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Prevalence, Severity, and Persistence of Chemotherapy-Induced Peripheral Neuropathy in Early-Stage Breast Cancer Patients Treated with Paclitaxel: an Observational Study in a Referral Hospital in Latin America

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ABSTRACT

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the main adverse effects of antitumor treatment. The aim of our study was to examine the prevalence and severity of CIPN in breast cancer patients treated with paclitaxel. The association with specific patient-, tumour- and treatment-related variables was also explored. Thus, 45 patients with early-stage breast cancer were evaluated at a referral hospital in Argentina. Patient-reported CIPN-related symptoms were assessed using an abbreviated version of EORTC QLQ-CIPN20 questionnaire. Additional variables analyzed included age, weight, body mass index, tumor phenotype, and chemotherapy regimen. The study population included women aged 25-71 years. Most tumors were ER/PR-positive, and the most frequently used chemotherapy regimen was adjuvant anthracycline-based therapy. The prevalence of clinical CIPN, defined by the presence of at least one symptom experienced 'quite a bit' or 'very much', was 62%. In contrast, clinical records showed a prevalence of 24%. No significant associations were observed between patient-, tumor- or treatment-related variables and CIPN development. Among patients with neuropathy, mean CIPN score was 26,25. Of these patients, 50% presented both sensory and motor symptoms, 29% only motor and 18% only sensory symptoms. Two years after finishing chemotherapy, 46% of CIPN-patients still experienced at least one symptom. All patients with persistent symptoms had experienced motor disturbances during chemotherapy, with significantly higher motor scores. Our results indicate a high prevalence of CIPN-related symptoms during and after paclitaxel administration in our population. The presence and/or the severity of motor symptoms during chemotherapy could be postulated as possible predictors of CIPN persistence. Clinical underreporting and symptom persistence emphasize the need to incorporate patient-reported measures into clinical practice to better detect symptoms and guide interventions to improve patient's quality of life.

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Abbreviations

CIPN: Chemotherapy-Induced Peripheral Neuropathy
BMI: Body Mass Index
ER: Estrogen Receptor
PR: Progesterone Receptor
HER2: Human Epidermal Growth Factor Receptor 2
PAX: Paclitaxel
PAX-AC: Doxorubicin + Cyclophosphamide followed by PAX
PAX-T: PAX and Trastuzumab

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is among the most common and debilitating side effects of cancer treatment, affecting a substantial proportion of patients [1-3]. This condition manifest as sensory, motor, and autonomic dysfunctions, causing severe discomfort and functional impairments such as difficulty with fine motor tasks, problems with balance and increased fall risk, leading to a marked reduction in quality of life [1,2,4]. CIPN can persist long after chemotherapy concludes, leading to chronic symptoms that complicate post-treatment recovery and management [2,4].

Among the various chemotherapeutic agents, paclitaxel, a widely used drug for treating solid tumors -including breast, ovarian, esophageal and lung cancers- is particularly recognized for its neurotoxic effects [2,4].

Breast cancer, the most commonly diagnosed cancer among women worldwide, accounts for over 2.3 million new cases annually (Global Cancer Observatory). In Argentina, breast cancer is the most prevalent malignancy, with approximately 22.000 new cases each year (National Cancer Institute). As paclitaxel is critical for managing early-stage breast cancer, addressing its adverse effects, particularly neuropathy, is essential. Despite its efficacy, paclitaxel-induced neuropathy can lead to considerable morbidity [2,4,5], sometimes even requiring dose adjustments or therapy discontinuation, potentially compromising cancer treatment outcomes [1,5].

It is estimated that 60% of patients receiving paclitaxel-based regimens develop CIPN globally [2,4]. With prevalence rates varying from 30% to 80% depending on the region. However, data on CIPN prevalence in Latin America, and particularly in Argentina, remain scarce. The diagnosis of this iatrogenic neuropathy typically relies on clinical evaluation performed by oncologists using toxicity grading scales [6]. Recently, specific questionnaires, such as the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, EORTC-QLQ-CIPN20, have been developed to better capture patient-reported symptoms and functional impairments [6-8].

As paclitaxel-induced peripheral neurotoxicity is a potentially preventable adverse effect, recent efforts have focused on identifying variables associated with increased risk, including demographic, anthropometric, clinical, genetic, tumor-related, and chemotherapy-related factors [9-11]. Variables with demonstrated value could be then used to stratify patients, implement preventive strategies, and tailor chemotherapy regimens.

