Chemotherapy-induced peripheral neuropathy: a literature review

Neuropatia periférica induzida por quimioterapia: uma revisão de literatura

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ABSTRACT
Peripheral neuropathy is a common side effect in patients undergoing cancer treatment with chemotherapy. This condition can affect patients in several different ways, interfering in their activities of daily living and autonomy. The present study aimed to review the literature on chemotherapy-induced peripheral neuropathy and its treatment or other possible interventions. The findings reveal that chemotherapy-induced peripheral neuropathy is a common condition that affects patients undergoing treatment with some specific drugs. Besides, several different substances have been used to treat or control this condition, although no significant evidence could be found in these studies.

Keywords: Peripheral nervous system diseases/chemically induced; Drug therapy/adverse effects

RESUMO
A neuropatia periférica é um efeito colateral comum em pacientes sob tratamento quimioterápico. Essa condição pode se manifester de diversas maneiras, interferindo na qualidade de vida e na autonomia nas atividades de vida diária dos pacientes em questão. O presente trabalho teve como objetivo revisar a literatura referente à neuropatia periférica induzida por quimioterapia, bem como propostas de tratamento e intervenção para o efeito colateral em questão. Foi possível observar que a neuropatia periférica induzida por quimioterapia é uma condição comum a pacientes sob tratamento com alguns quimioterápicos específicos. Além disso, foi possível identificar, embora sem evidência significativa, que diversas substâncias vêm sendo utilizadas como possível tratamento ou paliativo para o efeito colateral em questão.

Descritores: Doenças do sistema nervoso periférico/induzido quimicamente; Quimioterapia/efeitos adversos

INTRODUCTION
Several studies indicate that chemotherapy is the treatment of choice for most cases of cancer¹². However, despite widespread clinical use in oncology, several reports are presented in the literature of complaints associated with side effects of this treatment³. One of the side effects is neurotoxicity. In the literature the following drugs used in cancer chemotherapy are listed as neurotoxic: vincristine, vinblastine, vinorelbine, cisplatin, oxaliplatin, cytarabine, ifosfamide, 5-fluorouracil, methotrexate, paclitaxel, docetaxel, altretamine, procarbazine, interleukin-2, fludarabine, cladribine, and pentostatin⁴.

Peripheral neuropathy is the involvement of neurons that form the peripheral nerves or nerve roots. This condition causes motor and sensory symptoms, which may include weakness, muscle atrophy and hypotonia, hyporeflexia or areflexia, hypesthesia, paresthesia, dysesthesia, sensory ataxia, leading to impaired performance of the individual in daily activities and functional independence. As to its etiology, peripheral neuropathy can be associated with general medical conditions, infectious or inflammatory processes, metabolic processes, and heredity. This study addresses the peripheral neuropathy associated with metabolic processes, due to the toxic effect of chemotherapy and its interference in the healthy metabolism of the nerve cell⁵⁶⁷⁸.

The main symptoms of chemotherapy-induced peripheral neuropathy (CIPN) may depend on the drug and dose used, but usually manifest as predominantly distal weakness, loss of sensation and reflexes. Discontinuation of the drug which induced peripheral neuropathy appears to suppress the symptoms, however, the remaining signs of toxicity should be observed, taking heed of the presence of permanent injury⁷⁸.

It is estimated that 30 to 40% of patients who receive chemotherapy develop peripheral neuropathy⁹–¹¹. There are reports, however, of incidences up to 60% when the
drugs used are cisplatin\textsuperscript{(12,13)}, paclitaxel\textsuperscript{(14)}, docetaxel\textsuperscript{(15)}, vincristine\textsuperscript{(16)}, oxaliplatin, and bortezomib\textsuperscript{(17)}.

This study focuses on investigating chemotherapy-induced neurotoxicity manifested as peripheral neuropathy. In the literature, there are several studies that investigate the relation among the use of chemotherapy drugs, their neurotoxicity and the presence of neurological diseases, including peripheral neuropathy\textsuperscript{(18-23)}.

Given the evidence shown in the literature, it is necessary to investigate the incidence, symptoms, and therapeutic procedures associated with CIPN. Thus, cancer care professionals may outline patterns in the disease development, as well as plans for early intervention and, above all, therapeutic strategies that include support and adaptation in daily activities for this population, assuring greater independence, autonomy, and quality of life.

