




# Chemotherapy-induced neuropathic pain characteristics in Mexico's National Cancer Center pain clinic

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**Introduction:** Chemotherapy (CT) is one of the most commonly used pharmacological approaches in cancer treatment. However, CT induces damage to several tissues causing significant deleterious effects in cancer survivors being chemotherapy-induced neuropathic pain (CINP) among the most commonly reported. CINP is thought to be present in up to 68.1% of the patients within 1 month of receiving CT. Due to the fact that reliable statistic information is scarce in several Latin American countries' diagnosis and treatment of this side-effect may be delayed directly affecting patients. Therefore, the aim of the present study was to determine and present the incidence and features of CINP in patients with cancer attending the Pain Management Clinic at Mexico's National Institute of Cancerology in Mexico City.

**Methods:** We performed a retrospective, file-based analysis of all the patients treated in the Pain Management Clinic at the National Institute at Cancer in Mexico from January 2016 to January 2017.

**Results:** CINP was found in 30.9% of the patients. The basal VAS was on average 2.5 upon arrival to the Pain Management Unit and 2.4 at the end of treatment ( $p > 0.05$ ). The patients with the highest risk of developing CINP were those treated with paclitaxel Odds ratio 8.3 ( $p < 0.01$ ), followed by platins OR 4 ( $p < 0.01$ ), vincristine OR 1.5 ( $p = 0.01$ ) and thalidomide OR 1.1 ( $p = 0.01$ ).

**Conclusion:** Incidence of CINP was similar to previous reports; however, the number of variables related to this type of pain in our cohort may open a new line of research and highlight the importance of this particular issue to our health system. It is necessary to develop a mechanism to predict the risk of patients to suffer CINP and to search the mechanism to control and reduce the suffering related to the current treatments.

**Keywords:** Pain, chemotherapy, neuropathy, paclitaxel

## Introduction

Chemotherapy (CT) is one of the most commonly used pharmacological approaches in cancer treatment as its use has been proven to expand patients' survival rates dramatically.<sup>1</sup> However, most chemotherapeutic agents also induce damage to several tissues causing significant deleterious effects that can have a serious long-term impact in surviving patients' quality of life.<sup>2</sup> Among the most commonly reported, chemotherapy-induced neuropathy (CIN) and chemotherapy-induced neuropathic pain (CINP) have been proven to be some of the most difficult to treat consequences of CT.<sup>3-5</sup>

Although commonly underestimated, CINP is thought to be present in up to 68.1% of the patients within 1 month of receiving CT and about 30% may still be presenting symptoms 6 months after treatment discontinuation.<sup>6</sup> This type of

neuropathy is important as its presence not only alters a cancer survivor quality of life,<sup>2,7</sup> but it also has been found to induce an overall reduction in CT dose thus decreasing its benefits.<sup>8</sup> Various chemotherapeutic agents such as paclitaxel, docetaxel or vincristine have been reported to induce CINP;<sup>5</sup> therefore, as some of these molecules are considered first-line treatment for several types of cancer,<sup>9</sup> there is a high probability for a cancer patient to be afflicted by this side-effect. Moreover, other comorbidities such as diabetes, old age, vitamin B12 and amino acid deficiencies<sup>10,11</sup> or several CT courses have been related to CINP incidence and severity.<sup>6</sup>

Due to this high degree of complexity and relevance, the oncologic patient with pain, particularly those diagnosed with CINP, should have an early and continuous access to a pain management unit to ensure an adequate pain control. However, these are not always feasible in the reality of the public health care system of developing countries where pain management is not always a priority.<sup>12</sup> Moreover, reliable statistic information is scarce in several Latin American countries including Mexico.

Therefore, the aim of the present study was to determine and present the incidence and features of CINP and to compare its features and management with other neuropathic conditions in patients with cancer attending the Pain Management Clinic and the National Institute of Cancerology in Mexico City.

