

# CLINICAL PREVALENCE OF CHEMOTHERAPY- INDUCED PERIPHERAL NEUROPATHY IN ONCO- HEMATOLOGICAL PATIENTS

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**Abstract:** Chemotherapy-Induced Peripheral Neuropathy (CIPN) is a side effect common to many drugs in cancer treatment. CIPN symptoms are mainly sensory, as paresthesia and pain, especially in body extremities. It can affect the patient's life, requiring a dose reduction or interruption of therapy, which can impact patient's survival. Twenty-one hematology outpatients who were treated by neurotoxic potential drugs were selected. The *Douleur neuropathique en 4* questionnaire was applied, a patient form was made for data collection, and the data obtained was analyzed. The prevalence of CIPN was 47,62%. Five patients (23,81%) did not had signs of neurotoxicity, four (19,05%) patients were classified as Grade 1, seven (33,33%) as Grade 2, four (19,05%) as Grade 3, and one (4,76%) patient as Grade 4. Patients who had symptoms of CIPN had already received an average of 55,42% of the scheduled treatment. Three patients (14,29%) had to reduce the dose or change the drugs, and one patient (4,76%) had to discontinue it. This study support the hypothesis that CIPN is an important side effect in cancer treatments. Being a cause of reducing the dose or temporarily suspending it, which can affect the success of the treatment and patient's survival.

**Keywords:** peripheral nervous system diseases, antineoplastic agents, hematology.

## INTRODUCTION

Cancer treatment aims to cure or alleviate the symptoms of the disease. One of the most used options, are potential neurotoxic drugs, which, in an attempt to achieve this purpose, can cause side effects that vary among patients depending on multiple factors, and may differ in intensity and duration[1].

Chemotherapy-Induced Peripheral Neuropathy (CIPN) is a common side effect of many drugs in cancer treatments: its global incidence varies from 50-90% depending on

the drug[1]. Therefore, it is a potentially dose-limiting side effect of several commonly used cytotoxic chemotherapy agents[2].

CIPN is one of the most common reasons for cancer patients to drop out of treatment. For some people, symptoms can be alleviated by decreasing the drug dose or temporarily suspending it, reducing pain, which leads to dose reduction or even premature interruption of treatment[1-3]. But for other patients, symptoms remain for months, years or even indefinitely after treatment, potentially affecting the patient's function and quality of life[2-4].

The main clinical factor influencing the occurrence of CIPN is the type of cancer, which is what determines the use of a neurotoxic drug. Solid tumors, including colorectal, breast, gynecological, testis, lung, and hematological malignancies, represent the most common cancers treated with neurotoxic chemotherapy[1].

The main pharmacological classes that can cause CIPN include classic cancer drugs such as platinum compounds (cisplatin, carboplatin and oxaliplatin), taxanes (paclitaxel and docetaxel), vinca alkaloids (vincristine and vinblastine), proteasome inhibitors (bortezomib), epothilones (ixabepilone), other chemotherapeutic agents (eribulin, thalidomide and lenalidomide), as well as the recently introduced immunological checkpoint inhibitors[1].

The CIPN is generally associated with the dosage, both in the amount and in the number of administrations, and with the infusion time of the medication[3-5]. Some drugs have dose-dependent toxicity and others have, instead, idiosyncratic non-dose-dependent toxicities[6]. It is also associated with risk factors such as diabetes, obesity, chronic use of alcohol or a history of smoking, and preexisting peripheral neuropathy (PN) [2,5].

These drugs are effective in killing cancer cells by acting against markedly different but well-identified cellular targets (tubulin, proteasome, cancer-related vessels, etc). However, its neurotoxicity mechanisms are much less known and this is one of the main limitations in the discovery of effective treatments capable of preventing CIPN or limiting its severity[1].

Chemotherapy treatments lead to several changes in cell structure and function, such as the loss of sensory terminals in the skin. They also lead to changes in membrane receptors and ion channels, intracellular signaling, neurotransmission, excitability and metabolism. All these factors can negatively influence glial and neuronal cell phenotypes, contributing to the development of CIPN[1].

CIPN symptoms are mainly sensitive, such as paresthesia, dysesthesia and pain, especially in the hands and feet[4-5,7]. However, motor symptoms such as weakness and autonomic neuropathy may also be present[7].

