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Photobiomodulation Therapy for the Management of Chemotherapy-Induced Peripheral Neuropathy: An Overview

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Abstract

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of chemotherapy (CT), affecting 68% of patients. Current treatment strategies are based on pharmacological symptom management, but have limited results. Photobiomodulation therapy (PBMT) is a new and emerging therapeutic tool in the supportive care of cancer patients. In this overview, we explore the usability of PBMT for management of CIPN.
Objective: To provide a comprehensive overview of management of CIPN with PBMT.
Methods: Specific terms, including ''Photobiomodulation Therapy,'' ''Drug Therapy,'' and ''Peripheral Nervous System Diseases,'' were identified for the literature research in PubMed.
Results: Three articles were considered eligible for this review. Primary outcome measures were highly variable across the included studies.
Conclusions: PBMT might be an effective treatment strategy to manage CIPN, with very encouraging reports from renowned teams, but evidence is limited. More methodologically uniform research (mainly regarding the parameters of PBMT) is needed to support the use of PBMT for this indication.

Keywords: photobiomodulation, chemotherapy, peripheral neuropathy, cancer, supportive care

Introduction

In 2018, 17 million new cases of cancer were diagnosed worldwide.[1] As the number of cancer survivors is increasing, more attention is being paid to the long-term unwanted side effects of cancer therapy and the impact they can have on the patient's quality of life (QOL).[2] Chemotherapy-induced peripheral neuropathy (CIPN) is one of these common side effects, with an incidence of 68% the first month after chemotherapy (CT), 60.0% at 3 months, and 30.0% at 6 months or more.[3] CIPN is associated with symmetrical symptoms such as paresthesia, numbness, burning pain, loss of temperature sensation, and loss of tendon reflexes, typically appearing in distal extremities and indicating an increased vulnerability of the neurons with the longest axons.[4,5]

The pathophysiology of CIPN depends on the type of CT used. Platinum-based CT irreversibly binds to DNA, inducing apoptosis in the primary sensory neurons.[6,7] Antitubulins such as paclitaxel, docetaxel, and vincristine bind to microtubulins, resulting in neuronal death by interruption of axonal transport, and affect the soma and axons of sensory neurons.[6,8,9] Thalidomide is thought to cause CIPN through its immunomodulation and antiangiogenic effects, resulting in damage to distal axons and dorsal root ganglion neurons from capillary damage and anoxemia in the nerve fibers.[10–12] Despite the different neurotoxic targets, loss of intraepidermal nerve fibers has been observed in nerve biopsies from rodents and patients treated with a wide variety of anticancer agents (e.g., cisplatin, paclitaxel, oxaliplatin, vincristine, and bortezomib).[6,13,14]

In clinical practice, CIPN is often inaccurately diagnosed and undertreated, although it has a high health impact.[15] It impairs patients' daily activities because of comorbidities such as psychological distress, fall risk, and poor sleep quality, resulting in a significant decrease in QOL.[16] For cancer survivors, CIPN is a constant reminder of their

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disease and its corresponding treatment.[4,12] Further, CIPN represents a heavy economic burden because of its association with medical and work loss costs.[17–19]

Current treatment strategies

Current treatment strategies for CIPN are based on symptom management and include mostly neuropathic pain medication (e.g., opioids, tricyclic antidepressants, anticonvulsants, serotonin–norepinephrine reuptake inhibitors, and nonsteroidal anti-inflammatory agents) and nutritional supplements.[20–25] Experimental treatment options consist of antioxidants (e.g., alpha-lipoic acid, glutathione, and vitamin E), substances influencing ion channels (calcium/magnesium supplementation, pregabalin, and carbamazepine), and neuroprotectors (ginkgo biloba, glutamine).[20,22–24,26,27] However, results are limited and no gold standard to manage CIPN has been identified to date. Reduction of the CT dose or withdrawal of CT is currently regarded as the most effective method to manage CIPN.[4,20]

Photobiomodulation therapy

Low-level laser therapy or photobiomodulation therapy (PBMT) was discovered in 1967 by Endre Mester.[28] PBMT is based on the application of visible and/or (near)-infrared light produced by laser diodes or light-emitting diodes to stimulate tissue repair and reduce inflammation and neuropathic pain.[29] Over the last 20 years, PBMT has become a new treatment modality within supportive cancer care (e.g., oral mucositis and radiodermatitis).[29–35]

The principal chromophores for PBMT are located inside the mitochondria. As a result, cells with a large number of mitochondria, such as muscle cells and neurons, are particularly sensitive to this therapy.[36]

The goal of this article is to provide a comprehensive overview of the treatment of CIPN with PBMT and to evaluate the strengths and weaknesses of each study.

