RESEARCH ARTICLE

Editorial Process: Submission:03/20/2025 Acceptance:01/07/2026 Published:01/21/2026

Incidence and Risk Factors Associated with Platinum Derivative Chemotherapy-Induced Peripheral Neuropathy during Antineoplastic Treatment

Aline Cattiussi Araujo Feitosa, Francisca Thays dos Santos Alexandre, Jennifer Vianna Barbosa, Giulianna Aparecida Vieira Barreto, Ana Beatriz Silva Marques Araújo, Larissa Mont'Alverne Arruda, Sérgio Ferreira Juaçaba, Paulo Goberlânio de Barros Silva*, Flávio da Silveira Bittencourt

Abstract

Background: This study retrospectively analyzed the incidence and risk factors associated with platinum-induced sensory peripheral neuropathy (PSPN). **Methods:** Before each chemotherapy cycle, patients were routinely evaluated for the presence and severity of PSPN based on the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 scale, which ranges from 0 to 4. Information from two years of evaluations was collected, and patient medical records were reviewed to obtain data on chemotherapy cycle, sex, age, body mass index, body surface area, primary tumor, chemotherapy protocol, history of head and neck radiotherapy, and overall survival. The X^2 test, multinomial logistic regression, and Kaplan-Meier curves were used for statistical analysis (SPSS 20.0, $p < 0.05$). **Results:** Among 3,140 patients, 16,878 events were evaluated, with 7,187 (42.58%), 5,514 (32.67%), and 4,177 (24.75%) patients treated with cisplatin, carboplatin, or oxaliplatin, respectively. The incidence of any event of PSPN was 98.85% and 1867 (11.16%) showed scores two or higher (PSNP interfering with activities of daily living (ADL). Carboplatin and oxaliplatin ($p<0.001$), ≥5 CT cycles ($p<0.001$), body mass index >25 ($p=0.005$), advanced T ($p<0.001$), N ($p=0.025$) and M ($p=0.010$) clinical stages as well as association with capecitabine ($p=0.021$), paclitaxel ($p=0.027$) or vinorelbine ($p=0.031$) significantly increased risk of PSNP interfering in ADL. Over 48 months of evaluation, overall survival was 87.3% (n = 2741/3140), and PSNP interfering with ADLs significantly increased the risk of death by 1.52-fold (95% CI = 1.19-1.95, $p = 0.001$). **Conclusion:** PCPN has a high incidence, and significant risk factors include BMI, age, number of CT cycles, advanced stages, and associations with capecitabine, paclitaxel, and vinorelbine, all of which are associated with lower overall survival.

Keywords: Peripheral neuropathy- Antineoplastic agents- Neoplasms

Asian Pac J Cancer Prev, **27 (1)**, 87-96

Introduction

Chemotherapy (CT) is a systemic treatment that employs antineoplastic agents targeting different phases of the cell cycle. Due to their non-selective action, these agents also affect healthy proliferating cells, resulting in significant adverse effects that negatively impact patients' quality of life (QoL) [1]. Among these toxicities, chemotherapy-induced peripheral neuropathy (CIPN), particularly when associated with platinum-based compounds, stands out. With an incidence ranging from 19% to 85%, CIPN is one of the most prevalent neurological complications of cancer therapy and frequently leads to dose reductions or treatment discontinuation, thereby compromising oncological outcomes [2].

Platinum agents, such as cisplatin, carboplatin, and oxaliplatin, are widely used and exert their cytotoxic effects by forming DNA crosslinks, which inhibit DNA replication. In dorsal root ganglion (DRG) sensory neurons, these compounds cause chronic damage through mechanisms involving mitochondrial dysfunction, oxidative stress, and alterations in sodium channels, ultimately leading to neuronal death [3]. Oxaliplatin is also associated with acute cold-induced neurotoxicity, characterized by transient dysesthesias, muscle spasms, and perioral paresthesia [4].

CIPN symptoms include sensory (paresthesia, hypoesthesia), motor (distal weakness, gait disturbances),

*Oncogenetics Laboratory, Hospital Haroldo Juaçaba, Ceará Cancer Institute, Rua Papi Júnior, 1222 - Rodolfo Teófilo, Fortaleza - CE,60430-230. Fortaleza, Ceará, Brazil. *For Correspondence: paulo_goberlanio@yahoo.com.br*

and autonomic manifestations (gastrointestinal, cardiovascular, and urinary dysfunction), primarily affecting the extremities and orofacial region. These symptoms impair functional capacity, interfere with activities of daily living (ADLs and IADLs), and are often accompanied by anxiety, depression, and sleep disturbances. The severity of CIPN is commonly assessed using scales such as ECOG, WHO, Ajani, and the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE v5.0), which correlate neuropathic symptoms with degrees of functional limitation [5, 6].

Despite its high prevalence, practical strategies for preventing platinum-induced CIPN are still lacking. In this context, early identification of at-risk patients, education regarding signs and symptoms, and close clinical monitoring are essential [7]. Therefore, this study aims to investigate the primary risk factors associated with platinum-induced CIPN, to support early identification, inform clinical decision-making, and contribute to the preservation of patients' functional autonomy and quality of life.

Materials and Methods

This retrospective observational study was conducted at a CACON (High-Complexity Cancer Center) in Ceará, northeastern Brazil. A retrospective, cross-sectional, and quantitative design was conducted over two years to investigate the prevalence of PN. A cohort study was also conducted to determine whether PN impairs overall survival (January 1, 2020, to December 31, 2021). The study included patients from the Brazilian Unified Health System (SUS) who were undergoing antineoplastic chemotherapy with platinum compounds and who presented peripheral neuropathy (PN) as an adverse effect.

Two methodological approaches were employed: a cross-sectional design to assess the prevalence and severity of PN based on evaluations performed prior to chemotherapy sessions, and a retrospective cohort design to analyze overall survival using Kaplan–Meier analysis by comparing patients with and without PN.

This study complied with the ethical guidelines established by Resolution No. 466/2012 of the Brazilian National Health Council. It was submitted to and approved by the institution's technical-scientific committee and the Research Ethics Committee (CEP) via Plataforma Brasil (approval number: 60747622.0.0000.5528).