The primary aim of this study was to examine the prevalence and severity of CIPN in early-stage breast cancer patients treated with paclitaxel at a referral hospital in Argentina. Additionally, it sought to investigate potential associations between patient-, tumor- and treatment-related variables. By addressing these aspects, this research seeks to enhance the understanding of CIPN, emphasizing the importance of improving early detection, symptom management, and overall patient care.

Patients and Methods

This retro - prospective, observational study was conducted at the Department of Clinical Oncology at Austral University Hospital (accredited by Joint Commission International), Buenos Aires, Argentina. The study was evaluated and approved by the Review Board on Ethics in Research from the School of Biomedical Sciences, Austral University (protocol #23-066). informed consent was obtained from all participants, confidentiality principles established by the Declaration of Helsinki were respected, and endorsement was obtained from the clinical institution to access the data.

The clinical records of adult (>18 years) female patients with early-stage breast cancer treated with paclitaxel (12 cycles, 1/ week, 80 mg/m²) at Austral University Hospital from 01/2021 till 12/2023 were evaluated. Patients with neuropathy or chronic pain conditions unrelated to chemotherapy (e.g., those caused by traumatic injuries) that occurred before or during the antitumor treatment period were excluded from the study.

Demographic, anthropometric and clinical data were retrospectively abstracted from the patient`s electronic clinical records. The following variables were analysed to characterize the clinical syndrome and also to identify potential risk factors for CIPN: age, height, weight, body mass index (BMI), body weight categories (underweight, normal weight, overweight, and obesity, according to BMI), tumor phenotype, treatment modality, chemotherapy regimen, additional anti-hormonal treatment, and clinician-documented CIPN.

Tumors were classified into the three broad phenotypes used in clinical practice based on combined receptor status of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 receptor (HER2). Thus, three categories were included: ER/PR+ (ER and/or PR positive, HER2−), HER2+ (independent of ER/PR status), and triple-negative (ER−/PR−/ HER2−) [12].

An abbreviated version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Chemotherapy-Induced Peripheral Neuropathy 20 (EORTC-QLQ-CIPN20) was used to evaluate the impact of patient-reported CIPN-related symptoms [13,14]. Questions regarding blurred vision, hearing difficulties, using pedals while driving, and erectile function were excluded due to the low prevalence of these symptoms in paclitaxel-induced neuropathy, the fact that many patients did not drive, and because all participants were women [7,14,15]. Thus, a 16-item questionnaire (CIPN16), divided into three subscales assessing sensory, motor, and autonomic symptoms, was used to evaluate prevalence and severity of clinical CIPN. Patients rated the "extent to which they had experienced" CIPN-related symptoms on a 4-point Likert scale: 'not at all' (1), 'a little' (2), 'quite a bit' (3), and 'very much' (4) [13,14]. Total CIPN scores ranged from 1 to 64. The summed scores of each subscale, as well as total CIPN scores, were subsequently linearly transformed to a 0–100 scale, with higher scores indicating greater symptom severity or functional impairment [8,14].

Patients were asked to provide information about the presence and severity of symptoms during paclitaxel treatment period, and following its completion, with interviews conducted on average 19 months after finishing chemotherapy. The prevalence of clinical CIPN was defined as the presence of at least one symptom that bothered them 'quite a bit' or 'very much' [8]. set as a threshold for identifying clinically relevant and functionally significant CIPN.

Descriptive statistics were used to evaluate demographic data. Continuous numerical variables were expressed as median (interquartile range) and analysed using Mann–Whitney-Wilcoxon test. Categorical variables were informed as n (%) and analysed using the $\chi 2$ test or Fisher's exact test, as appropriate. The relationship between the most relevant numeric variables and the total score was analyzed using the Pearson correlation test. Statistical significance was defined as a p value <0.05.

Results

Demographic, Anthropometric and Clinical Data

The study population included 45 women aged 25-71 years at the time of tumor diagnosis, with 85% being over 36 years old (Table 1). According to BMI, 34% of our patients were obese. Regarding personal medical history, 27% of patients had an underlying metabolic (type II diabetes, 7%) and/or endocrine (hypothyroidism, 23%) condition at the time of cancer diagnosis. In addition, 7% were smokers.