Methods

Study selection

For this review, randomized controlled trials (RCTs) and prospective nonrandomized, case–control, cohort, crossover, retrospective, and *in vivo* studies published in English were selected. No restrictions were set on the year of publication. Case reports, case series, abstracts, book chapters, review articles, letters to the editor, and newspaper articles were excluded.

Literature search

A search was performed using PubMed. The search strategy was designed to identify studies treating CIPN with PBMT (Fig. 1). The medical subject heading terms included ''Photobiomodulation Therapy,'' ''Drug Therapy,'' and ''Peripheral Nervous System Diseases.''

Different combinations of the search terms were applied by using the Boolean operators ''AND,'' ''OR,'' and ''NOT'' (Table 1). In addition, references were examined in

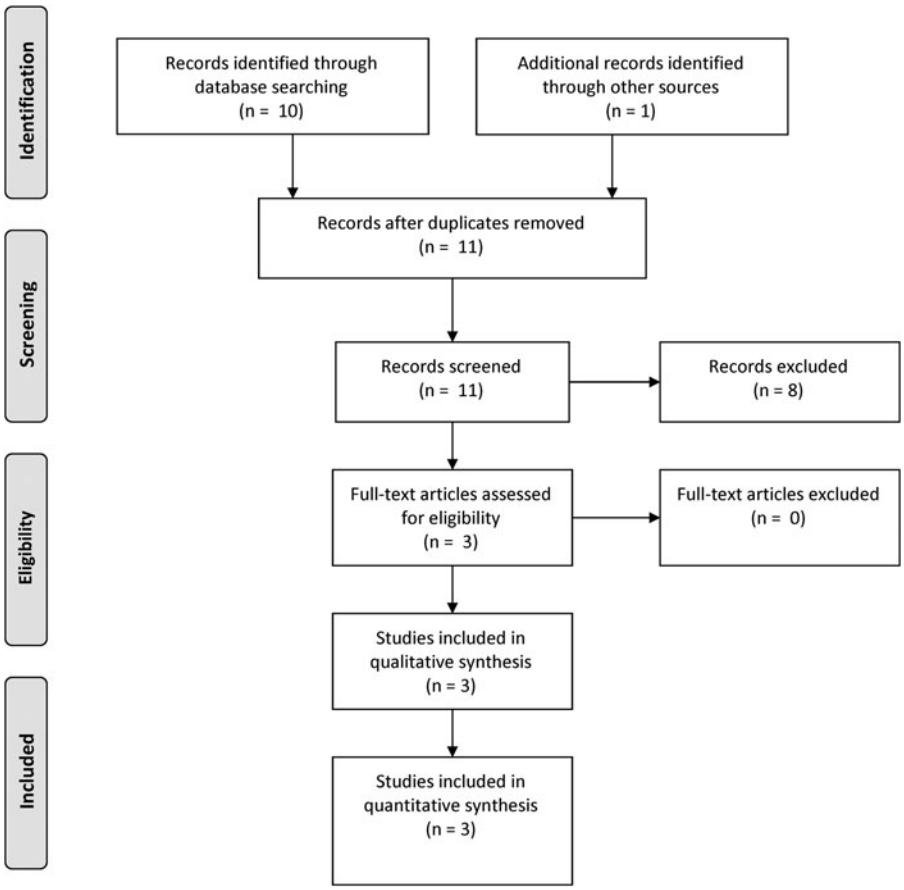

FIG. 1. Flow chart of the literature research.