Inclusion and Exclusion Criteria

The study population consisted of approximately 3,140 medical records of SUS oncology patients undergoing platinum-based chemotherapy between January 2020 and December 2021, documented through severity scores for PN in the Toxicity Scales tool.

Inclusion criteria were all evaluations conducted during the specified period for patients on a platinum-based regimen who were available in the system and reported PN as an adverse effect.

Exclusion criteria included patients undergoing treatment for myeloproliferative disorders or metastatic disease with an unknown primary site, evaluations not associated with a platinum-based regimen, and records lacking the necessary clinical information for risk factor analysis. Patients with myeloproliferative disorders were excluded due to the potential for neurological and hematological manifestations intrinsic to these conditions, which could interfere with the specific assessment of platinum-induced PN and compromise the analysis of risk factors and oncological outcomes [8].

Toxicity Scale Assessment

The multidisciplinary team at the chemotherapy outpatient clinic routinely assesses patients for PN before each session, recording severity scores using the Toxicity Scales tool available in the institution's Tasy Electronic Patient Record (EPR) system. Nurse assistants and pharmacists use this tool to clinically assess the presence and severity of multiple adverse effects prior to chemotherapy sessions, aiming to triage and reduce complications.

The toxicity scales include the following adverse effects: mucositis, nausea, vomiting index, diarrhea, constipation, anorexia, dysgeusia, alopecia, hand–foot syndrome, sensory PN, fatigue, insomnia, and dysuria.

For each assessment, toxicity scores for palmoplantar dysesthesia (adapted from CTCAE v5.0 and the INCA toxicity scales to include region-specific terminology) are recorded as follows: Grade 0 – None (no symptoms); Grade I – Paresthesia with formication not interfering with function; Grade II – Paresthesia with formication interfering with function but not compromising daily activities; Grade III – Paresthesia interfering with daily activities; Grade IV – Permanent sensory loss interfering with function.

Collection of Clinical and Sociodemographic Data

Data on the PN adverse effect during platinum-based chemotherapy were retrieved from the EPR and exported into a standardized Microsoft Excel spreadsheet, which contained the visit number, date of attendance, and severity grade.

Using the visit number from the toxicity scales tool, a manual review was performed in the EPR for each case to collect relevant clinicopathological data. For patients with multiple evaluations, records were sorted chronologically to identify the chemotherapy cycle in question. The following variables were collected: age, sex, weight, height, treatment intent (neoadjuvant, adjuvant, or palliative), clinical stage, TNM classification, chemotherapy protocol, primary tumor site, and dates of treatment initiation and discharge or death.

Statistical Analysis

Data were expressed as absolute and relative frequencies and analyzed using Pearson's chi-square test to assess associations with other characteristics. Variables with statistically significant associations were included in a multinomial logistic regression model. Additionally, Kaplan–Meier survival curves were generated to compare overall survival between patients with and without PN, and the differences were tested using the Mantel–Cox

log-rank test. All analyses were performed using SPSS version 20.0 for Windows, with a 95% confidence level.

Results

The sample comprised 3,140 patients receiving platinum-based chemotherapy, of whom 1,623 (51.7%) were treated with cisplatin, 1,143 (36.4%) with carboplatin, and 375 (11.9%) with oxaliplatin. These patients underwent a total of 16,878 evaluations, averaging 5.37 chemotherapy cycles per patient, with a range of one to fifteen cycles. Patients who had undergone more than 15 cycles of chemotherapy were excluded.

Among the evaluations, only 25 (0.15%) showed no signs of peripheral neuropathy (PN). Grade I PN (asymptomatic sensory neuropathy) was observed in 14,986 (88.79%) evaluations, Grade II (moderate sensory PN with limitation of activities of daily living [ADLs]) in 1,700 (10.07%), Grade III (severe sensory PN limiting self-care and ADLs) in 162 (0.96%), and Grade IV (life-threatening sensory PN requiring urgent intervention) in 5 (0.03%) evaluations. The highest number of assessments was recorded in patients treated with cisplatin (n=7,187; 42.58%), followed by carboplatin (n=5,514; 32.67%) and oxaliplatin (n=4,177; 24.75%). Cisplatin was associated with the highest frequencies of Grade 0 and Grade I PN, oxaliplatin with Grade II, and carboplatin with Grades II to IV (p<0.001) (Table 1). So, we categorized patients into two groups: a control group with Grade 0 (no symptoms) and Grade I (Paresthesia with formication not interfering with function), because there is no interference in function and Grade II (Paresthesia with formication interfering with function but not compromising daily activities) or more because there is interference in neural function.

Regarding clinical characteristics, most patients underwent 3–4 chemotherapy cycles (n=3,976; 23.55%), were treated during the morning shift (n=15,742; 93.26%), were female (n=10,368; 61.42%), aged 41–60 years (n=7,387; 43.76%) or 61–80 years (n=7,349; 43.54%), and had a normal body mass index (BMI) (n=9,085; 54.84%). The number of chemotherapy cycles (p<0.001), age over 60 years (p<0.001), and BMI over 25 (p=0.013) were directly associated with PN accompanied by limitation of ADLs (Table 2).

The tumors most frequently treated with platinum-based chemotherapy were colorectal (n = 3,910; 23.16%), cervical (n = 3,631; 21.51%), head and neck (n = 2,018; 11.95%), and lung (n = 1,764; 10.45%). Patients with colorectal, lung, ovarian, endometrial, and stomach cancers had a higher frequency of PN with ADL limitations (p<0.001). In contrast, patients with head and neck and cervical tumors showed an inverse association with PN limiting ADLs (p<0.001) (Table 3).

Most patients had stage IV tumors (n = 5,125; 47.27%), with T3 (n = 3,227; 46.62%), N1 (n = 2,468; 37.96%), and M0 (n = 3,895; 63.62%) classifications. The majority received adjuvant chemotherapy (n=7,627; 45.18%) or neoadjuvant chemotherapy (n=7,455; 44.16%). Tumors classified as stage IV (p<0.001), T2 or T3 (p<0.001), N2 (p<0.001), M1 (p = 0.003), and treated with adjuvant chemotherapy (p<0.001) were associated with higher frequencies of PN with ADL limitations (Grade II-IV) (Table 4).