Table 1: Demographic, Anthropometric and clinical Profile of Patients Included in the Study

Variables	All Patients	Without CIPN	With CIPN
n	45	17	28
Age			
20-35 years	7 (15)	2 (12)	5 (18)
36-51 years	21 (47)	8 (47)	13 (46)
52-67 years	14 (31)	6 (35)	8 (29)
68-83 years	3 (7)	1 (6)	2 (7)
Height (cm)	160 (146-172)	160 (146-172)	160 (150-170)
Weight (kg)	68 (61-83)	65 (55-93)	68 (50-96)
BMI (kg/m^2)	28 (24-31)	27 (23-32)	28 (25-30)
Weight Categories by BMI			
Underweight	0 (0)	0 (0)	0 (0)
Normal	19 (43)	7 (41)	12 (45)
Overweight	10 (23)	4 (24)	6 (22)
Obese	15 (34)	6 (35)	9 (33)
Receptor Status			
ER, PR positive	24 (53)	9 (53)	15 (53)
HER2 positive	18 (40)	8 (47)	10 (36)
Triple negative	3 (7)	0 (0)	3 (11)
Treatment Modality			
Neoadyuvant	17 (39)	9 (53)	8 (30)
Adjuyant	27 (61)	8 (47)	19 (70)
Chemotherapy Regimen			
PAX-AC	36 (82)	14 (88)	22 (79)
PAX-T	8 (18)	2 (12)	6 (21)
Anti-Hormonal Therapy			
Yes	36 (82)	16 (94)	20 (74)
No	8 (18)	1 (6)	7 (26)

Data is expressed as n (%) or median (interquartile range).

The most common tumor phenotype was ER/PR+ (71%) (Table 1). Paclitaxel treatment was predominantly administered as adjuvant therapy (61%) and anthracycline-based (78%). Additionally, most patients (82%) received hormonal therapy (Table 1). No patient received other neurotoxic drugs, including other antineoplastics, before, during, or after paclitaxel treatment.

Prevalence and Severity of Clinical CIPN

Upon completing the questionnaire, 82% of the responding patients (n=37) reported experiencing at least one CIPN-related symptom during paclitaxel treatment. However, 9 patients reported only mild symptoms (categorized as 'a little'). Clinical CIPN was identified in 28 patients, based on the presence of at least one symptom reported as 'quite a bit' or 'very much', resulting in an overall prevalence of 62% (Figure 1A). In contrast, clinical records registered a CIPN prevalence of only 24%, suggesting significant underreporting.

Among patients with CIPN (n=28), mean total CIPN score was 26,25, with a mean score of 29,50 on the sensory subscale and 25,64 on the motor subscale (Figure 1B). Significant differences were observed when comparing total scores, as well as sensory and motor subscale scores, between patients with and without clinical CIPN (Figure 1B). Interestingly, while all patients without CIPN had total and subscale scores below 15, approximately 40% of those who developed neuropathy exhibited total, sensory, or motor scores over 30. Finally, within those patients diagnosed with clinical CIPN (n=28), only 2 patients (7%) required a reduction in paclitaxel dose due to severe discomfort or burden. Total CIPN scores in those patients reached values of 54 and 65.

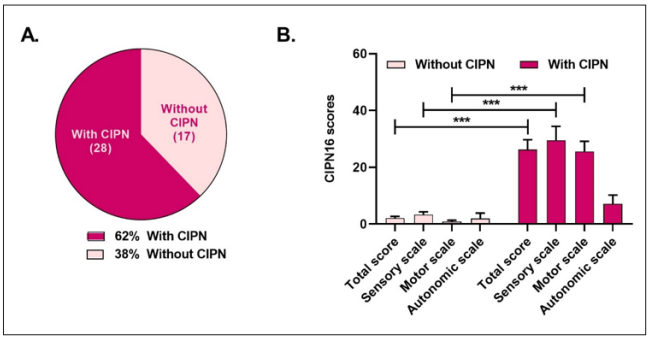

Figure 1A: Prevalence of Clinical CIPN.
Figure 1B: CIPN16 Mean Scores in Patients with (n=28) and without (n=17) CIPN.

Potential Risk Factors
Patients who developed clinical CIPN (n=28) and those who did not (n=17) had similar age, height, weight, weight category, and BMI at the time of tumor diagnosis (Table 1, p>0.05 in all cases). The prevalence of metabolic and/or endocrine conditions was also comparable between the two groups. Additionally, no significant associations were observed between tumor-related variables (e.g.: tumor phenotype) or treatment-related variables (e.g.: treatment modality, chemotherapy regimen, or additional hormonal therapy) and CIPN development (p>0.05 for all comparisons). Finally, we did not find any significant correlation between age, BMI or cumulative paclitaxel dose (mg) and total CIPN score (p>0.05 for all cases).

