months or more.[26] The risk for developing CIPN is determined by the type of CTx agents, the administration time, and the cumulative dose. Most patients with CIPN develop sensory dysfunctions. Sometimes motor dysfunctions such as muscle weakness and/or autonomic neuropathy can also establish. The underlying mechanism causing CIPN is still unclear but is known that chemotherapeutic agents can damage the peripheral and/or central nerve system, affecting the communication in the nerve tracts. Patients with CIPN have to cope with functional problems during their daily life. In severe cases of CIPN, CTx dose reductions, changes in the CTx dosing or even a CTx termination need to be performed, leading to diminished overall survival.[27]

To date, there is still no effective treatment for CIPN. Currently, the main focus in the management of CIPN is reducing the symptoms by medication and/or physical therapy.

PBMT AND CIPN

The use of PBMT for the management of CIPN has only been investigated in three clinical trials (*Table 4*). Yamada *et al.* investigated the use of LD-PBMT in a single-arm, prospective study with 34 female BC patients undergoing taxane-based

TABLE 3. Summary of clinical studies investigating the use of PBMT for the management of RD in cancer patients.

First author (ref.)	Year	Publication type	Study type	Sample size	PBMT device	Wavelength (nm)	Power (mW)	Energy density (J/cm²)	Laser schedule	Evaluation schedule	Assessment scale	Results
Schindl[22]	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	Accelerated wound healing.
DeLand[23]	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.
Fife[24]	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 significant effects.
Censabella[25]	2016	Full article	Prospective quasi-experimental study with control and PBMT 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 reduced incidence of RD grade.

Partially adapted from Robijns et al. (2017)[5]

Abbreviations: 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; RD, radiodermatitis; ref, reference; LD, laser diode; PBMT, photobiomodulation therapy; RCT, randomised controlled trial.

CTx. The patients evaluated the effectiveness of the treatment by using a 10-point scale Brief Pain Index (BPI) questionnaire before and after each laser session. At the end of the trial the BPI score of the patients ameliorated with an average of four points.[28] In a more recent, prospective cohort study with pre- and post-intervention design by Hsieh *et al.*, seventeen patients with gastrointestinal cancer were treated with LD-PBMT. Results revealed that after twelve sessions of PBMT, the patients' neurotoxicity symptoms were diminished and moreover their cold and mechanical allodynia was resolved.[29] Argenta *et al.* enrolled 70 patients treated with CTx for cancer of different aetiology in a randomised-control, crossover trial to determine if LD-PBMT (eighteen sessions) with or without physiotherapy reduced the symptoms of CIPN compared to a sham treatment. This study demonstrated that LD-PBMT could reduce the CIPN associated symptoms effectively.[30] These findings indicate that LD-PBMT might be an effective therapeutic option for CIPN. However, it was not taken up in the guidelines developed by Zecha *et al.*[1] Our research unit is now performing a RCT investigating the effectiveness of PBMT in the prevention of CIPN in breast cancer patients undergoing taxane treatment.

Osteonecrosis of the jaw (ONJ)

Patients with bone metastases or multiple myeloma are generally treated with bisphosphonates (BP) or denosumab. These treatments inhibit bone turnover by inducing osteoclastic apoptosis and inhibiting the osteoblast-mediated osteoclastic activity. A serious side effect is osteonecrosis of the jaw (ONJ), which occurs in 0.8% to 12% of the patients.[31] ONJ is a serious and painful side effect.[32] Each case of ONJ needs to be evaluated and treated individually. The American Association of Oral and Maxillofacial Surgeons (AAOMS) developed guidelines based on the stage of the disease, good oral hygiene, pharmacological therapy (e.g. antibiotics, pain medication) and, in case of exposed bone, surgical removal is recommended.[32]

PBMT FOR THE TREATMENT OF ONJ

PBMT is known to have bio stimulatory effects that can upregulate the production and mineralisation of the bone.[33] Additionally, PBMT also has anti-bacterial effects and is proangiogenic.[34]

A recent review by Latifyan *et al.*, summarised the results of seven clinical trials that investigated the efficiency of PBMT for the treatment of ONJ (*Table 5*).[35] They showed that

TABLE 4. Summary of clinical studies investigating the use of PBMT for the management of CIPN in cancer patients.

First author (ref.)	Year	Publication type	Study type	Sample size	Treatment	PBMT device	Wavelength (nm)	Power (mW)	Energy density (J/cm²)	Laser schedule	Evaluation schedule	Assessment scale	Results
Yamada[28]	2010	Abstract	Single group; pretest-post test	34 BC	LD-PBMT	GaAlAs LD	830	NA	NA	NA	Before and after irradiation	BPI score	BPI score decreased with an average of 4.
Argenta[30]	2016	Full article	Double-blind, placebo-controlled, RC cross-over trial	68 (≠aetiology)	-LD-PBMT -LD-PBMT/PT -Sham laser	Class IV therapeutic laser (Eltech K1200)	800-970	NA	NA	3x/week for 6 weeks	At the first laser session and at 4, 8, and 16 weeks following initiation of treatment	mTNS score	Significant reduction in mTNS score at all time points in the PBMT group.
Hsieh[29]	2016	Full article	Prospective, single-arm study	17 GIC	-LD-PBMT	GaAlAs LD	780	50	7.5	12 sessions	Before the first and after the last session	Neurotoxicity symptom evaluation	Neurotoxicity symptoms (pain, cold- and mechanical allodynia) significantly improved.