Among the platinum compounds, carboplatin and oxaliplatin were associated with the highest frequency of PN with ADL limitation (Grade II-IV) (p<0.001). Among the chemotherapeutic agents combined with platinum compounds, paclitaxel (n = 5,385; 31.90%) and fluoracil (n = 4,314; 25.56%) were the most commonly used. Most patients received protocols containing two chemotherapeutic agents (n=7,617; 45.12%). The use of capecitabine (p<0.001), paclitaxel (p<0.001), pembrolizumab (p<0.001), and vinorelbine (p<0.001), as well as chemotherapy regimens containing two or three drugs (p<0.001), were directly associated with PN with ADL limitations (Grade II-IV). Docetaxel (p=0.003) and epirubicin (p=0.017) were inversely associated with PN (Grade II-IV) (Table 5).

In multivariate analysis, the number of chemotherapy cycles (p<0.001), tumor stages T3/T4 (p<0.001), N2/N3 (p=0.025), and M1 (p=0.010), as well as the use of capecitabine (p=0.021), paclitaxel (p=0.027), and vinorelbine (p=0.031), were independently associated with an increased frequency of PN with ADL limitations (Grade II-IV) (Table 6).

During the 48-month follow-up, overall survival was 87.3% (n = 2,741/3,140), with a mean survival time of 39.67 months (95% CI: 38.94–40.40). Patients with PN limiting ADLs (Grade II-IV) had significantly shorter overall survival (mean 34.64 months; 95% CI: 32.43–36.86) compared to those without this adverse effect (Grade 0-I) (mean 40.29 months; 95% CI: 39.53–41.05) (p=0.001), corresponding to a 1.52-fold increased risk of death (95% CI: 1.19–1.95) (Figure 1).

Discussion

This study described the main risk factors for peripheral

Table 1. Incidence and Severity of PCPN during Antineoplastic CT with Platinum Derivatives

		PCPN Grade					
	Total	0	I	II	III	IV	p-value
Total	16,878	25 (0.15%)	14.986 (88.79%)	1.700 (10.07%)	162 (0.96%)	5(0.03%)	
Platinum							
Cisplatin	7187 (42.58%)	15 (60.00%)*	6572 (43.85%)*	546 (32.12%)	54 (33.33%)	0 (0.00%)	<0.001
Carboplatin	5514 (32.67%)	6 (24.00%)	4770 (31.83%)	651 (38.29%)*	82 (50.62%)*	5 (100.00%)*	
Oxaliplatin	4177 (24.75%)	4 (16.00%)	3644 (24.32%)	503 (29.59%)*	26 (16.05%)	0(0.00%)	

*p<0.05, Pearson's chi-square test (n, %).

Table 2. Influence of Clinical Features on the Incidence of PCPN during Antineoplastic CT with Platinum Derivatives

		PN with ADLs limitation		
	Total	Grade <II	Grade II-IV	p-Value
CT cycle				
1 cycle	3140 (18.60%)	3076 (20.49%)*	64 (3.42%)	<0.001
2 cycles	2659 (15.75%)	2508 (16.71%)*	151 (8.08%)	
3-4 cycles	3976 (23.55%)	3610 (24.05%)*	366 (19.58%)	
5-7 cycles	3153 (18.68%)	2739 (18.25%)	414 (22.15%)*	
8-10 cycles	1553 (9.20%)	1238 (8.25%)	315 (16.85%)*	
>10 cycles	2399 (14.21%)	1840 (12.26%)	559 (29.91%)*	
Shift				
Morning	15742 (93.26%)	13987 (93.18%)	1755 (93.90%)	0.240
Afternoon	1138 (6.74%)	1024 (6.82%)	114 (6.10%)	
Sex				
Female	10368 (61.42%)	9238 (61.54%)	1130 (60.46%)	0.365
Male	6512 (38.58%)	5773 (38.46%)	739 (39.54%)	
Age				
Up to 20 years	47 (0.28%)	47 (0.31%)*	0 (0.00%)	<0.001
21-40 years old	1708 (10.12%)	1601 (10.67%)*	107 (5.72%)	
41-60 years old	7387 (43.76%)	6598 (43.95%)*	789 (42.22%)	
61-80 years old	7349 (43.54%)	6439 (42.90%)	910 (48.69%)*	
>80 years old	389 (2.30%)	326 (2.17%)	63 (3.37%)*	
BMI				
18.5-25.00	9085 (54.84%)	8134 (55.25%)*	951 (51.57%)	0.013
25.00-30.00	4908 (29.63%)	4339 (29.47%)	569 (30.86%)*	
30.00-35.00	1984 (11.98%)	1735 (11.79%)	249 (13.50%)*	
>35.00	588 (3.55%)	513 (3.48%)	75 (4.07%)*	

*p<0.05, Pearson's chi-square test (n, %).