Table 1. PubMed Research Strategy, Performed on October 18, 2019

Search	*Query*
No. 4	Search ((((''Photobiomodulation therapy''[Mesh] OR Light Therapies, Low-Level[tiab] OR Light Therapy, Low Level[tiab] OR Low Level Light Therapy[tiab] OR Low-Level Light Therapies[tiab] OR Therapies, Low-Level Light[tiab] OR Therapy, Low-Level Light[tiab] OR Photobiomodulation Therapy[tiab] OR Photobiomodulation Therapies[tiab] OR Therapies, Photobiomodulation[tiab] OR Therapy, Photobiomodulation[tiab] OR LLLT[tiab] OR Laser Therapy, Low-Level[tiab] OR Laser Therapies, Low-Level[tiab] OR Laser Therapy, Low Level[tiab] OR Low-Level Laser Therapies[tiab] OR Laser Irradiation, Low-Power[tiab] OR Irradiation, Low-Power Laser[tiab] OR Laser Irradiation, Low Power[tiab] OR Low-Power Laser Therapy[tiab] OR Low Power Laser Therapy[tiab] OR Laser Therapy, Low-Power[tiab] OR Laser Therapies, Low-Power[tiab] OR Laser Therapy, Low Power[tiab] OR Low-Power Laser Therapies[tiab] OR Low-Level Laser Therapy[tiab] OR Low Level Laser Therapy[tiab] OR Low-Power Laser Irradiation[tiab] OR Low Power Laser Irradiation[tiab] OR Laser Biostimulation[tiab] OR Biostimulation, Laser[tiab] OR Laser Phototherapy[tiab] OR Phototherapy, Laser[tiab])) AND (''Drug Therapy''[Mesh] OR Therapy, Drug[tiab] OR Drug Therapies[tiab] OR Therapies, Drug[tiab] OR Chemotherapy[tiab] OR Chemotherapies[tiab] OR Pharmacotherapy[tiab] OR Pharmacotherapies[tiab])) AND (''Peripheral Nervous System Diseases''[Mesh] OR Peripheral Nervous System Disease[tiab] OR PNS Diseases[tiab] OR PNS Disease[tiab] OR Peripheral Neuropathies[tiab] OR Neuropathy, Peripheral[tiab] OR Peripheral Neuropathy[tiab] OR Peripheral Nervous System Diseases[tiab] OR Peripheral Nerve Diseases[tiab] OR Nerve Disease, Peripheral[tiab] OR Nerve Diseases, Peripheral[tiab] OR Peripheral Nerve Disease[tiab] OR Peripheral Nervous System Disorders[tiab]))
No. 3	Search (''Peripheral Nervous System Diseases''[Mesh] OR Peripheral Nervous System Disease[tiab] OR PNS Diseases[tiab] OR PNS Disease[tiab] OR Peripheral Neuropathies[tiab] OR Neuropathy, Peripheral[tiab] OR Peripheral Neuropathy[tiab] OR Peripheral Nervous System Diseases[tiab] OR Peripheral Nerve Diseases[tiab] OR Nerve Disease, Peripheral[tiab] OR Nerve Diseases, Peripheral[tiab] OR Peripheral Nerve Disease[tiab] OR Peripheral Nervous System Disorders[tiab])
No. 2	Search (''Drug Therapy''[Mesh] OR Therapy, Drug[tiab] OR Drug Therapies[tiab] OR Therapies, Drug[tiab] OR Chemotherapy[tiab] OR Chemotherapies[tiab] OR Pharmacotherapy[tiab] OR Pharmacotherapies[tiab])
No. 1	Search (''Photobiomodulation therapy''[Mesh] OR Light Therapies, Low-Level[tiab] OR Light Therapy, Low Level[tiab] OR Low Level Light Therapy[tiab] OR Low-Level Light Therapies[tiab] OR Therapies, Low-Level Light[tiab] OR Therapy, Low-Level Light[tiab] OR Photobiomodulation Therapy[tiab] OR Photobiomodulation Therapies[tiab] OR Therapies, Photobiomodulation[tiab] OR Therapy, Photobiomodulation[tiab] OR LLLT[tiab] OR Laser Therapy, Low-Level[tiab] OR Laser Therapies, Low-Level[tiab] OR Laser Therapy, Low Level[tiab] OR Low-Level Laser Therapies[tiab] OR Laser Irradiation, Low-Power[tiab] OR Irradiation, Low-Power Laser[tiab] OR Laser Irradiation, Low Power[tiab] OR Low-Power Laser Therapy[tiab] OR Low Power Laser Therapy[tiab] OR Laser Therapy, Low-Power[tiab] OR Laser Therapies, Low-Power[tiab] OR Laser Therapy, Low Power[tiab] OR Low-Power Laser Therapies[tiab] OR Low-Level Laser Therapy[tiab] OR Low Level Laser Therapy[tiab] OR Low-Power Laser Irradiation[tiab] OR Low Power Laser Irradiation[tiab] OR Laser Biostimulation[tiab] OR Biostimulation, Laser[tiab] OR Laser Phototherapy[tiab] OR Phototherapy, Laser[tiab])

each eligible article and further relevant articles were screened when a positive match was observed.

Data extraction and synthesis

Two researchers independently examined all abstracts of the sourced studies. Full articles were then analyzed in more detail to determine whether they met eligibility criteria. Afterward, the individual searches were combined and compared.

Results

Search results

Eleven records were identified through database searching and other sources. No duplicates were present. A total of three relevant studies were identified by the literature search. These studies included one RCT, one prospective study, and one *in vivo* study (Table 2).

