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Laser therapy in the treatment of peripheral neuropathy induced using paclitaxel in breast cancer: An integrative review

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Suzana Grings de Oliveira da Silva
Nurse at Hospital de Clínicas de Porto Alegre, Master in Nursing at UFCSPA

Yanka Eslabão Garcia
Nurse Graduated from UFRGS

Kimberly Bueno
Nursing Student at UFCSPA

Eliane Goldberg Rabin
Doctor in Medical Sciences from UFCSPA

Bibiana Fernandes Trevisan
Nurse at the Hospital de Clínicas de Porto Alegre and Specialist in Oncology at Faculdade Moinhos de Vento

Vanessa Belo Reyes
Master's degree from UFRGS

Mariana Cardoso de Oliveira
HCPA nurse and oncology specialist

Maryana Schwartzhaupt de Matos
Nurse from HCPA and specialist in oncology

Carla Patrícia Michelotti Pereira
Nurse at HCPA and specialist in Oncology

ABSTRACT
Objective: To synthesize knowledge about the use of photobiomodulation for the treatment of peripheral neuropathies induced by paclitaxel, seeking evidence for the care of patients undergoing treatment for breast cancer. Method: this is an integrative review between the years 2018 and 2023, using the Embase, Latin American and Caribbean Health Sciences Literature (LILACS), and PubMed databases. Results: 28 articles that met the inclusion criteria were reviewed, of which, based on the most prevalent outcomes, three topics were evidenced that discuss chemotherapy-induced peripheral neuropathy; treatments used; and photobiomodulation and peripheral neuropathy. Conclusions: paclitaxel proved to be the main causative agent of neurotoxicity, requiring urgent coping strategies. The benefits evidenced by photobiomodulation therapy in peripheral neuropathies are directly proportional to the damage that paclitaxel causes to the peripheral nerve, providing recovery from deterioration.

Keywords: Breast neoplasms, Paclitaxel, Low-level light therapy, Peripheral nervous system diseases.

1 INTRODUCTION

Breast cancer is a disease with multiple factors, manifesting itself in different clinical and genetic ways, as well as its effects on treatments. Treatments for breast cancer may include surgery, radiotherapy, adjuvant, neoadjuvant or palliative systemic chemotherapy, adjuvant hormonal treatment, and immunotherapy[1 2 3].

The therapies can be adjuvant or neoadjuvant, the latter being advised in advanced cases in which the breast tumor has no surgical indication or it is not possible to be resected. The recommendation, according to the classification of the disease, is also for high-risk patients. The use of anthracyclines followed by taxane is recommended when this therapy is chosen, and the sequential

use of taxane as a neoadjuvant regimen for breast cancer more than doubles the complete response rate[4] [5].

Among the types of treatments aimed at this disease, antineoplastic drugs called taxanes are widely used for the cure or control of the disease, and among the toxicities caused by the use of this drug, peripheral neuropathy occurs in approximately 62% of cases; It is characterized by paresthesia, numbness and pain in the hands and feet, fine motor changes, loss of tendon reflexes, among others[6]. A 2014 systematic review with meta-analysis included 31 studies on the incidence, prevalence, and predictors of Chemotherapy-Induced Peripheral Neuropathy (CIPN), and when stratified by drug, paclitaxel alone, used for the treatment of breast cancer, accounted for 70.8% of CIP[7] prevalence.

CIPN affects the quality of life of these patients, directly affects functionality due to pain, loss of sensitivity, muscle weakness and paresthesias, which brings serious complications to the performance of activities of daily living. Low-level laser therapy has been shown to be effective in analgesic control of neuropathic pain[8]. Studies point to the positive action of photobiomodulation to induce trophic-regenerative, anti-inflammatory and analgesic effects in tissues[9]. Specifically in use in CIPN, about 90% of patients had a significant clinical response of symptom improvement with its use[10].

2 METHOD

This is an integrative review (IR), which searched for studies within the literature on the use of laser therapy as a treatment purpose for peripheral neuropathy induced by the use of paclitaxel, with a filter of publications from the last 5 years. The method was chosen due to the fact that it is an important tool in the synthesis of available research on the subject to be studied, being a valid instrument for evidence-based practice.