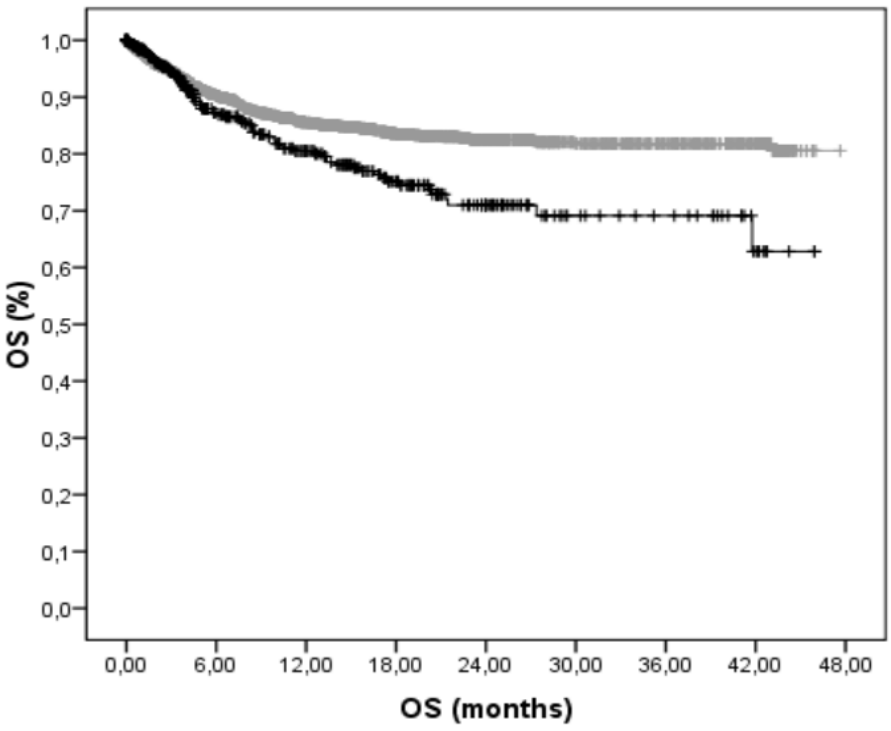

Figure 1. Influence of Palmoplantar Dysesthesia on Overall Survival of Patients during CT. Black line = patients with PN with limitation of ADLs; gray line = patients without PN with limitation of ADLs (p=0.001, Mantel-Cox log-rank test).

Table 3. Influence of Primary Tumor Location on the Incidence of PCPN during Antineoplastic CT with Platinum Derivatives

		PN with ADLs limitation		
	Total	Grade <II	Grade II-IV	p-value
Primary tumor location				
Mama	652 (3.86%)	582 (3.88%)	70 (3.75%)	<0.001
Colorectal	3910 (23.16%)	3433 (22.87%)	477 (25.52%)*	
Abdomen	104 (0.62%)	93 (0.62%)	11 (0.59%)	
Lung	1764 (10.45%)	1512 (10.07%)	252 (13.48%)*	
Head and neck	2018 (11.95%)	1868 (12.44%)*	150 (8.03%)	
Sarcomas	98 (0.58%)	97 (0.65%)	1 (0.05%)	
Thyroid	15 (0.09%)	14 (0.09%)	1 (0.05%)	
Bladder	143 (0.85%)	135 (0.90%)	8 (0.43%)	
Uterus	3631 (21.51%)	3399 (22.64%)*	232 (12.41%)	
Esophagus	1067 (6.32%)	933 (6.22%)	134 (7.17%)	
SNC	23 (0.14%)	21 (0.14%)	2 (0.11%)	
Liver	156 (0.92%)	143 (0.95%)	13 (0.70%)	
Skin	72 (0.43%)	58 (0.39%)	14 (0.75%)	
Ovary	1215 (7.20%)	1027 (6.84%)	188 (10.06%)*	
Endometrium	367 (2.17%)	280 (1.87%)	87 (4.65%)*	
Stomach	1237 (7.33%)	1051 (7.00%)	186 (9.95%)*	
Melanoma	29 (0.17%)	27 (0.18%)	2 (0.11%)	
Pancreas	97 (0.57%)	87 (0.58%)	10 (0.54%)	
Penis	19 (0.11%)	19 (0.13%)	0 (0.00%)	
Prostate	61 (0.36%)	54 (0.36%)	7 (0.37%)	
Renal	6 (0.04%)	6 (0.04%)	0 (0.00%)	
Testicle	56 (0.33%)	54 (0.36%)	2 (0.11%)	
Urothelial	31 (0.18%)	24 (0.16%)	7 (0.37%)	
Bile ducts	59 (0.35%)	51 (0.34%)	8 (0.43%)	
Vagina / vulva	50 (0.30%)	43 (0.29%)	7 (0.37%)	

*p<0.05, Pearson's chi-square test (n, %).

neuropathy (PN) in patients treated with platinum derivatives during antineoplastic chemotherapy for solid tumors. Analysis of the sample revealed that cisplatin was the most commonly used platinum compound (42.58%) among patients, with a predominance of PN grades 0 and 1 and a lower frequency of PN limiting activities of daily living (ADLs). Literature reports cisplatin as the most neurotoxic platinum agent, inducing sensory neuropathy in approximately 50% of patients, primarily affecting the upper and lower extremities [3].

However, the onset of toxicity is delayed until a cumulative dose exceeds 300 mg/m², as cisplatin-induced PN is dose-dependent. This may explain the low rate of severe toxicity in patients treated with cisplatin in this study [9]. Previous studies demonstrate that neurotoxicity related to cisplatin use strongly correlates with cumulative doses above 350 mg/m², with almost all patients receiving 500–600 mg/m² showing objective evidence of nerve damage [9, 10]. Moreover, the incidence of cisplatin-induced PN may depend on the dose per cycle, cumulative dose, and infusion duration [4].

In contrast, carboplatin and oxaliplatin are associated with an increased risk of severe neuropathy. Oxaliplatin exhibits dose-dependent neurotoxicity, occurring in 10–20% of patients receiving cumulative doses of 750–850 mg/m² and in 50% of those receiving 1,170 mg/m², predisposing them to grade 3 neuropathy [11]. In this study, approximately 28.3% of patients treated with oxaliplatin presented PN limiting ADLs. A literature review by Amptoulach and Tsavaris noted that oxaliplatin-induced acute neuropathy occurs in about 90% of patients, peaking within three days post-infusion and resolving within a week [3, 12].

Oxaliplatin also causes more chronic late neurotoxicity compared to cisplatin, with PN persisting in 26–46% of patients at 12 months, 24% at 15–18 months, and up to 84% at 24 months. In contrast, cisplatin-induced PN persists in 5–20% of patients after one year [4]. Despite higher severity, grade 2 toxicity predominated in oxaliplatin-treated patients, consistent with the phase III C-07 study in operable colon cancer patients receiving FULV (5-fluorouracil/leucovorin) versus FLOX (FULV plus oxaliplatin), which mainly reported low-grade sensory neurotoxicity with only 0.7% grade 3–4 in FULV versus 8.4% in FLOX [13].

Simpson et al. report that prolonging oxaliplatin infusion

Table 4. Influence of Staging and Intention of Systemic Therapy on the Incidence of PCPN during Antineoplastic CT with Platinum Derivatives.