**OBJECTIVES**
- To identify studies in the literature addressing CIPN.
- To identify plans in the literature for prevention and treatment of CIPN.

**METHODS**
This study was a descriptive, exploratory narrative review of the literature. Guiding questions: “How to characterize CIPN? Are there prevention and treatment for this condition?”

Selected databases during the second half of 2010: Scientific Electronic Library Online (SciELO), Latin American and Caribbean Literature on Health Sciences (LILACS), Pubmed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Web of Science. Scientific studies in Portuguese, English, and Spanish published from September 2005 to September 2010 were included.

Keywords researched: “treatment” and “chemotherapy-induced peripheral neuropathy”.

The cataloging of contents from the publications included in the data collection was performed according to a semi-structured routine (Chart 1).

The data were cataloged and the relevant topics addressed in the studies generated thematic categories, which were discussed in the results and discussion of this study.

**RESULTS**
A total of 57 studies were identified, and 26 of them met the inclusion criteria established.

From the 26 studies selected, 5 themes were identified (Figure 1). It must be highlighted that in this study only the results for the treatment of CIPN will be discussed.

**DISCUSSION**
In presenting the results, we found that most of the publications identified had CIPN treatment as the main theme. There was heterogeneity in the substances and techniques used in the treatment of CIPN. Thus, the following techniques and substances identified in the articles of this review are presented.

**Radiofrequency ablation**
An Indian study published a case study of a 63 year-old male patient diagnosed with prostate cancer with bone metastases in acetabulum, left ischium, femoral head, vertebrae, ribs, pelvis, and skull. The patient underwent surgery and subsequent radiotherapy and adjuvant chemotherapy with docetaxel and prednisone. Three months after surgery and the end of the chemotherapy cycles, the patient started to have pain and tingling in the right palm, followed by numbness in the arm, forearm, and right palm. The report indicates that the patient was refractory to CIPN treatments that included gabapentin, pregabalin, and morphine. After excluding the differential diagnosis of carpal tunnel syndrome, radiofrequency treatment was initiated. The continued radiofrequency stimulation occurred in two cycles of 90 seconds in the ulnar and median nerves. After 2 to 4 hours of stimulation, the patient reported improvement of symptoms. The next day the patient reported a 40% decrease in the pain, and 2 days later, an improvement of 90%, and the use of morphine and other pain medications was discontinued. We observed that this study addressed the technique of ablation by continued radiofrequency energy as an alternative treatment for the management of CIPN pain. However, there were no reports of decrease in sensory and motor
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<th>Type of study</th>
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<td>1</td>
<td>PUBMED</td>
<td>Persistent mobility disability after neurotoxic chemotherapy</td>
<td>Hile ES, Fitzgerald GK, Studenski SA</td>
<td>2010</td>
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<td>Case Study</td>
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<td>3</td>
<td>PUBMED</td>
<td>Glutamate carboxypeptidase inhibition reduces the severity of chemotherapy-induced peripheral neurotoxicity in rats</td>
<td>Carozzi VA, Chiorazzi A, Canta A, Lapidus RG, Shuster BS, Wozniak KM, Cavaletti G</td>
<td>2010</td>
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<td>5</td>
<td>PUBMED</td>
<td>Patient perceptions associated with chemotherapy-induced peripheral neuropathy</td>
<td>Tofthagen C</td>
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<td>10</td>
<td>PUBMED</td>
<td>Neuropatia inducida por quimioterapia: un problema no resuelto</td>
<td>Velasco R, Bruna J</td>
<td>2009</td>
<td>Spain</td>
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<td>11</td>
<td>PUBMED</td>
<td>Chemotherapy-induced peripheral neuropathy as a predictor of neuropathic pain in breast cancer patients previously treated With Paclitaxel</td>
<td>Reyes-Gibby CC, Morrow PK, Buzdar A, Shere S</td>
<td>2009</td>
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<td>12</td>
<td>WEB OF SCIENCE</td>
<td>Therapy of chemotherapy-induced peripheral neuropathy</td>
<td>Kaley TJ, DeAngelis LM</td>
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<td>16</td>
<td>WEB OF SCIENCE</td>
<td>The use of cannabinoids (CBs) for the treatment of chemotherapy-induced peripheral neuropathy (CIPN): A retrospective review</td>
<td>Gingerich J, Wadhwa D, Lemanski L, Krahm M, Daeninck PJ</td>
<td>2009</td>
<td>Canada</td>
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<td>Treatment</td>
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deficits that could interfere in improving quality of life related to greater independence in daily activities\(^{(24)}\).