To guide the study, the following steps were followed: 1) elaboration of the guiding question; 2) literature search or sampling; 3) data collection; 4) critical analysis of the included studies; 5) discussion of the results and 6) presentation of the integrative review. As a first step of the process, the question was "What is the evidence available in the literature on the use of laser therapy (FBM) to reduce the symptoms of Paclitaxel-Induced Peripheral Neuropathy in women with breast cancer?". The PICO strategy, an acronym that describes Population (women with breast cancer undergoing treatment with Paclitaxel), Intervention (Laser Therapy), and Outcome (Paclitaxel-Induced Peripheral Neuropathy), was used to elaborate the research question and the choice of descriptors. It is noteworthy that for the Control or Comparison element, although it is not directly implicit in the guiding question, treatments related to drug therapy, other complementary therapies or no treatment at all were considered.

The following databases were used: MEDLINE/PubMed, Embase, and Latin American and Caribbean Health Sciences Literature (LILACS) with the following descriptors: Breast Neoplasms, Paclitaxel, Low-Level Light Therapy, and Peripheral Nervous System Diseases. Inclusion criteria included fully published studies with human beings, and exclusion criteria were publications that were not indexed articles.

3 RESULTS

A total of 131 articles were found as a result of the search in the databases, 8 of which were excluded before selection because they were duplicates or unavailable in full. Of the 116 articles selected, 88 were excluded because they did not answer the research question. A total of 31 articles were eligible to be read in full, and of these, 3 did not meet the inclusion and exclusion criteria. In total, 28 articles were considered in a CIPN category and 8 articles in Paclitaxel-Induced Peripheral Neuropathy.

Regarding the level of evidence, four studies are systematic reviews of randomized clinical trials, three systematic reviews of cohort studies, one systematic case-control review, two controlled clinical trial studies, ten cohort studies, two case-control studies, and six observational studies of therapeutic outcomes. The results are presented according to the most prevalent topics found in the articles of this review, the first being related to paclitaxel-induced peripheral neuropathy.

Among the main results found in these studies are the morphological characteristics of the CIPN related to paclitaxel, in which apoptosis, oxidative stress and axon morphology were evidenced as the main triggers of neuropathy. Six studies showed a higher incidence of CIPN in patients treated with paclitaxel compared to docetaxel or other neurotoxic drugs. Table 1 describes the studies included in the integrative review.

Chart 1 - Description of articles included in the integrative review in terms of title, objective, methodological design, and results and conclusions. Porto Alegre, RS, Brazil, 2023.

Title	Objective	Method	Results and conclusions
Expression of mitochondrial dysfunction-related genes and pathways in paclitaxel-induced peripheral neuropathy in breast cancer survivors[11]	To evaluate the differential expression of genes and disturbed pathways between breast cancer survivors with and without paclitaxel-induced peripheral neuropathy.	Prospective Cohort Study; Gene expression in peripheral blood was tested using RNA-seq. Differentially expressed genes and pathways associated with mitochondrial dysfunction were identified among survivors who	No difference between the groups was found in the dose cumulative paclitaxel received or the percentage of patients that have had a reduction or dose delay due to PN. Five differentially expressed genes

		received paclitaxel and developed (n:25) and did not develop (n:25) paclitaxel-induced peripheral neuropathy.	and nine disturbed roads were associated with dysfunction mitochondrial related to the oxidative stress, homeostasis of the iron, mitochondrial fission, Apoptose is auto-driven.
Long-term peripheral neuropathy symptoms in breast cancer survivors[12]	To explore the symptoms of peripheral neuropathy and associated risk factors among breast cancer survivors at least 2 years after diagnosis.	Retrospective observational study; The prevalence of numbness, tingling, and anesthesia symptoms reported by the patient as a surrogate for PN in breast cancer survivors was investigated.	Overall, 17% reported long-term PN symptoms after no chemotherapy, 20% non-taxane chemotherapy, 31% docetaxel chemotherapy, and 44% paclitaxel chemotherapy.
Patient-Reported and Clinician Reported Chemotherapy Induced Peripheral Neuropathy in Patients With Early Breast Cancer: Current Clinical Practice[13]	Inquire incidence of neuropathy peripheral chemotherapy-induced (CIPN) moderate to severe for Schemes chemotherapy commonly used in current clinical practice for the treatment of patients with Mother song.	Cohort study prospective; Patients filled out a *monitoring of patient-reported symptoms* and oncologists filled out a *Common Form of terminology criteria for adverse events*. Reports of Peripheral Neuropathy Induced by Chemotherapy were prospectively collected during infusion visits scheduled regularly throughout the duration of chemotherapy.	The dose of chemotherapy was reduced in 52 patients (28%), and in 15 it was due to PN. Chemotherapy was discontinued in 26 patients (14%), 8 because of PN. Reports of moderate to severe PN were higher for paclitaxel compared to docetaxel. Pre-treatment arthritis and/or rheumatism and paclitaxel-containing regimens were associated with higher severity of NP . In addition, a discrepancy was observed between the patients' reports and the