		PN with ADLs limitation		
	Total	Grade <II	Grade II-IV	p-value
Stage				
1	392 (3.62%)	375 (3.87%)*	17 (1.48%)	<0.001
2	1887 (17.40%)	1757 (18.13%)*	130 (11.29%)	
3	3439 (31.72%)	3107 (32.06%)*	332 (28.84%)	
4	5125 (47.27%)	4453 (45.95%)	672 (58.38%)*	
T				
1	609 (8.80%)	538 (8.80%)	71 (8.80%)	<0.001
2	1105 (15.96%)	937 (15.32%)	168 (20.82%)*	
3	3227 (46.62%)	2835 (46.36%)	392 (48.57%)*	
4	1981 (28.62%)	1805 (29.52%)*	176 (21.81%)	
N				
0	1729 (26.59%)	1589 (27.69%)*	140 (18.35%)	<0.001
1	2468 (37.96%)	2179 (37.97%)	289 (37.88%)	
2	1763 (27.11%)	1496 (26.07%)	267 (34.99%)*	
3	542 (8.34%)	475 (8.28%)	67 (8.78%)	
M				
0	3895 (63.62%)	3432 (64.33%)*	463 (58.83%)	0.003
1	2227 (36.38%)	1903 (35.67%)	324 (41.17%)*	
CT Intent				
Neoadjuvant	7455 (44.16%)	6748 (44.95%)*	707 (37.83%)	<0.001
Adjuvant	7627 (45.18%)	6658 (44.35%)	969 (51.85%)*	
Neoadjuvant and adjuvant	412 (2.44%)	383 (2.55%)	29 (1.55%)	
Palliative	1386 (8.21%)	1222 (8.14%)	164 (8.77%)	

*p<0.05, Pearson's chi-square test (n, %).

to 6 hours significantly reduces severe neurotoxicity compared to the standard 2-hour infusion. Additionally, "stop-and-go" strategies, administering oxaliplatin for shorter periods (usually three months) followed by breaks, result in lower rates of severe neurotoxicity (3–25%) [9]. The development of oxaliplatin-induced PN is estimated to occur at cumulative doses above 780–850 mg/m²; current guidelines recommend not exceeding 850 mg/m² and discontinuing oxaliplatin in cases of severe neurotoxicity, which negatively impacts treatment efficacy [14]. This was corroborated in our sample, where patients with PN exhibited lower overall survival.

Carboplatin showed the highest toxicity (grades 2–4) and greatest frequency of ADL-limiting PN in the study population. Similar findings report severe neurotoxicity in 94–96% of carboplatin-treated patients [3, 4]. Extremely high doses (600 mg/m²), combination with other neurotoxic agents, or prior exposure to neurotoxic drugs (e.g., cisplatin, etoposide) increase neurological risk. Carboplatin-induced sensory neuropathy resembles that caused by cisplatin, with similar clinical features and impact on ADLs [11, 15]. In our study, combination therapies with platinum derivatives, especially capecitabine, paclitaxel, and vinorelbine, significantly increased this risk.

Regarding gender, both sexes were included; however, the majority of patients were female (61.42%). This aligns with INCA estimates indicating that the most common cancers among women in Ceará (2020–2022) include trachea, bronchus, lung (2nd), colon and rectum (3rd), cervix (5th), ovary (6th), uterine body (7th), and stomach (8th), all treated with platinum-based chemotherapy [16]. No significant association was found between gender and PN with ADL limitation.

PN with ADL limitation predominated in patients aged 61–80 (p<0.001), consistent with literature linking older age to severe platinum chemotherapy-induced peripheral neuropathy (PCPN). Australian and Canadian cohort studies reported advanced age (≥70 years) as a significant risk factor for severe PCPN [17]. Age-related hearing loss and neuropathies may exacerbate platinum-induced ototoxicity and neurotoxicity in older adults [10].

Regarding BMI, a study of 102 high-risk stage II/III colorectal cancer patients treated with CAPOX showed that BMI >30 was significantly associated with chronic neurotoxicity, and BMI ≥25 correlated with worse disease-free survival, supporting our findings of increased PN with ADL limitation in patients with BMI >25 [18]. Obesity measures, such as body surface area ≥2.0 m², also relate to PN risk, possibly due to higher treatment doses and cumulative exposure [17].

PN with ADL limitation markedly increased after the fifth chemotherapy cycle (p<0.001). Pachman et al. reported worsening neuropathy severity across 12 cycles of FOLFOX treatment, reinforcing the link between cycle

Table 5. Influence of Drugs Used during CT on the Incidence of PCPN during Antineoplastic CT with Platinum Derivatives

		PN with ADLs limitation		
	Total	Grade <II	Grade II-IV	p-Value
Platinum				
Carboplatin	5516 (32.68%)	4776 (31.82%)	740 (39.59%)*	<0.001
Cisplatin	7190 (42.59%)	6590 (43.90%)*	600 (32.10%)	
Oxaliplatin	4177 (24.75%)	3648 (24.30%)	529 (28.30%)*	
Other chemotherapeutics				
Zoledronic Acid	193 (1.14%)	177 (1.18%)	16 (0.86%)	0.215
Bevacizumab	8 (0.05%)	7 (0.05%)	1 (0.05%)	0.898
Bleomycin	18 (0.11%)	18 (0.12%)	0 (0.00%)	0.134
Capecitabine	678 (4.02%)	570 (3.80%)	108 (5.78%)*	<0.001
Cyclophosphamide	4 (0.02%)	4 (0.03%)	0 (0.00%)	0.480
Cytarabine	5 (0.03%)	5 (0.03%)	0 (0.00%)	0.430
Docetaxel	239 (1.42%)	227 (1.51%)*	12 (0.64%)	0.003
Doxorubicin	94 (0.56%)	85 (0.57%)	9 (0.48%)	0.643
Epirubicin	228 (1.35%)	214 (1.43%)*	14 (0.75%)	0.017
Etoposide	261 (1.55%)	234 (1.56%)	27 (1.44%)	0.706
Filgastrima	41 (0.24%)	39 (0.26%)	2 (0.11%)	0.206
Fluoracillin	4314 (25.56%)	3806 (25.35%)	508 (27.18%)	0.088
Gemcitabine	877 (5.20%)	775 (5.16%)	102 (5.46%)	0.588
Ifosfamide	20 (0.12%)	18 (0.12%)	2 (0.11%)	0.878
Irinotecan	58 (0.34%)	56 (0.37%)	2 (0.11%)	0.064
Paclitaxel	5385 (31.90%)	4616 (30.75%)	769 (41.14%)*	<0.001
Pembrolizumab	53 (0.31%)	32 (0.21%)	21 (1.12%)*	<0.001
Pemetrexed	4 (0.02%)	4 (0.03%)	0 (0.00%)	0.480
Pertuzumab	1 (0.01%)	1 (0.01%)	0 (0.00%)	0.724
Trastuzumab	251 (1.49%)	220 (1.47%)	31 (1.66%)	0.516
Vinblastine	16 (0.09%)	16 (0.11%)	0 (0.00%)	0.158
Vincristine	4 (0.02%)	4 (0.03%)	0 (0.00%)	0.480
Vinorelbine	103 (0.61%)	77 (0.51%)	26 (1.39%)*	<0.001
Zoladex	7 (0.04%)	7 (0.05%)	0 (0.00%)	0.350
Number of chemotherapy drugs				
1	4687 (27.77%)	4405 (29.35%)*	282 (15.09%)	<0.001
2	7617 (45.12%)	6588 (43.89%)	1029 (55.06%)*	
3	4527 (26.82%)	3969 (26.44%)	558 (29.86%)*	
4	49 (0.29%)	49 (0.33%)	0 (0.00%)	