These sensory and sometimes motor changes can affect the patient's quality of life due to the significant loss of functional abilities to the point where a dose reduction or interruption of therapy is necessary, an action that can negatively impact the time of oncologic disease progression and even patient survival[1-2]. Also, unfortunately, CIPN is not always reversible. Although recovery from induced PN after treatment interruption is common, recovery in some patients may take months or even 2 years, and some patients will never fully recover their neurological functions[2-3].

The Brazilian National Cancer Institute (INCA) summarizes and classifies neurotoxicities in symptoms that affect the Peripheral Sensory Nervous System[8], namely:

- Grade 1: mild paresthesias, reduced reflexes;

- Grade 2: moderate paraesthesia, reduced sensitivity;
- Grade 3: intolerable paraesthesia, marked reduction in sensitivity;
- Grade 4: lack of reflexes and sensitivity.

The development of accurate and sensitive assessment tools for CIPN is essential to allow clinical monitoring during treatment, follow-up of long-term results and measurement of toxicity[9]. As with all treatment toxicities, a balanced approach between patient reporting, physical examination, and physician description is required.

There are several tools available to assess PN and neuropathic pain, but there is no consensus on the ideal method[9-10]. Among the most used tools for screening neuropathic pain is the *Douleur Neuropathique en 4* (DN4) questionnaire. DN4 comprises seven symptom items (burning, painful cold, electric shocks, tingling, pins and needles, numbness and itching) and three clinical examination items (hypoesthesia to touch, hypoesthesia to prick, and brushing). This questionnaire showed a sensitivity of 83% and a specificity of 90% when compared to the medical diagnosis[10]. This questionnaire showed a sensitivity of 83% and a specificity of 90% when compared to the medical diagnosis[10].

Electroneuromyography (ENMG) can be used as a complementary diagnostic test, where it is expected to find a predominantly sensory, peripheral and symmetrical neuropathy pattern[11-12]. However, conventional ENMG does not detect fine-fiber neuropathy and thus may not identify cases of CIPN restricted to them, which in general only present with pain. There are other limiting factors, such as the fact that it is uncomfortable and high costly, and is performed only by specialists in clinical neurophysiology[11].

The treatment of CIPN is still limited, in part due to the complexity of its mechanisms,

which are not yet fully understood[5,7]. So far, the American Society of Clinical Oncology (ASCO)[7] only recommended duloxetine for CIPN treatment.

Opioids, which are one of the mainstays of chronic pain treatment, provide only limited relief for CIPN, in addition, they present a risk of dependence[5].

In the absence of an effective drug solution, dose modification (reduction or discontinuation depending on the degree of PN) remains the gold standard for the management of CIPN[2-3]. Immediate adherence to the dose reduction algorithm is important to limit the severity of PN and to increase the chances of reversibility[2].

The combination of the trend towards an increased incidence of cancer in the future, with an estimated number of cases reaching approximately 29.5 million in 2040, associated with earlier diagnosis, greater availability of chemotherapy protocols and greater survival, will lead to a greater number of cancer survivors, who will live longer, but a considerable number of them will be affected by CIPN[1]. These numbers underscore the importance of recognizing the CIPN and offering neuroprotective and modifying strategies for the disease in its early stages and/or to prevent its onset, and new symptomatic treatments once it has been established[1].

## METHODS

This is an observational, cross-sectional, uncontrolled study. The sample of this study included individuals with oncohematological diseases followed up in an outpatient clinic of Hematology at the Gaffrée and Guinle University Hospital (HUGG) in Rio de Janeiro (RJ), Brazil, from August 2019 to February 2021, who used drugs with neurotoxic potential of the following classes: proteasome inhibitors, thalidomide and its analogues, vinca alkaloids and platinum.

Were excluded from this study the patients with neuropathy from another cause, using other drugs with potential for neurological toxicity, with sensory alterations or cognitive deficit that made it difficult to apply the scale, or using medication for neuropathic pain.

The project was approved by the Research Ethics Committee (REC) of the HUGG, and all the patients sign the Informed Consent Form (ICF).

The population of the study consisted of 88 patients with oncohematological diseases who used potential neurotoxic drugs, being monitored at the hematology clinic, in addition to the others who needed to carry out this treatment during the data collection and analysis phases. Of these 88 patients, 52 were excluded due to comorbidities that can also lead to PN, such as Systemic Arterial Hypertension (SAH), Diabetes Mellitus (DM), and HIV (Human Immunodeficiency Virus).

Of the remaining 36 patients, 21 attended the consultation during the period of approval of the work by the REC.