## Materials and methods

A retrospective file-based observational study was performed. Clinical charts of all patients treated in the Pain Management Clinic of the National Institute of Cancerology (*Instituto Nacional de Cancerología*–INCAN) in Mexico City from January 2016 to January 2017 were included. Our research was part of a thesis accepted by INCAN’s Research Committee (No. Ref. INCAN/CI/0830/18). This study was conducted in accordance with the principles of the Declaration of Helsinki<sup>13</sup> and Mexico’s “Ley General de Salud” in Health Research Matter.<sup>14</sup> All patient information was guarded and maintained confidential. INCAN is the keeper of all patient information system data, and all information used within the study was anonymized and not traceable to a single individual. Patient consent to review their medical records was waived by our institution as our protocol was considered not to threaten patients’ security in accordance with Mexico’s “Ley General de Salud” in Health Research Matter, article 23.<sup>14</sup>

Sample was divided in those clinical charts in which chemotherapy-induced neuropathic pain (CINP group) was included as a main diagnosis and those clinical charts with other reported sources of neuropathic pain (OSNP group). If a medical chart showed a clinical description of chemotherapy-induced peripheral neuropathy, but CINP was not included as a main diagnosis that chart was included in the OSNP group.

Five major areas were assessed in the clinical charts: 1) Demographic features, 2) Cancer characteristics, 3) Type of chemotherapeutic 4) Pain assessment and 5) Pain perception and management. *Demographic features* include the identification of the sex and age of the patient. Other medical comorbidities (diabetes, hypertension, thyroid and autoimmune diseases) were registered as well as the history of substance use (alcohol and tobacco). *Cancer characteristics* include the patients’ main type of cancer, the state of progression and the main chemotherapy agents used during the assessment period. *Type of chemotherapeutic* refers to the type of drug last used to treat cancer with a curative or palliative purpose. If a drug was not used more than twice in a patient or it was an adjuvant to the main chemotherapy course, it was included in “others”. *Pain assessment* refers to the type of pain perceived by the patient, pain distribution and the DN4 questionnaire score. Finally, *Pain perception and management* includes the self-report perception of pain of the patients (in a resting state), the maximum pain perceived and the main medications used for pain management.

The DN4 questionnaire design to evaluate neuropathic pain comprises 10 items (seven based on a face-to-face interview with the patient and three based on clinical examination) and has been widely used as a screening diagnostic instrument. Visual Analog Scales (VAS), included in clinical charts, were used for the assessment of pain perception.<sup>15</sup> For the present study, VAS scores range from 0 (no pain perception at all) to 10 (maximum perception of pain).

## Statistical analysis

All analyses were performed using the version 21.0 of the SPSS statistical software. Descriptions of demographic and clinical characteristics were done with frequencies and percentages for categorical variables and with means and standard deviations (SD) for continuous variables. The comparisons between patients with and without chemotherapy-induced neuropathy were analyzed using Chi-square tests ( $\chi^2$ ) for categorical variables and with Independent

Samples *t* Tests for continuous variables. Changes in time in pain-management medications were analyzed with McNemar's test for paired proportions. Patients were included in a repeated measures analyses of variance (ANOVA) model to examine direction of changes (time effect) among groups (interaction effect) in terms of the intensity of pain perception, assessed with the VAS. The significance level for tests was established at  $p<0.05$ .

## Results

### General results

We analyzed 754 medical charts that comprised the complete medical history of patients that were attended at INCANs' pain clinic from January 1, 2016 until January 1, 2017. After thorough research, we found that out of the 754 patients attended in our clinic 525 were women (69.6%) and 229 men (30.4%) with a mean age of 59 years old (SD=14, range 18–94 years). Patients in the CINP group (n=233) represented 30.9% of the total cohort with OSNP group (n=521) representing 69.1%. At least one medical comorbidity was present in 750 patients (99.5%) with systemic hypertension as the most common comorbidity (24.8%, n=186) followed by diabetes mellitus (18.9%, n=142), thyroid disease (4.8%, n=36) and autoimmune disease (2.1%, n=16). At the time of the study, 12.2% (n=92) showed a history of alcohol consumption and 21.3% (n=160) were smokers. (see Table 1)

The most common type of cancer was breast with 28.8% (n=217), hematologic malignancies 12.1% (n=91), cervix 10.5% (n=79), lung 5.6% (n=42), colon 1.9% (n=14) and other 41.2% (n=311); according to stage of progression, 4.1% (n=31) were on stage 1, 9.5% (n=72) on stage 2, 19.8% (n=149) on stage 3 and 33.2% (n=250) on stage 4, and 18.7% (n=141) was still undetermined at the time of the study; this means that over half of the patients had advanced cancer (52.8% were on stage 3 and 4). The most frequently used chemotherapeutics were paclitaxel (17.0%, n=127) and cisplatin (10.7%, n=80) (see Table 1)