**Baclofen, amitriptyline HCL, and ketamine**

In a randomized, placebo-controlled study, American researchers investigated the efficacy of a topical lecithin organogel composed of baclofen 10 mg, amitriptyline HCL 40 mg, and ketamine 20 mg, in 203 CIPN patients under treatment with various chemotherapeutic agents (vinca alkaloids, oxaliplatin, cisplatin, taxanes, thalidomide, and others). The selection of the organogel compounds was based on the mechanism of action of the drugs: baclofen is a GABA receptor agonist, amitriptyline HCL affects adenosine A receptors and sodium channels, and ketamine inhibits glutaminergic NMDA receptors. The patients in the study were instructed to apply a tablespoon of the gel in the body region affected by pain, loss of sensation and/or tingling, twice a day – upon rising and at bedtime – for 4 weeks. CIPN was assessed using a 20-item questionnaire entitled European Organization for Research and Treatment of Cancer – Chemotherapy Induced Peripheral Neuropathy (EORTC – CIPN20), containing questions that evaluates sensory, motor, autonomic and functional symptoms. After statistical analysis of recorded data, researchers found that patients who applied the topical gel, compared to placebo-control group, showed improvement trends in sensory components (\(p = 0.053\)), and statistically significant improvement (\(p = 0.021\)) in motor components\(^{(25)}\).

**Vitamin E**

Some researchers suggest that CIPN symptoms – such as loss of reflexes and glove-and-stocking paresthesia – are similar to those presented by patients with Chart 1. Continuation

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<td>18</td>
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<td>Alford M</td>
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<td>Acetyl-L-carnitine for the treatment of chemotherapy-induced peripheral neuropathy</td>
<td>De Grandis D</td>
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<tr>
<td>22</td>
<td>PUBMED</td>
<td>Vitamin E for the prevention of CIPN: rationale for an ongoing clinical trial</td>
<td>Kottschade L, Loprinzi C, Rao R</td>
<td>2007</td>
<td>United States</td>
<td>Clinical trial</td>
<td>Treatment</td>
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<td>25</td>
<td>PUBMED</td>
<td>Diagnosis, management, and evaluation of chemotherapy-induced peripheral neuropathy</td>
<td>Hausheer FH, Schilsky RL, Bain S, Berghorn EJ, Lieberman F</td>
<td>2006</td>
<td>United States</td>
<td>Review</td>
<td>Pathophysiology</td>
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<tr>
<td>26</td>
<td>PUBMED</td>
<td>Acupuncture treatment of CIPN – a case series</td>
<td>Wong R, Sagar S</td>
<td>2006</td>
<td>Canada</td>
<td>Case study</td>
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Peripheral neuropathy caused by vitamin E deficiency syndromes, such as lipid malabsorption and cystic fibrosis. Furthermore, it is noted that cisplatin treatment significantly reduces vitamin E levels, and as a result patients may experience CIPN\(^{26,27}\).

Based on these assumptions, a clinical study was conducted to evaluate the neuroprotective effects of vitamin E, in 47 patients receiving cisplatin (median cumulative dose of 420 mg/m\(^2\)). Patients were randomly divided into two groups: one group received only cisplatin, and the other group received cisplatin and vitamin E (300 mg/day). A significant decrease in the incidence of CIPN was observed in the group receiving vitamin E with chemotherapy (31 versus 86\%)\(^{27}\).

A second randomized study evaluated 40 patients undergoing chemotherapy with cisplatin and paclitaxel, using the same methodology described in the study above, except for a difference in dose: some patients received 300 mg of vitamin E twice a day, in addition to chemotherapy. The results from the comparison between the two groups are similar to the findings of the previous study. There was a 25% incidence of CIPN in the group treated with vitamin E, and 73% incidence of CIPN in the control group\(^{28}\).