CIPN symptoms

The three studies investigated CIPN symptoms using different methods. The study by Argenta et al. is an RCT of 68 patients with self-reported peripheral neuropathy and a history of taxane or platinum-based CT exposure. The authors evaluated CIPN symptoms using the modified total neuropathy score (mTNS) at baseline and at 4, 8, and 16 weeks following initiation of treatment. A significant reduction in mTNSs was observed in the PBMT group, while there was no reduction in scores in the sham-treated group.[37]

In contrast, the studies by Hsieh et al. assessed CIPN symptoms by evaluating cold and mechanical allodynic responses. In this prospective cohort study, 17 patients with gastrointestinal cancer who had been treated with oxaliplatin-based chemotherapies were examined using the Pain Quality Assessment Scale, Chemotherapy-Induced Neurotoxicity Questionnaire, Oxaliplatin-Specific Neurotoxicity Scale, quantitative touch detection threshold (using von Frey filaments), and cold-triggered pain withdrawal latency (using the cold-water immersion test). Patients were tested before and after their last PBM treatment and showed a significant improvement in CIPN symptoms.[38]

In the *in vivo* study by Hsieh et al., an oxaliplatin-treated animal model was used to assess sensory behavioral responses. The electronic von Frey anesthesiometer and the acetone and cold-water limb-immersion test were used at five specific time points during the PBM treatment. After

Table 2. Summary of the Studies Regarding the Treatment of Chemotherapy-Induced Peripheral Neuropathy with Photobiomodulation Therapy

Author	*Study design*	*Neurotoxic CT agent*	*Sample size*	*PBMT parameters*	*Outcome measures*	*Outcome*
Argenta et al.[37]	RCT with two groups: (1) PBMT group (2) Sham group	Taxanes and/or platinum-based CT	68 self-reported CIPN patients	Class IV K-Laser, Mod. K1200 (Eltech K-Laser S.r.l., Treviso, Italy) Wavelength of 800–970 nm Power of 6.75–12 W Frequency of 3×/week for 6 weeks	mTNS	Significant reduction in mTNS in the PBMT group
Hsieh et al.[38]	Prospective with only a PBMT group	Oxaliplatin-based CT	17 CIPN patients	GaAlAs diode laser Wavelength of 780 nm Power of 80 mW Fluence of 48 J/cm^2 Frequency of 3×/week for 4 weeks	Oxaliplatin-Specific Neurotoxicity Scale CT-Induced Neurotoxicity Questionnaire Pain Quality Assessment Scale Quantitative touch-detection threshold Quantitative cold-triggered pain withdrawal latency	Neurotoxicity symptoms (pain, cold, and mechanical allodynia) significantly improved
Hsieh et al.[39]	CIPN animal model with four groups: (1) Oxaliplatin and PBMT (2) Oxaliplatin and sham laser irradiation (3) Vehicle-only injection and PBMT (4) Vehicle-only injection and sham laser irradiation	Oxaliplatin	24 Sprague-Dawley rats	GaAlAs diode laser Wavelength of 780 nm Power of 50 mW Fluence of 7.5 J/cm^2 Frequency of 1×/day for 12 days	Grip strength test meter Mechanical allodynia using the electronic von Frey anesthesiometer Cold allodynia using the acetone and cold-water limb-immersion tests Menthol-evoked nocifensive behavior	Significant reduction in oxaliplatin-induced cold and mechanical allodynic responses in the von Frey test, acetone test, cold-water limb-immersion test, and menthol-evoked nocifensive behavior

CIPN, chemotherapy-induced peripheral neuropathy; CT, chemotherapy; mTNS, modified total neuropathy score; PBMT, photobiomodulation therapy; RCT, randomized controlled trial.

sacrifice, levels of nerve growth factor (NGF) and transient receptor potential M8 (TRPM8), both from the dorsal root ganglia, and substance P (SP) in the spinal horn were measured by Western blot analysis and immunohistochemical staining, respectively. Protein levels of TRPM8, NGF, and SP were increased after oxaliplatin administration, but decreased after PBMT administration. Overall, a significant improvement in neurotoxicity symptoms such as pain, cold, and mechanical allodynia was observed in the rats.[39]

Discussion

This review provides an up-to-date overview of the treatment of CIPN with PBMT. Based on the current outcome, PBMT holds promise for reducing symptoms associated with CIPN. However, the studies included in this review were limited and not methodologically uniform; one study was undertaken in animals, and the PBMT parameters were not the same. Further, participant numbers were small.