			doctors' evaluations.
Persistent taxane induced neuropathy in elderly patients treated for localized breast cancer[14]	Report to frequency and Neuropathy Risk Factors persistent induced by Taxane between Elderly patients treated for localized breast cancer and propose a Score of prognosis to help clinicians choose the right treatment most appropriate in your daily practice.	Cohort study prospective; The sample included all women over 65 years of age treated between 2001 and 2016 at the Paul Strauss Regional Comprehensive Cancer Center with taxane chemotherapy for localized breast cancer. All included cases were followed up for at least 2 years, with deaths from causes unrelated to PN were excluded.	Among the 302 patients included, 21% and 9% developed grade 2 and 3 persistent PN, respectively. Two patients died from complications of grade 3 PN. Risk factors for persistent neuropathy grade 2 and higher included age, BMI, and diabetes. Persistent PN was more frequent with paclitaxel than with docetaxel. Patients With all four major risk factors, they had a 97.2% probability of developing long-term symptoms, versus 1.2% for patients who had no risk factor.
Risk of Incident Claims for Chemotherapy Induced Peripheral Neuropathy Among Women with Breast Cancer in a Medicare Population[5]	Compare to Occurrence of neuropathy peripheral induced by chemotherapy (CIPN) by Different Chemotherapeutic Agents Received To explain to heterogeneity in the risk of CIPN among patients with cancer of breast.	Cohort study retrospective; We examined predictors of PN among 11,149 women aged 66 years and older with stage AJCC II-IV breast cancer (and no diagnosis of secondary cancer or pre-existing neuropathy) who received chemotherapy.	Overall, the risk emerged ± 3 months after starting chemotherapy and increased over 1 year. Paclitaxel as part of therapy first-line increased the risk of PN 2.7-fold relative to non-neurotoxic agents. And it is concluded that the rate of The incidence of PN was higher for women who, at the time of diagnosis, were relatively

			younger, in AJCC stage II and III, and had less comorbidities, but did not differ by race/ethnicity or poverty level.
Signaling pathways and gene co-expression modules associated with cytoskeleton and axon morphology in breast cancer survivors with chronic paclitaxel induced peripheral neuropathy[16]	Assess whether the differential gene expression and CO Standards expression in these pathways are Associated with with peripheral neuropathy induced by paclitaxel.	Cohort study Exploratory; Signaling pathways and gene co-expression modules associated with the cytoskeleton and morphology of the axon were identified among the survivors who received paclitaxel and developed (n = 25) or no (n = 25) induced PN. These patients were the sample for the study.	The track impact analysis identified four pathways of signage related to cytoskeletal and axon morphology significantly Disturbed. The weighted analysis of the gene co-expression network identified three modules, one of which was associated with adherence to the paclitaxel-induced peripheral neuropathy group. Functional analysis found that This module was associated with four signaling pathways and two ontology annotations related to the cytoskeleton and morphology of axons.
Taxane-Induced Peripheral Neuropathy: Objective and Subjective Comparison Between Paclitaxel and Docetaxel in Patients With Breast Cancer[17]	Compare neuropathy peripheral induced by taxane (TIPN) between docetaxel and paclitaxel in breast cancer patients and examine the Consistency of TIPN measurement between researchers and patients.	Observational study retrospective; Data were The study included 64 breast cancer patients from two university hospitals in Taiwan. Peripheral Neuropathy Taxane-Induced objective and subjective were measured.	The study indicated that the paclitaxel-treated group had a higher prevalence and severity of NP objective than those of the docetaxel group. However, no significant difference was found in the subjective PN between the two groups. In addition, sensory neuropathies and motors were highly