It should be remembered that the work was interrupted from March 2020 to October 2020 due to the virus SARS-CoV-2 (COVID-19) pandemic. Due to external factors, patients with an appointment scheduled for later periods could not be approached to agree with the terms of the project, and were not included in the research.

As a screening tool for neuropathic pain, the form *Douleur Neuropathique en 4* (DN4) was applied to produce a reliable indicator of neuropathic pain in clinical practice.

For data collection, a follow-up form was prepared, which contained the patient's identification, comorbidities, diagnosis of their oncohematological disease, medications in use, treatment planned, the history of the current disease and the neurological assessment performed through the physical neurological examination.

In the physical neurological examination, the inspection was carried out and the patients evaluated: level of consciousness; march; static; strength; tactile sensitivity and painful sensitivity; vibratory sensitivity and proprioceptive; coordination; and the deep reflexes (biceps, triceps, flexor of the carpus and fingers, flexor of the fingers, stylo-radial, patellar and achilles).

Patients who presented severe cases of PN were referred to the Neurology Outpatient Clinic for symptom treatment.

The data generated were used in the preparation of tables, with the help of *Microsoft Excel* software, and *Matlab* was used for graphical representation. As there was no crossing of variables, the data generated were analyzed in a simplified way, without the need for biostatistical analysis or the use of specific software to assess the level of significance.

## RESULTS

The final population consisted of 21 patients. Of these patients, 11 were diagnosed with Multiple Myeloma (MM), which was the most prevalent onco-hematological disease (52.38%). Of the remaining patients, 5 of them had Diffuse Large B-Cell Lymphoma (DLBCL) (23.81%), 3 Follicular Lymphoma (14.29%), and 2 *Hodgkin's* Lymphoma (HL) (9.52%).

On the DN4 questionnaire, 10 patients (47.62%) scored 4 points or more, with pain being classified as neuropathic (Fig. 1).

According to the Classification of the Brazilian National Cancer Institute (INCA), 5 patients (23.81%) had no signs of neurotoxicity affecting the Peripheral Nervous System (PNS) on physical examination, 4 (19.05%) patients were classified as Grade 1, 7 (33.33%) patients in Grade 2, 4 (19.05%) patients in Grade 3, and 1 (4.76%) patient in Grade 4 (Fig. 2).

Of the 10 patients who scored for pain of neuropathic origin according to the DN4

questionnaire, 2 of these patients (20%) had already completed the programmed treatment. Two patients (20%) had already completed 75% of the scheduled regimen. Another 2 patients (20%) had undergone 50% of the scheduled doses. Another 2 patients (20%) had completed 62.5% of the programmed regimen. One of the patients (10%) had completed 66.67% of the scheduled treatment and one of the patients (10%) had only completed 12.5% of the scheduled medication dose and already had symptoms of neuropathic pain. On average, patients who presented symptoms of neuropathic pain had performed 55.42% of the programmed regimen.

Three patients (14.29%) had to reduce the dose or change the treatment and one patient (4.76%) had to interrupt it.

## DISCUSSION

The results of this research support the hypothesis that CIPN is a prevalent problem in patients exposed to chemotherapy treatments, with a prevalence of 47.62% according to the data in this study.

As shown in previous studies, the prevalence of CIPN varies widely, mainly as a function of the drug used and the cumulative dose. In addition, many patients have used another chemotherapy regimen before, thus, the toxicity may have added. In a systematic meta-analysis review of 31 studies carried out by the University of Edinburgh[13], of 4179 adult patients, it showed a prevalence of CIPN of 68.1% (57.7–78.4) when measured in the first month after chemotherapy.

Bortezomib belongs to the proteasome inhibitor class and is a first-line treatment for multiple myeloma, which was the most prevalent disease in this group of patients. The incidence of CIPN using bortezomib in large clinical trials ranges from 31% to 64%[14]. Bortezomib-induced peripheral