Both studies showed a protective effect of vitamin E on the incidence of CIPN. However, these studies did not have quantitatively representative samples to confirm that this substance actually has similar effects on other samples of patients undergoing chemotherapy. However, we found a phase III, double-blind, randomized, placebo-controlled study in progress in the North Central Cancer Treatment Group, in the United States. This research will include the analysis of the neuroprotective effects of vitamin E in 200 patients undergoing chemotherapy. It is hoped that the results of the study may elucidate the effects of vitamin E on CIPN, and provide data about the efficacy of the substance in the treatment of CIPN\(^{29}\).

### Glutamine

Several studies suggest that glutamine may affect several side effects experienced by patients undergoing chemotherapy, including: mucositis, myalgia, arthralgia, diarrhea, cardiotoxicity, and cachexia. In addition, due to the regulatory function of the neuronal growth factor, it is believed that glutamine may have a potentially neuroprotective effects, thereby reducing CIPN\(^{30-32}\).

Some researchers evaluated the neuroprotective effects of glutamine in 45 patients with stage 4 breast cancer receiving treatment with high doses of paclitaxel. The first cohort (n = 33) received no glutamine, whereas the second (n = 12) received 10 g of glutamine orally, 3 times a day, for 4 days, starting 24 hours after the administration of paclitaxel. The results of the study showed that patients receiving glutamine had significantly fewer paresthesia symptoms and moderate to severe reduction in proprioception in the fingers and toes. Also, patients treated with glutamine had less loss of reflexes and less impairment in daily activities. It is noteworthy that all symptoms of toxicity proved to be reversible over time\(^{33}\).

Another group of researchers evaluated the role of oral glutamine in 86 patients with metastatic colorectal cancer treated with oxaliplatin (85 mg/m\(^2\) on days 1 and 15 of each 28-day cycle). Patients were randomized to receive glutamine (n = 42) or not (n = 44). The group that received glutamine at a dose of 15 g, twice a day, for 7 days, every 2 weeks, was compared to the group that received glutamine according to the CIPN symptoms evaluated after 2, 4, and 6 cycles of treatment, using the NCI-CTC scale. The study also evaluated nerve conduction, response to chemotherapy, and impaired daily activities. The results showed that patients receiving glutamine had fewer CIPN symptoms and less interference in daily activities when compared to controls. The researchers noted that there were no differences in nerve conduction, response to chemotherapy, or median survival for these patients. This study therefore suggests that glutamine may reduce the occurrence of CIPN, avoiding both the efficacy of oxaliplatin and the need for lowering the dose of the drug\(^{34}\).

Therefore, although the studies showed favorable results with the use of oral glutamine in patients undergoing chemotherapy, they fail to evaluate the neuroprotective effects of the substance in quantitatively adequate samples that can provide statistically significant data to prove the efficacy of glutamine in reducing the incidence of CIPN\(^{35}\).

### Cannabinoids

Canadian researchers investigated the impact of cannabinoids in reducing CIPN symptoms in eight patients, of whom six received treatment with platinum derivatives. After the administration of cannabinoids to these patients, an improvement was noted in seven of eight patients, by comparing the scores of the NCI-CTC scale before and after treatment. As this was a study with a very small sample, the authors pointed out limitations of the study concerning its replication in quantitatively
more significant samples. They also identified the need for more extensive investigations on the therapeutic effects of cannabinoids in patients with CIPN(36).

**FINAL COMMENTS**

This review achieved its objectives, since it identified studies that explored CIPN, and its several interrelated aspects, particularly some interventions proposed to minimize the damage caused by involvement of peripheral nerve fibers.

**CONCLUSIONS**

The field for study, research, and intervention in the area is large and needs further investigation. It was noted that several studies have been conducted recently to evaluate the response of drugs and procedures that hypothetically minimize CIPN symptoms and bouts. However, the studies have limitations that converge on the need for methodological adjustments, such as selection of quantitatively representative samples and research designs that may yield more reliable data, which can be generalized to other samples of patients with similar pathological conditions.

**REFERENCES**