### Pain assessment

Multiple causes of pain were observed in the patients treated in the pain clinic (n=752). Metastases was the most frequent cause (47.2%, n=355), followed by CINP (30.9%, n=233), osteoarthritis (19.5%, n=147), surgery (18.6%, n=140), radiculopathy (14.7%, n=111), radiotherapy (9.6%, n=72), trauma (3.2%, n=24), herpes zoster infection (3.1%, n=23), phantom limb pain (1.6%,

n=12), rheumatoid arthritis (0.7%, n=5) and other unidentifiable causes (22.6%, n=170). As can be seen in Table 2, upon exploration (n=716 assessed patients) dysesthesias like tingling, numbness and electric shock-like pain were the most common, suggesting a heavy burden of neuropathy. The mean score of the DN4 scale was 2.8 (SD=2.2, range 0–9) indicating that mean neural compromise was generally low. The main distribution of pain was in the location site of the tumor/malignancy or glove and stocking.

The comparison of demographic features and cancer characteristics between patients in CINP group and OSNP group are displayed in Table 1. No significant differences emerged between groups in terms of demographic features, medical comorbidities or types of cancer although type of cancer was more clearly identified in the group of CINP than in the remaining patients. Cancer progression in stages 3 or 4 was more common in CINP patients ( $p<0.001$ ). Paclitaxel, platins, vincristine and thalidomide were more frequently used in CINP patients. Regarding pain assessment, as seen in Table 2, electric shock-like pain ( $p=0.02$ ), tingling ( $p<0.001$ ), pinprick pain ( $p=0.03$ ), numbness ( $p=0.004$ ) and hypoesthesia were more frequently reported in this group. DN4 mean score was higher ( $p<0.001$ ) and glove and stocking distribution of pain was also more frequently reported in CINP patients ( $p<0.001$ ).

### Pain perception and management

The average number of consultations in the Pain Management Clinic during the assessment period was 4 (SD=4.1, range 1–30). Upon entering the Pain Management Clinic Patients, pain perception assessed with a VAS (where 0 denotes no pain perception and 10 the maximum perception of pain), was of 2.5 (SD=2.6, range 0–10) with the maximum pain perceived reported as 5.5 (SD=3.1, range 0–10). After the follow-up period, pain perception was 2.3 (SD=2.5, range 0–10) with the maximum pain perception of 4.9 (SD=3.3, range 0–10). The ANOVA model showed no differences in time or by groups in terms of pain perception. Nevertheless, and as seen in Table 3, significant differences arise in the maximum pain perception, where patients in the OSNP reported a reduction of maximum pain in time while it remains the same for patients with CINP.

Patients were under treatment for pain with several medications, which are displayed in Table 3. On average patients were treated with a combination of 2 drugs (range 0–6 medications) with paracetamol (60.2%, n=453) and neuromodulators (50.8%, n=382) as the most frequently prescribed medications