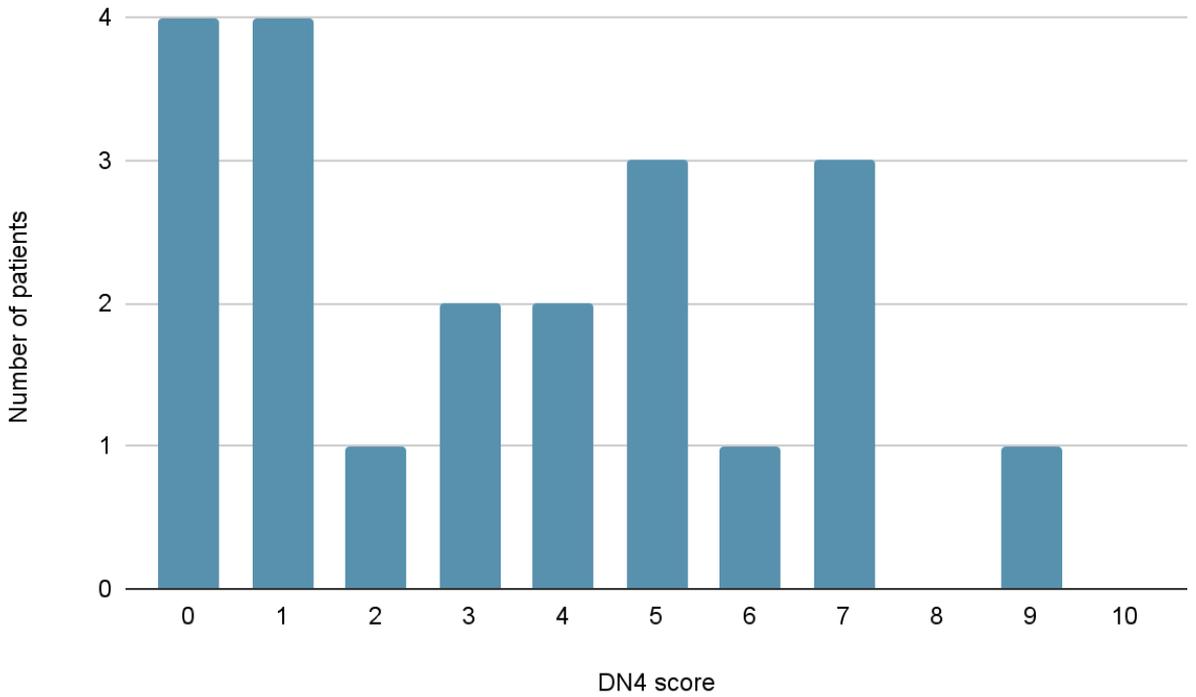


Figure 1 - Patient's DN4 score.

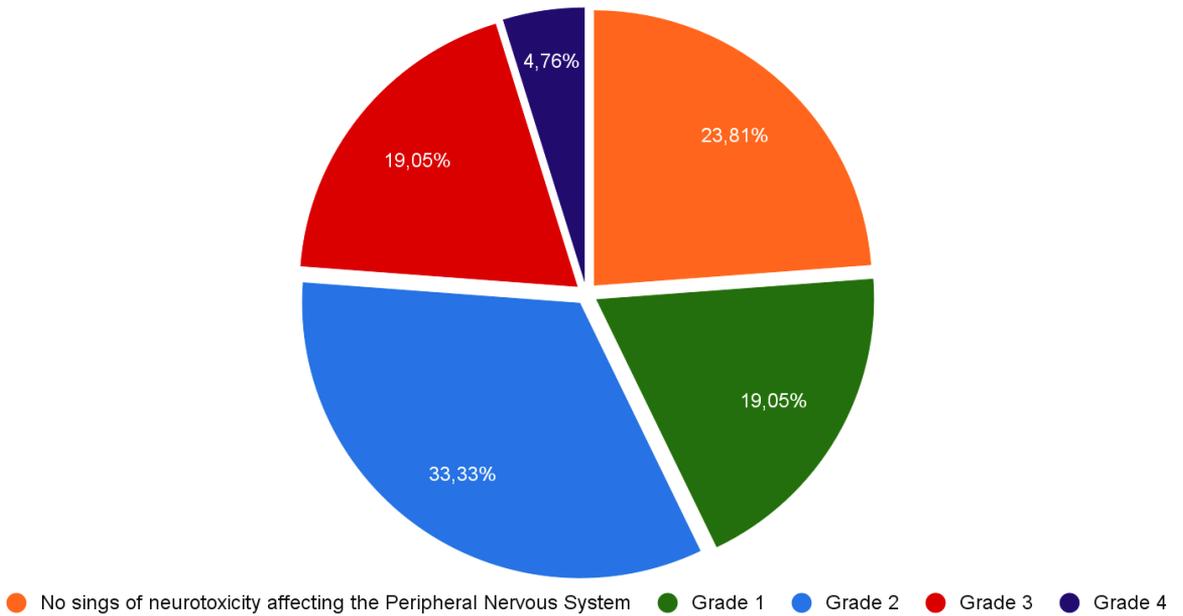


Figure 2 - Classification of neurological symptoms presented by patients according to the INCA's classification.

neuropathy is generally a predominantly sensory axonopathy, but neuropathic pain is an important feature, occurring in 25 to 80% of cases[14].