*p<0.05, Pearson's chi-square test (n, %).

number, cumulative dose, and PCPN severity [4, 14].

The most common tumors treated with platinum in this study were colorectal (23.16%), cervical (21.51%), head and neck (11.95%), and lung (10.45%). PN with ADL limitation was more frequent in colorectal (25.52%), lung (13.48%), and ovarian (10.06%) tumors (p<0.001). Colorectal cancer is the second and third most common cancer in men and women in Ceará, respectively, with oxaliplatin-based regimens such as FOLFOX and CAPOX as standard treatments [19]. Oxaliplatin is highly neurotoxic, with chronic PN incidence around 70% [20]. A study from the Sydney Cancer Survivorship Center found that 80% of colorectal cancer patients receiving oxaliplatin required dose reduction or interruption, primarily due to PN [12].

Lung cancer, the leading cause of cancer deaths worldwide and the third (men) and fourth (women) most common in Ceará, is primarily treated systemically with platinum compounds combined with third-generation agents such as vinorelbine, gemcitabine, and taxanes. This combination improves survival but increases the risk of PN due to the neurotoxicity of these agents [21]. Ilkhan and Celikhisar reported that sensory neuropathy was most common with cisplatin + etoposide, and mixed polyneuropathy was more frequent with cisplatin + vinorelbine in lung cancer patients [21].

Ovarian cancer, the most lethal gynecological malignancy in Ceará, is treated with cytoreductive surgery

Table 6. Multivariate Analysis of Risk Factors for PCPN during Antineoplastic CT with Platinum Derivatives.

	p-Value	Adjusted POR (95%CI)
PN with limitation of ADLs (Grade II-IV)		
CT cycle >4	<0.001	105.83 (22.16-505.39)
Age	0.930	0.80 (0.47-3.57)
BMI >25	0.005	3.82 (1.49-9.82)
Location	1,000	1.29 (0.56-2.76)
Stage	0.426	1.23 (0.73-2.08)
T (T3/T4)	<0.001	4.63 (2.17-9.87)
N (N2/N3)	0.025	2.46 (1.12-5.41)
M (M1)	0.010	1.87 (1.16-3.01)
CT Type	0.786	0.91 (0.47-1.78)
Platinum (Cisplatin/ Carboplatin/ Oxaliplatin)	0.259	7.18 (0.23-219.59)
Capecitabine	0.021	5.77 (1.31-25.48)
Docetaxel	0.255	2.69 (0.49-14.77)
Epirubicin	0.965	1.05 (0.16-6.73)
Paclitaxel	0.027	3.63 (1.16-11.39)
Pembrolizumab	0.972	2.34 (0.12-4.63)
Vinorelbine	0.031	3.41 (1.12-10.43)

*p<0.05, multinomial logistic regression; POR, adjusted prevalence odds ratio; 95% CI, 95% confidence interval.

followed by carboplatin and paclitaxel chemotherapy. PN is a significant adverse effect affecting quality of life, presenting as painful paresthesia and decreased vibratory sensation [22, 23]. A retrospective study in China found 69.3% of women receiving taxane-platinum regimens reported PN, which decreased to 19.3% after 12 months, confirming taxane-related sensory neuropathy [22].

Most patients had advanced-stage tumors (stage 4), predominantly T3, N1, M0, treated mainly with adjuvant or neoadjuvant chemotherapy. Advanced disease management is prevalent at tertiary cancer centers in Brazil. Adjuvant chemotherapy is first-line for stage III tumors, and oxaliplatin-associated persistent toxicity is reported long-term, suggesting that high platinum doses in advanced tumors contribute to increased neurotoxicity risk. Treatment regimen choice, duration, and patient factors must balance benefits and neurotoxicity risk [24].

Among chemotherapy agents combined with platinum, capecitabine showed the highest frequency of PN with ADL limitation. Capecitabine is an oral fluoropyrimidine prodrug used in colorectal and metastatic breast cancer treatment. Its main adverse effect is hand-foot syndrome, causing dysesthesia, tingling, erythema, and severe skin changes, contributing to increased neurotoxicity in combination regimens [25]. A 2022 Indian study found 42% of newly diagnosed colorectal cancer patients treated with CAPOX developed sensory-motor peripheral neuropathy (SMP), with 12% grade 3 toxicity, also associated with oxaliplatin-related PN [26]. SMP and sensory PN have overlapping symptoms but are distinct toxicities requiring specific management.