No consensus exists regarding which measures are best for assessing the outcomes of CIPN treatments. To improve confidence in the results of clinical trials concerning CIPN and PBMT, two aspects of the study design should be standardized: primary outcome measurements and CT.[40,41]

Primary outcome measurements

In daily practice, the diagnosis of CIPN is based on a clinical assessment performed by a physician using a traditional clinical grading scale, including the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), World Health Organization (WHO), or TNS. However, the subjective nature of these clinical assessments leads to a high degree of inter-rater variability.[42,43] Multiple patient-based assessment tools, such as the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Ntx Scale, have been developed to help improve the evaluation of CIPN. Yet, these scores mix impairment, disability, and QOL measures, which could lead to misinterpretation of the results and an unpredictable over- or underestimation of the effect.[42,44]

Nerve conduction studies (NCS) can be used as an objective measure to evaluate CIPN, but are rarely used in the clinical oncology setting due to the need for specially trained personnel and specialized equipment, discomfort for the patients, and high costs.[42] Further, NCS only detect large myelinated fibers and some CT drugs only affect small myelinated and unmyelinated fibers.[10] NGF regulates the development and survival of neurons in the central and peripheral nervous system. The involvement of NGF in the pathogenesis of CIPN has been reported in several experimental studies, including the *in vivo* study by Hsieh et al.[13,39,45–47] However, a reliable clinical biomarker to evaluate the neurological outcome of the CT treatment has not yet been established.[48]

Chemotherapeutic agents and timing

To treat or even prevent CIPN, a better understanding of the pathophysiological mechanism of CIPN is needed. Further, the lack of uniformity in the initiation of PBMT administration among the few identified studies makes it difficult to make a comparison between studies. Hou et al. suggest a timing of at least 3 months after completion of CT as an adequate entry point to start a CIPN treatment since this period would allow enough time for self-recovery of involved peripheral nerves after cessation of CT.[10] An RCT investigating the effect of PBMT in prevention of taxane-induced peripheral neuropathy is currently running at the Jessa Hospital, Hasselt, Belgium (ClinicalTrials.gov Identifier: NCT03391271), and may provide some guidance on these and other matters.

Diabetic peripheral neuropathy

During diabetes mellitus, hyperglycemia causes an increase in neuronal glucose levels, resulting in neuronal damage and eventually peripheral neuropathy. The pathophysiology of CIPN is different and depends on the type of CT used.[6,49,50]

Although both conditions do not share the same etiology, the presenting clinical neuropathic features are similar, and PBM has been noted to have beneficial results in people with diabetic neuropathy.[49,51–54] Khamseh et al. showed a statistically and clinically significant increase in nerve conduction velocity after 10 PBMT sessions (InGaAs laser, with a wavelength of 808–905 nm and an energy dose of 10 J/cm^2) in patients with diabetic distal symmetric polyneuropathy.[51] *In vitro* studies have demonstrated increased neuron viability and neurogenesis when treated with PBMT. This result was modulated by activation of the antiapoptotic AKT pathway.[49,55] However, more research needs to be done to investigate the underlying mechanism by which PBMT induces regenerative effects on tissue and cells and its relationship with the pathophysiology of CIPN.

Safety

The use of PBMT for several cancer therapy-related complications is increasing.[29] However, the safety of PBMT and tumor cells needs to be examined, especially because of the proliferative nature of this therapy. Cell culture studies demonstrate contrasting results regarding the growth of cancer cells.[56,57] *In vivo* studies suggesting a proliferative effect of PBMT on animal tumor models are limited. A few studies use high fluence (1050 J/cm^2) or immunodeficient mouse models, which do not accurately reflect the clinical setting.[56,58,59] Two clinical trials investigating the use of PBMT for prevention and management of oral mucositis were associated with a better cancer prognosis. This positive result can possibly be explained by the avoidance of oral mucositis, leading to better nutrition and more complete chemoradiotherapy.[60–62]

Conclusions

Based on the results in this review, PBMT for management of CIPN might be an effective noninvasive strategy for this serious adverse effect. By reducing the prevalence and manifestation of CIPN, patients' discomfort may improve, resulting in an increased QOL and better compliance with their CT regimen, resulting in increased patient survival. However, current evidence is limited, and great heterogeneity exists between the available research articles. Basic evidence of dosing parameters is lacking. Future studies should focus on animal models designed to identify appropriate wavelengths and dosing characteristics for application of PBMT to manage CIPN. Additionally, RCTs to define and refine the optimal PBMT parameters and CIPN outcome measures are necessary to implement this technique within a standard clinical setting.

Author Disclosure Statement

No competing financial interests exist.

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