Thalidomide is also a drug used to treat multiple myeloma. The incidence of CIPN ranges from 10% to 55%, depending on the patient population, types of treatment and diagnostic criteria[14]. Thalidomide-induced CIPN appears to be more severe than most neurotoxic chemotherapy drugs, and is associated with cumulative dose. A dual role for thalidomide has been demonstrated by clinical observations suggesting that thalidomide may be neuroprotective in patients receiving a combination with bortezomib, although it is neurotoxic when given alone. The reason is not clear, but a possible explanation is that the anti-inflammatory action of thalidomide may protect against CIPN caused by bortezomib[15].

Regarding platinum-based chemotherapy drugs, such as carboplatin, used by some patients in this study, few studies specifically allowed the study of PN induced by carboplatin, because carboplatin is very often associated with paclitaxel, such as in ovarian cancer and cancer bronchopulmonary. On average, in previous studies, 6% of patients treated with carboplatin report moderate peripheral neuropathy[14].

Vinca alkaloids such as vincristine and vinblastine are used in the treatment of acute lymphoblastic leukemia, *Hodgkin's* lymphoma, non-*Hodgkin's* lymphoma, and many other oncological diseases (rhabdomyosarcoma, osteosarcoma, uterus, breast, lung, etc.). The literature shows that CIPN affects about 35-45% of patients who use this class of medication[14]. Symptoms usually develop after several weeks of treatment, but may occur after the first cycle[14].

When performing R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine

and prednisone), a chemotherapy regimen widely used in oncohematological diseases, the neurotoxicity of vincristine is a limiting factor in the treatment. In the Johnson(2011) [14] study, a randomized controlled clinical trial in patients with multiple myeloma, the incidence of CIPN in patients taking vincristine was 19.6%.

The highest prevalence of CIPN symptoms occurred on average when they completed 55.42% of the scheduled regimen, confirming what was observed in previous studies that showed a peak in neuropathy symptoms around the third treatment cycle, when 6 cycles were scheduled[16].

Of the 21 patients in the study, three of them (14.29%) had to reduce the dose or change the chemotherapy regimen, and one patient (4.76%) had to interrupt the treatment, which can affect the success of the treatment and the survival of these patients[14].

One of the limitations of this work was the data collection in COVID-19 pandemic. Another limitation found was the lack of availability of ENMG as a complementary test in the diagnosis of all patients.

Despite the study's small sample, its comparison with other previously published studies contributes to the hypothesis that CIPN is a common side effect of many drugs in cancer treatments. Although the quest to explore CIPN in its clinical aspects, its results were limited by the size of the included sample. This research allows for several developments, but there is still extensive work ahead.

## CONCLUSION

In this study, we evaluated the clinical prevalence of peripheral neuropathy by clinical criteria in patients with hematologic malignancies and undergoing chemotherapy followed at the hematology outpatient clinic of a University Hospital in Rio de Janeiro.

We classified the neurological symptoms

presented by the patients according to the INCA classification, evaluate the time of treatment and how many patients had to reduce the dose, change or stop the treatment due to CIPN.

Despite the small study sample, its comparison with other previously published studies contributes to the hypothesis that CIPN is a common side effect of many drugs in chemotherapy treatments.

Although the search to explore CIPN in its clinical aspects and its results were limited by the size of the sample included, this research allows for several developments, such as support the hypothesis that CIPN is an important side effect in cancer treatments, but there is still extensive work ahead.

## **DECLARATIONS**

### **ETHICAL APPROVAL AND CONSENT TO PARTICIPATE**

This study was approved by the Gaffrée and Guinle University Hospital Research Ethics Committee (Certificate of Presentation of Ethical Appreciation: 14241719.0.0000.5258). Written informed consent was obtained from each patient.

### **CONSENT FOR PUBLICATION**

All authors agree to publish this article.

### **AVAILABILITY OF DATA MATERIALS**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### **CONFLICTS OF INTEREST**

The authors declare no conflicts of interest.

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## **AUTHORS' CONTRIBUTIONS**

Katia Gleicielly Frigotto, collected the clinical data, performed the experiments, and analyzed the data. Vitor Ribeiro Gomes de Almeida Valviessa and Karina Lebeis Pires designed and supervised the experiments. Giovana Salviano Braga Garcia wrote the paper. All authors read and approved the final manuscript.

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