CIPN Clinical Presentation during Chemotherapy Treatment
When analyzing the entire cohort (n=45), the most frequently reported sensory symptoms were tingling in the hands (49%), tingling in the feet (44%), numbness in the feet (42%), and numbness in the hands (38%), encompassing responses of 'a little', 'quite a bit', and 'very much' (Figure 2A). Sharp or burning pain was reported by 22% of patients in the hands and/or the feet, with greater severity noted in the feet. Among motor symptoms, regardless of severity, 36% of patients reported weakness in the hands, 33% reported weakness in the legs, and 27% experienced cramps in the hands (Figure 2A).

Among patients reporting symptoms as 'a little' (n=9), most (67%) reported exclusively sensory alterations (Figure 2B). Among patients diagnosed with CIPN (n=28), 50% presented both sensory and motor symptoms, while 29% and 18% presented exclusively motor and sensory symptoms, respectively (Figure 2B). Additionally, only one patient (3%) manifested both sensory and autonomic symptoms (Figure 2B).

In patients with CIPN (n=28), the predominant sensory symptoms were paresthesias (tingling in hands (46%) and feet (50%), numbness in hands (32%) and feet (32%)), followed by shooting or burning pain in hands (21%) and feet (29%). The predominant motor symptom was weakness in hands (39%) and legs (39%), leading to functional impairments.

CIPN-Related Symptoms after Paclitaxel Treatment
Two years after completing chemotherapy, nearly half of the patients with CIPN (46%) still experienced at least one symptom. Among these patients, 31% indicated they had only sensory symptoms, 38% had only motor symptoms, and 31% reported experiencing both types of symptoms (Figure 2C). The most frequently reported persistent symptoms were tingling in the hands or feet (41%) and weakness in the hands or legs (41%).

Interestingly, all patients who reported persistent symptoms had experienced motor disturbances during the chemotherapy period (Figure 2B). A significant association was observed between the presence of motor symptoms during chemotherapy and the persistence of CIPN-related symptoms (p<0.05). Furthermore, patients with persistent symptoms reported higher severity of motor symptoms (higher motor scores) during chemotherapy compared to those whose symptoms had resolved (p<0.05). In fact, more than 60% of patients with ongoing symptoms had motor scores greater than 30 during the period of chemotherapy administration. Importantly, patient-, tumor-, and treatment-related variables did not differ significantly between patients with or without persistent CIPN symptoms (p>0.05 for all comparisons).

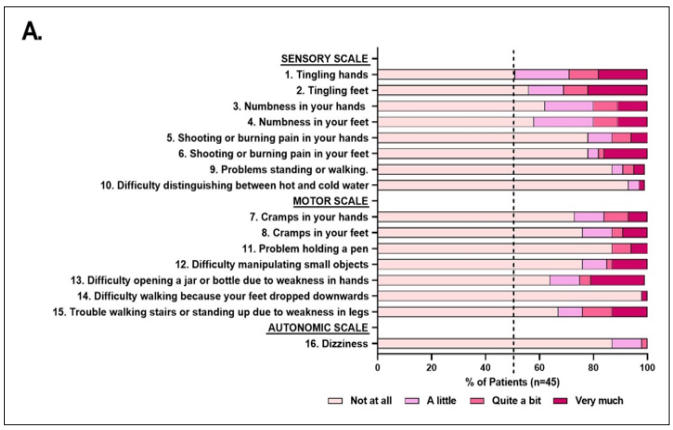

Figure 2A: Distribution of Responses to CIPN16 Questionnaire in the Whole Cohort (n=45).

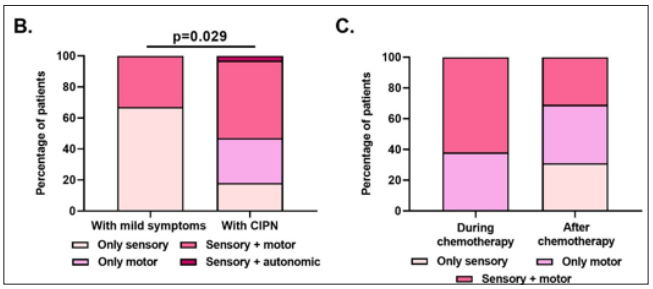

Figure 2B: Percentage of Patients with Specific Symptom Modalities among Those Reporting Mild Symptoms (n=9) and Those Diagnosed with Clinical CIPN (n=28).
Figure 2C: Percentage of Patients Reporting Specific Symptom Modalities During and after Chemotherapy among Those with Persistent Symptoms (n=13).