Partially adapted from Robijns et al. (2017)[5]

Abbreviations: BC, breast cancer; GIC, gastro-intestinal cancer; CIPN, chemotherapy-induced peripheral neuropathy; PBMT, photobiomodulation therapy; BPI, Brief Pain Index; NA, not available; ref, reference; LD, laser diode; RC randomised controlled; mTNS, modified Total Neuropathy Score.

the overall response rate was 55% in PBMT treated patients, which was significantly higher than in the control group (30%). The studies revealed that PBMT was able to improve ONJ by improving the healing process of the lesions and reducing the accompanied pain.[35]

Zecha *et al.* also formulated some clinical guidelines on a therapeutic base in which they recommended to use LD- or LED-PBMT two to three times a week up to daily by using an extra- (wavelength 750-830 nm; power density 20-80mW; energy density 6 J/cm²) or intra-oral device (wavelength 630–680; power density 20-200mW; energy density 6 J/cm²) on five or more points (1 cm apart) along lingual and buccal aspects of the maxilla and/or mandible depending on site and size of region affected.[1]

Hyposalivation and xerostomia

RT to the head and neck region destroys the function of the salivary glands leading to hyposalivation (i.e. reduced saliva production), which is accompanied by xerostomia (i.e. subjective oral dryness). Other cancer therapies (e.g. CTx, immunotherapy, radioactive iodine treatment and total body irradiation/HSCT) can also induce hyposalivation and xerostomia, although to a minor severity. Hyposalivation increases the risk of oral infections and can lead to teeth damage, oral mucosal discomfort, pain, and eating problems. Consequently, patients with hyposalivation cannot fully perform their daily activities and have diminished general well being.[36]

Intensity-modulated radiation therapy (IMRT) has the greatest potential to spare the salivary gland tissue and prevent the development of hyposalivation. Furthermore, good oral hygiene and dental care is recommended before, during, and after treatment.

PBMT FOR THE TREATMENT OF HYPOSALIVATION AND XEROSTOMIA

To date, there were only a small number of studies investigating the use PBMT for the management of hyposalivation (*Table 6*). Cowen *et al.* performed a placebo-controlled RCT with 30 patients that underwent HSCT to investigate the efficiency of LD-PBMT. Xerostomia and the ability to swallow improved in the patients that were treated with LD-PBMT.[37] Simoes *et al.* reported on a prospective study with two patient groups of which one group was treated once a week with LD-PBMT

TABLE 5. Summary of clinical studies investigating the use of PBMT for the management of ONJ in breast cancer patients.

First author (ref.)	Year	Publication type	Study type	Sample size	Treatment	PBMT device	Wavelength (nm)	Power (mW)	Energy density (J/cm²)	Laser schedule	Evaluation schedule	Results
Angiero[35]	2009	Full article	Three groups; pretest-posttest	49	-LD-PBMT (n=10) -Surgical intervention (n=20) -Conservative therapy (n=19)	Er:YAG laser	880	NA	27-54	3 applications	12—80 months follow up period	CR=6; PR=4
Scoletta[35]	2010	Full article	Single group; pretest-posttest	20	LD-PBMT	Pulsed LD	904	7	28.4	10 sessions over a period of 20 days	1h before the laser procedure and 28 days after	Significant decrease in pain score, clinical size, oedema, and presence of pus and fistulas.
Atalay[35]	2011	Full article	RCT	20	-Laser surgery + LD-PBMT (n=10) -Conventional surgery (n=10)	Nd:YAG laser	950	250	6.25	5 sessions over a period of 10 days	Every other day for the first 10 days and monthly for the next 6 months	No significant difference between the groups.
Romeo[35]	2011	Full article	Single group; pretest-posttest	7	LD-PBMT	Double LD	650 904–910	100-500	NA	Every 3 days for 2 weeks	Twice before each PBMT cycle, once before the initial laser application and 3 days after the last laser application	Significant difference in NRS score.
Vescovi [35]	2012	Full article	Five groups; pretest-posttest	190	-Medical therapy -Medical therapy + LD-PBMT -Surgery -Surgery+ LD-PBMT -Er:YAG laser surgery	Nd:YAG Laser	1064	NA	14.37	Weekly during 2 months	NA	-LD-PBMT + surgery: improved healing in 82.3% of the sites and complete healing in 70.6% of the sites -LD-PBMT + medication: improvement in 64.3% of the sites and complete healing in 21.4% of the sites
Martins[35]	2012	Full article	Three groups; pretest-posttest	22	-Clinical protocol (n=3) -Surgical protocol (n=5) -PRP+LD-PBMT (n=14)	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[35]	2014	Full article	Single group; pretest-posttest	11	LD-PBMT	GaAlAs LD	808	500	5	Five session on post- operative day 1, 3, 5, 7, and 10	Before the start of laser and follow-up (6-25 months)	CR=4; PR=7

Partially adapted from Robijns et al. (2017)[5]

Abbreviations: ONJ, osteonecrosis of the jaw; PBMT, photobiomodulation therapy; PRP, platelet-rich plasma; LD; CR, complete remission; PR, partial remission; NRS, numerical rating scale; NA, not available; ref, reference; LD, laser diode.