			detected and reported among patients who were undergoing taxane treatment.
The revalence and pattern of chemotherapy induced peripheral neuropathy among women with breast cancer receiving care in a large community oncology practice[18]	Describe prevalence severity and risk of neuropathy peripheral induced by chemotherapy and its impact on women's quality of life treated for breast cancer in a large Community of oncology practice in the USA.	Retrospective observational study; Women previously treated with taxane-based chemotherapy for cancer of Early-stage breast completed Questionnaires from Quality of Life (QLQ) of the European Organization for Research and Cancer Treatment, including QLQ-C30, QLQ-BR23, and QLQ CIPN20. The subscales were scored from 0 to 100, with higher scores indicating greater symptom severity. Pre-hypotheses specified were Tested.	73.0% of patients reported PN. The mean CIPN20 QLQ scores for the subscales sensory, motor and autonomic scores were 18.9, 18.6 and 17.1, respectively. Thus, it was concluded that NP affects significantly improve function and quality of life. In addition, it was not associated with age, body mass index, diabetes, or cumulative chemotherapy, but it was higher for black or African-American women. Also, the Sensory impairment of PN was slightly higher for patients treated with paclitaxel compared to docetaxel.

4 DISCUSSION

The pathophysiology of paclitaxel-induced peripheral neuropathy is not completely known, but the findings corroborate the literature that points to the use of taxanes associated with degeneration and interference in axonal transport[1920]. The damaging effects of oxidative stress are mainly linked to the formation of free radicals that lead to aging and cell death[21 22]. Paclitaxel acts on microtubules and not on DNA or RNA like many chemotherapy drugs[3]. Cellular microtubules are responsible for shaping the cell, and during cell division, there is a need for balance between tubulin association and dissociation, ensuring that the process occurs in a stable way[24]. Due to these characteristics described, paclitaxel is shown to be a potent neurotoxic agent, potentially causing CIPN.

Among the risk factors for the development of CIPN, advanced age is mentioned in the studies, however, an impasse is established regarding age and taxane, because advanced age is a known risk factor for the incidence of breast cancer as well as this drug causes CIPN, which may have established a relationship between both[25]. Nutritional status had an impact as a predictor and severity of CIPN, and obesity or high body mass index was considered a risk factor for the development of CIPN. A study carried out at the Cancer Institute of the State of São Paulo (ICESP) highlights that patients in a nutritional status of obesity had a 2 times higher risk of developing CIPN, in an earlier and more severe form, correlating the appearance of this symptom with patients with this nutritional profile[26]. The relationship between overweight and CIPN seems to be associated with the health conditions that obesity predisposes to, such as diabetes and dyslipidemia. It is also related to the fact that obese patients have a larger body surface area, thus increasing the dose of the chemotherapy drug[51] However, clinical and sociodemographic parameters alone may not influence the development of CIPN, which is more related to the use of a chemotherapeutic agent to which the patient was exposed and its respective neurotoxic potential[27].

On the other hand, a study with 126 women in the United States showed no association with age, preexisting chronic diseases, or nutritional status, but found a relationship with race, showing a higher incidence of CIPN in black or African-American women[28]. The mortality of black women is also higher when compared to the white population with the same pathology, which leads us to believe that socioeconomic differences may influence this correlation, as well as the inequity of access to treatment faced by black women[29]. When compared to black women, they have less education, less access to diagnostic tests, and therefore a higher risk of not having been evaluated for the early detection of breast cancer. Thus, the race/ethnicity variable can be a demographic marker of inequality, with black women being in a state of greater economic, social and health care vulnerability[30].

Six studies showed a higher incidence of CIPN in patients treated with paclitaxel compared to docetaxel or other neurotoxic drugs. Due to the action of paclitaxel, microtubules become non-functional, inhibiting the usual dynamics of reorganization of their network, which is essential in the establishment of cellular functions. This process is believed to lead to the induction of peripheral neuropathy induced by this drug. There was also evidence of a significant impact on the function and quality of life of patients who had paclitaxel-related CIPN, with sensory impairment being the most affected, with considerable impact occurring within 3 months after the start of paclitaxel treatment. The CIPN causes damage and serious limitations to patients, which directly reflects on quality of life, causing deficits in the execution of daily activities, work, social, family and leisure relationships[31].

5 FINAL THOUGHTS

Although there is no consensus among the authors regarding age, weight and ethnicity as risk factors for the development of CIPN, paclitaxel has been shown to be the main causative agent of neurotoxicity, which leads to urgent thinking about strategies to cope with these symptoms presented by women undergoing breast cancer treatment. by the health team. Thus, the benefits evidenced by FBM therapy in Peripheral Neuropathies correspond to the supply of the demand that the damage of Paclitaxel exposes to the peripheral nerve, providing recovery of these deteriorations.

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