Discussion
This study highlights the significant burden of CIPN in early-stage breast cancer patients treated with paclitaxel. Our findings revealed a high prevalence of CIPN-related symptoms in our cohort, with 62% of patients reporting moderate-to-severe symptoms during treatment. Remarkably, clinical records captured only 24% of CIPN cases, underscoring the extent of underreporting when relying solely on routine clinician assessments.

As previously demonstrated discordance between patient-reported symptoms and clinician-documented CIPN suggests that patient-reported outcome measures may enable a better understanding of symptom manifestation and effects on function [7,11,16,6]. In fact, such measures are increasingly recognized as valuable tools that provide a patient-based perspective essential to accurate assessment [6,17,18]. Consistent with our findings, Salgado et al. reported that symptoms of CIPN were underreported in medical records compared to those captured by the CIPN20 questionnaire in

patients with early-stage breast cancer treated with paclitaxel [19]. Importantly, while we identified significant discrepancy between clinician-documented and patient-reported CIPN, the rates of clinician registered neuropathy were consistent with previous studies [20,21].

Thus, the prevalence observed in our cohort aligns with global reports, where CIPN prevalence for paclitaxel varies depending on the study population, diagnostic tools, and timing of assessment [2,4]. Our results add valuable insight into the Latin American context, a region with limited CIPN data, emphasizing the need for robust monitoring systems in this population. Additionally, the use of the abbreviated version of CIPN20 questionnaire enabled the detection of patient-reported outcomes often overlooked in routine clinical evaluations.

Half of the patients diagnosed with CIPN reported both sensory and motor symptoms, consistent with previous studies documenting mixed symptomatology in paclitaxel-induced neuropathy [1,2,4]. Sensory symptoms, such as tingling, numbness and burning pain were most frequently reported, affecting quality of life and daily functioning. Notably, motor symptoms like weakness and cramps were also prevalent, contributing to functional impairments during and after treatment. These findings reaffirm the multidimensional impact of CIPN, which extends beyond sensory disturbances.

Nearly half of the patients with CIPN continued to experience symptoms two years after completing treatment, illustrating the chronic nature of this condition. This persistence rate is consistent with reports from other cohorts where up to 40-60% of CIPN patients have ongoing symptoms years after chemotherapy [2,4,17]. Chronic neuropathy poses a significant challenge, as it can impair recovery, reduce long-term quality of life, and increase healthcare burdens [2,4,5].

Interestingly, all patients with persistent symptoms experienced motor symptoms during chemotherapy, and had higher motor symptom scores, suggesting that the presence and / or severity of motor involvement may predict chronicity. This observation aligns with prior findings suggesting that symptom severity during treatment may correlate with long-term outcomes. Moreover, it underscores the importance of early detection and intervention to mitigate nerve damage and prevent prolonged or severe neurotoxicity.

No significant associations were found between CIPN development and patient, tumor, or treatment-related variables in our cohort. While some previous studies have identified potential risk factors such as age, obesity, and cumulative dose [9-11], the lack of associations in our study may reflect the homogeneity of the sample or the relatively small cohort size. Future studies with larger and more diverse populations are warranted to validate these findings.

Conclusions

This study underscores the high prevalence, chronicity, and underreporting of CIPN in early-stage breast cancer patients treated with paclitaxel, particularly in a Latin American setting. The marked discrepancy between patient-reported symptoms and clinician-documented CIPN highlights the need for integrating patient-reported outcome measures into routine clinical care. By emphasizing patient-reported outcomes, our findings provide a deeper understanding of the multifaceted impact of CIPN and reinforce the need for improved detection and management strategies [6].

Furthermore, the high prevalence of persistent symptoms underscores the importance of developing effective preventive strategies and long-term management plans. Interventions such as physical therapy, pharmacological treatments, and supportive care have shown promise in alleviating CIPN symptoms and should be considered as part of comprehensive care. Future research should focus on identifying predictive markers and evaluating targeted interventions to enhance the quality of life for cancer survivors.

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