Paclitaxel, the most frequently combined agent with platinum, was second in frequency of PN with ADL limitation. As a taxane, paclitaxel treats various solid tumors and is commonly combined with platinum. It induces PN in 60–70% of patients, a cumulative and severe non-hematologic toxicity [4, 7]. Paclitaxel-induced neuropathic pain affects about 68% of patients in the first month, persisting up to six months in 30%, caused by microtubule inhibition, impairing axonal transport [27]. Risk factors include age, treatment regimen, dose per cycle, concomitant neuropathic drugs, and pre-existing neuropathy or comorbidities.

Conversely, docetaxel combined with platinum was associated with the lowest PN risk, inversely correlated with PN limiting ADLs. This aligns with literature showing docetaxel-induced neuropathy typically manifests after cumulative doses exceed 600 mg/m², with a lower incidence and severity than paclitaxel, affecting about 13% of patients [28].

Patients with PN limiting ADLs had lower overall survival and a 1.52-fold increased risk of death compared to those without PN. Development of PCPN can necessitate dose reduction or therapy discontinuation, increasing cancer-related morbidity and mortality, consistent with these findings [29].

Currently, there is an increase in the number of diabetic patients worldwide, along with this, there is an increase in the manifestation of various complications, such as neuropathy, which is quite disabling, as it can manifest neurosensory disorders, such as a decrease in the sense of protection, minimizing the quality of life of these patients [30].

The literature demonstrates several approaches to minimize neurotoxicity in patients taking neurotoxic drugs. For example, medication discontinuation, lengthening the pause between cycles, the use of neuroprotectors such as aminophylline, and medication changes for a limited period until full neurological recovery is achieved [31].

Limitations of this study include a lack of data on antineoplastic doses and infusion times, which are critical for evaluating PN causes. Laboratory tests, comorbidities, pre-existing diseases, and lifestyle factors (e.g., smoking, alcohol) were not collected, despite their known impact on PN risk [16, 18, 29]. Assessments were performed retrospectively by different professionals without neurologist involvement, reducing data standardization. Additionally, we could not control for confounders such as glycemic control and pre-existing neuropathies, because the sample size is enormous. However, the major strength of the study is its large sample size and the use of highly reliable electronic health record data tracking, which allows for the identification of significant PN risk factors and a robust multivariate analysis.

In conclusion, PCPN incidence is high, with carboplatin associated with more frequent PN than oxaliplatin or cisplatin. Significant risk factors include BMI, age, number of chemotherapy cycles, advanced tumor stages, and combined use of capecitabine, paclitaxel, and vinorelbine. Moreover, PN with ADL limitation is linked to reduced overall survival.

Author Contribution Statement

All authors contributed to the conception and design of the study. Aline Cattiussi Araujo Feitosa, Francisca Thays dos Santos Alexandre, Jennifer Vianna Barbosa, Giulianna Aparecida Barreto, and Ana Beatriz Silva Marques Araújo carried out the data acquisition and wrote the article. Larissa Mont'Alverne Arruda and Sérgio Ferreira Juaçaba were responsible for analysis and interpretation of data. Flávio da Silveira Bittencourt was responsible for the critical revision of the manuscript, reviewing the text and writing the paper, ensuring its intellectual content. Paulo Goberlânio de Barros Silva developed the concept and design of the study, performed the statistical analysis, supervised the study, and revised the text. All authors have read and approved the final manuscript.

Acknowledgements

None.

Ethics approval

The present study complied with the ethical requirements established in Resolution 466/2012 of the National Health Council. It was submitted and approved by the technical-scientific committee of the institution and by the Research Ethics Committee (CEP) Plataforma Brasil under Opinion No. 60747622.0.0000.5528.

Consent for publication

The authors declare consent for publication.