TABLE 6. Summary of clinical studies investigating the use of PBMT for the management of xerostomia/hyposalvation in cancer patients.

First author (ref.)	Year	Publication type	Study type	Sample size	Treatment	PBMT device	Wavelength (nm)	Power (mW)	Energy density (J/cm²)	Laser schedule	Evaluation schedule	Results
Cowen[37]	1997	Full article	Double-blind, placebo-controlled RCT	30	-LD-PBMT -Sham laser	HeNe LD	632.8	60	1.5	5 consecutive days before the HSCT	Daily starting first day of HSCT until day 20 post-HSCT	Xerostomia and ability to swallow improved.
Simoes[38]	2010	Full article	Prospective, two-group study	22	-LD-PBMT 3x/week -LD-PBMT 1x/week	AlGaIP LD	660	40	6	Started within the first 2 weeks of RT until complete healing of OM	First and last session of PBMT	Xerostomia improved in both groups, but was better in the group 3x/week.
Arbabi-Kalati[39]	2013	Full article	Double-blind randomized trial	48	-LD-PBMT -Sham laser	LD	630	30	5	Before each CTx session	Before the CTx and every 2 weeks until the end of CTx	Severe xerostomia (grade 3) was prevented.
Oton-Leite[40]	2013	Full article	Double-blind, placebo-controlled RCT	60	-LD-PBMT -Sham laser	InGaAlP diode laser	685	35	2	A week before RT and daily for 5 consecutive days before each session of RT until the end of RT	1 week after starting RT, at the 15th RT session and at the finale RT session	Significantly higher SFR in the PBMT group.
Saleh[41]	2014	Full article	Double-blind, placebo-controlled RCT	23	-LD-PBMT -Sham-laser	GaAlAs diode	830	100	71	2x/week for 6 weeks	Before the start of PBMT, at the 6th session of PBMT and at the last session (12)	No significant increase of SFR or decrease of xerostomia.

Abbreviations: CTx, chemotherapy; RT, radiotherapy; LD, laser diode; PBMT, photobiomodulation therapy; HSCT, hematopoietic stem cell transplantation; OM, oral mucositis; SFR, salivary flow rate; ref, reference; RCT, randomised controlled trial.

and the other one three times a week. Results showed that xerostomia improved in both groups, although it was better in the group that received LD-PBMT three times a week.[38] In a double-blind RCT by Arbabi-Kalati *et al.*, they demonstrated that LD-PBMT can reduce the incidence of severe xerostomia.[39] Oton-leite *et al.* enrolled 60 HNC patients receiving RT in a RCT investigating the effect of LD-PBMT on oral complications. They were able to demonstrate that the salivary flow of the patients treated with LD-PBMT significantly improved.[40] A recent study by Saleh *et al.* in HNC patients, found no significant improvement of hyposalivation and xerostomia after LD-PBMT treatment. This might be due to fibrosis and acinar atrophy of the glandular tissue.[41]

The guidelines by Zecha *et al.* suggested the use of an extra-(wavelength 750-830 nm; power density 20-80mW; energy density 3 J/cm²) and/or intra-oral LED/LD-PBMT device (wavelength 630-680 nm; power density 20-150mW; energy density 3 J/cm²) starting the first day of RT and continuing daily during RT for the prevention of xerostomia and hyposalivation by targeting the major and minor salivary glands.[1]

CONCLUSION

Based on evidence collected in this review, PBMT has the potential to become a new preventive and therapeutic option for a broad range of acute and chronic side effects associated with cancer therapy. Especially for the prevention and management of OM, the use of PBMT has already been accepted in the general treatment guidelines developed by the MAS-

KEY MESSAGES FOR CLINICAL PRACTICE

1. **Cancer therapy can have serious side effects such as, oral mucositis, lymphoedema, radiodermatitis, osteonecrosis of the jaw, chemotherapy-induced peripheral neuropathy, and xerostomia/hyposalivation.**
2. **PBMT is a non-invasive therapy based on the application of visible or near-infrared light on tissue to stimulate the wound healing process and reduce inflammation and pain.**
3. **There is a growing body of evidence that PBMT is beneficial for the prevention and/or management of acute and chronic cancer therapy-related side effects.**
4. **Future studies are necessary to elucidate appropriate treatment and irradiation parameters and to exclude possible effects of PBMT on the tumour process.**

CC and ESMO. For the other applications, more RCTs with larger patient populations are necessary to confirm the promising results of the current trials. In the future trials more attention needs to be paid towards the identification of the most effective PBMT parameters for each individual medical condition. Finally, more research is needed to evaluate any potential side effects of PBMT that might influence tumour behaviour and/or proliferation.

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