References

1. Zajączkowska R, Kocot-Kępska M, Leppert W, Wrzosek A, Mika J, Wordliczek J. Mechanisms of chemotherapy-induced peripheral neuropathy. Int J Mol Sci. 2019;20(6):1451. https://doi.org/10.3390/ijms20061451.
2. Seretny M, Currie GL, Sena ES, Ramnarine S, Grant R, MacLeod MR, et al. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. Pain. 2014;155(12):2461-70. https://doi.org/10.1016/j.pain.2014.09.020.
3. Amptoulach S, Tsavaris N. Neurotoxicity caused by the treatment with platinum analogues. Chemother Res Pract. 2011;2011:843019. https://doi.org/10.1155/2011/843019.
4. Staff NP, Cavaletti G, Islam B, Lustberg M, Psimaras D, Tamburin S. Platinum-induced peripheral neurotoxicity: From pathogenesis to treatment. J Peripher Nerv Syst. 2019;24 Suppl 2(Suppl 2):S26-s39. https://doi.org/10.1111/jns.12335.
5. Brewer JR, Morrison G, Dolan ME, Fleming GF. Chemotherapy-induced peripheral neuropathy: Current status and progress. Gynecol Oncol. 2016;140(1):176-83. https://doi.org/10.1016/j.ygyno.2015.11.011.
6. National Cancer Institute.Common Toxicity Criteria; Version 5.0 de 2017. Available from: http://safetyprofilerctep.nci.nih.gov/CTC/CTC.aspx. Acesso em: mar. 2022
7. Staff NP, Grisold A, Grisold W, Windebank AJ. Chemotherapy-induced peripheral neuropathy: A current review. Ann Neurol. 2017;81(6):772-81. https://doi.org/10.1002/ana.24951.
8. Arranz L, Sánchez-Aguilera A, Martín-Pérez D, Isern J, Langa X, Tzankov A, et al. Neuropathy of haematopoietic stem cell niche is essential for myeloproliferative neoplasms. Nature. 2014;512(7512):78-81. https://doi.org/10.1038/nature13383.
9. Park SB, Goldstein D, Krishnan AV, Lin CS, Friedlander ML, Cassidy J, et al. Chemotherapy-induced peripheral neurotoxicity: A critical analysis. CA Cancer J Clin. 2013;63(6):419-37. https://doi.org/10.3322/caac.21204.
10. Trendowski MR, El Charif O, Dinh PC, Jr., Travis LB, Dolan ME. Genetic and modifiable risk factors contributing to cisplatin-induced toxicities. Clin Cancer Res. 2019;25(4):1147-55. https://doi.org/10.1158/1078-0432.Ccr-18-2244.
11. Ewertz M, Qvortrup C, Eckhoff L. Chemotherapy-induced peripheral neuropathy in patients treated with taxanes and platinum derivatives. Acta Oncol. 2015;54(5):587-91. https://doi.org/10.3109/0284186x.2014.995775.
12. Teng C, Cohen J, Egger S, Blinman PL, Vardy JL. Systematic review of long-term chemotherapy-induced peripheral neuropathy (cipn) following adjuvant oxaliplatin for colorectal cancer. Support Care Cancer. 2022;30(1):33-47. https://doi.org/10.1007/s00520-021-06502-4.
13. Land SR, Kopec JA, Cecchini RS, Ganz PA, Wieand HS, Colangelo LH, et al. Neurotoxicity from oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage ii and iii colon cancer: Nsabp c-07. J Clin Oncol. 2007;25(16):2205-11. https://doi.org/10.1200/jco.2006.08.6652.
14. Hsu HT, Wu LM, Lin PC, Juan CH, Huang YY, Chou PL, et al. Emotional distress and quality of life during folinic acid, fluorouracil, and oxaliplatin in colorectal cancer patients with and without chemotherapy-induced peripheral neuropathy: A cross-sectional study. Medicine (Baltimore). 2020;99(6):e19029. https://doi.org/10.1097/md.0000000000019029.
15. Novak M, Miličević J, Bišof V. Impact of chemotherapy-induced peripheral neuropathy on the quality of life in cancer patients. Acta Clin Croat. 2022;61(1):52-61. https://doi.org/10.20471/acc.2022.61.01.07.
16. National Comprehensive Cancer Network. NCCN Guidelines; 2023. Available from: https://www.nccn.org/guidelines/category_1. Acesso em: mar. 2023.
17. Mizrahi D, Park SB, Li T, Timmins HC, Trinh T, Au K, et al. Hemoglobin, body mass index, and age as risk factors for paclitaxel- and oxaliplatin-induced peripheral neuropathy. JAMA Netw Open. 2021;4(2):e2036695. https://doi.org/10.1001/jamanetworkopen.2020.36695.
18. Ottaiano A, Nappi A, Tafuto S, Nasti G, De Divitiis C, Romano C, et al. Diabetes and body mass index are associated with neuropathy and prognosis in colon cancer patients treated with capecitabine and oxaliplatin adjuvant chemotherapy. Oncology. 2016;90(1):36-42. https://doi.org/10.1159/000442527.
19. Besora S, Santos C, Izquierdo C, Martinez-Villacampa MM, Bruna J, Velasco R. Rechallenge with oxaliplatin and peripheral neuropathy in colorectal cancer patients. J Cancer Res Clin Oncol. 2018;144(9):1793-801. https://doi.org/10.1007/s00432-018-2691-8.
20. Sałat K. Chemotherapy-induced peripheral neuropathy-part 2: Focus on the prevention of oxaliplatin-induced neurotoxicity. Pharmacol Rep. 2020;72(3):508-27. https://doi.org/10.1007/s43440-020-00106-1.
21. Dasdemir Ilkhan G, Celikhisar H. Evaluation of chemotherapy-related peripheral neuropathy in lung cancer treatment. Tumori. 2021;107(5):392-9. https://doi.org/10.1177/0300891620975868.
22. Jin L, Zhang Y, Yang W. Chemotherapy-induced peripheral neuropathy among patients with ovarian cancer. Int

J Gynaecol Obstet. 2020;149(3):303-8. https://doi.org/10.1002/ijgo.13137.
23. Sarkar S, Pal R, Mahata S, Sahoo PK, Ghosh S, Chatterjee P, et al. Evaluation of numerical rating scale and neuropathic pain symptom inventory pain scores in advanced ovarian carcinoma patients undergoing surgery and first-line chemotherapy. J Clin Transl Res. 2022;8(1):54-60.
24. Grothey A, Sobrero AF, Shields AF, Yoshino T, Paul J, Taieb J, et al. Duration of adjuvant chemotherapy for stage iii colon cancer. N Engl J Med. 2018;378(13):1177-88. https://doi.org/10.1056/NEJMoa1713709.
25. Lou Y, Wang Q, Zheng J, Hu H, Liu L, Hong D, et al. Possible pathways of capecitabine-induced hand-foot syndrome. Chem Res Toxicol. 2016;29(10):1591-601. https://doi.org/10.1021/acs.chemrestox.6b00215.
26. Kalidindi AV, Dubashi B, Jayanthi M, Shewade DG. Efficacy and safety of capecitabine and oxaliplatin (capox) treatment in colorectal cancer: An observational study from a tertiary cancer center in south india. Indian J Cancer. 2022;59(1):73-9. https://doi.org/10.4103/ijc.IJC_618_19.
27. Xu Y, Jiang Z, Chen X. Mechanisms underlying paclitaxel-induced neuropathic pain: Channels, inflammation and immune regulations. Eur J Pharmacol. 2022;933:175288. https://doi.org/10.1016/j.ejphar.2022.175288.
28. Wang Y, Herrstedt J, Havsteen H, DePoint Christensen R, Mirza MR, Lund B, et al. A multicenter, non-randomized, phase ii study of docetaxel and carboplatin administered every 3 weeks as second line chemotherapy in patients with first relapse of platinum sensitive epithelial ovarian, peritoneal or fallopian tube cancer. BMC Cancer. 2014;14:937. https://doi.org/10.1186/1471-2407-14-937.
29. Révész D, Bonhof CS, Bours MJL, Weijenberg MP, Vreugdenhil G, van de Poll-Franse LV, et al. Sociodemographic, clinical, lifestyle, and psychological correlates of peripheral neuropathy among 2- to 12-year colorectal cancer survivors. Oncol Res Treat. 2022;45(9):480-93. https://doi.org/10.1159/000524037.
30. Zakin E, Abrams R, Simpson DM. Diabetic neuropathy. Semin Neurol. 2019;39(5):560-9. https://doi.org/10.1055/s-0039-1688978.
31. Bhojwani D, Bansal R, Wayne AS. Managing therapy-associated neurotoxicity in children with all. Hematology Am Soc Hematol Educ Program. 2021;2021(1):376-83. https://doi.org/10.1182/hematology.2021000269.