**Table 1** Demographic and cancer features between groups

	<b>Total sample n=754 n, %</b>	<b>OSNP group n=521 n, %</b>	<b>CINP group n=233 n, %</b>	<b>Statistics</b>
<i>Demographic features and medical comorbidities</i>				
Sex-Women	525, 69.6	356, 68.3	169, 72.5	$\chi^2=1.3, p=0.24$
Diabetes-Yes <sup>a</sup>	142, 18.9	99, 19.1	43, 18.5	$\chi^2=0.03, p=0.86$
Hypertension-Yes <sup>a</sup>	186, 24.8	131, 25.2	55, 23.7	$\chi^2=0.2, p=0.65$
Thyroid disease-Yes	36, 4.8	27, 5.2	9, 3.9	$\chi^2=0.6, p=0.43$
Autoimmune disease-Yes <sup>a</sup>	16, 2.1	10, 1.9	6, 2.6	$\chi^2=0.3, p=0.56$
Alcohol-Yes <sup>b</sup>	92, 12.3	62, 12.0	30, 12.9	$\chi^2=0.1, p=0.71$
Smoker-Yes <sup>b</sup>	160, 21.3	108, 20.8	52, 22.4	$\chi^2=0.2, p=0.62$
<i>Type of cancer, stage of progression and chemotherapy agents</i>				
Breast	217, 28.8	143, 27.4	74, 31.8	$\chi^2=19.3, p=0.002$
Hematologic malignencies	91, 12.1	53, 10.2	38, 16.3	
Cervix	42, 5.6	22, 4.2	20, 8.6	
Lung	79, 10.5	62, 11.9	17, 7.3	
Colon	14, 1.9	9, 1.7	5, 2.1	
Other	311, 41.2	232, 44.5	79, 33.9	
Progression <sup>c</sup>				
Stage 1	31, 5.1	23, 5.5	8, 4.0	
Stage 2	72, 11.7	48, 11.6	24, 33.3	
Stage 3	149, 24.3	82, 19.8	67, 33.8	
Stage 4	250, 40.8	161, 38.8	89, 44.9	
Chemotherapy agents <sup>d</sup>				$\chi^2=32.2, p<0.001$ $\chi^2=8.5, p=0.003$ $\chi^2=6.6, p=0.01$ $\chi^2=106.7, p<0.001$ $\chi^2=3.8, p=0.06$ $\chi^2=9.9, p=0.002$ $\chi^2=4.5, p=0.09$ $\chi^2=57.6, p<0.001$
Platins	112, 15.0	52, 10.0	60, 26.1	
Cisplatin	80, 10.7	44, 8.5	36, 15.7	
Vincristine	31, 4.1	15, 2.9	16, 7.0	
Paclitaxel	127, 17.0	39, 7.5	88, 38.3	
Docetaxel	43, 5.7	24, 4.6	19, 8.3	
Thalidomide	37, 4.9	17, 3.3	20, 8.7	
Lenalidomide	2, 0.3	–	2, 0.09	
Other	355, 47.5	198, 38.2	157, 68.3	
	Mean, S.D.	Mean, S.D.	Mean, S.D.	
Age	59.0, 14.1	59.4, 14.8	58.0, 12.4	$t=1.2, p=0.21$

Notes: <sup>a</sup>n=751 <sup>b</sup>n=750 <sup>c</sup>n=613 <sup>d</sup>n=748.

(Table 3). As can be seen in Table 3, patients with CINP received more frequently tramadol, paracetamol and neuromodulators than OSNP patients at their initial pain treatment. After a year of treatment, no differences arise between patients in the medications used for pain management, where both groups were treated with similar medications. However, an important change of medications in time was observed in the group of OSNP. The prescription of tramadol (McNemar  $p<0.001$ ), morphine (McNemar  $p=0.02$ ), fentanyl (McNemar  $p=0.007$ ) and methadone (McNemar  $p=0.03$ ) increase, while prescription of celecoxib (McNemar  $p=0.02$ ) and non-steroidal

anti-inflammatory drugs (NSAID, McNemar  $p=0.003$ ) decrease. On the other hand, fewer changes in time were observed in the CINP group with only significant changes in the prescription of tramadol (McNemar  $p<0.001$ ), morphine (McNemar  $p<0.001$ ) and antidepressants (McNemar  $p=0.007$ ). Prescription of tramadol decreases while it increases for the later.

## Discussion

CINP is a non-fatal, treatment-related complication resulting from the use of anticancer chemotherapeutic agents.

**Table 2** Pain characteristics patients with chemotherapy-induced neuropathic pain and patients with other types of pain

	<b>Total sample n=754 n, %</b>	<b>OSNP group n=521 n, %</b>	<b>CINP group n=233 n, %</b>	<b>Statistics</b>
<i>Pain assessment<sup>a</sup></i>				
Tingling	333, 46.5	209, 42.0	124, 56.9	$\chi^2=13.5, p<0.001$
Numbness	326, 45.5	209, 42.0	117, 53.7	$\chi^2=8.3, p=0.004$
Electric shock-like	310, 43.3	202, 40.6	108, 49.5	$\chi^2=4.9, p=0.02$
Pinprick pain	300, 41.9	196, 39.4	104, 47.4	$\chi^2=4.3, p=0.03$
Burning	261, 36.5	171, 34.3	90, 41.3	$\chi^2=3.1, p=0.08$
Tactile hypoesthesia	148, 20.7	90, 18.1	58, 26.6	$\chi^2=6.7, p=0.009$
Itch	109, 15.2	75, 15.1	34, 15.6	$\chi^2=0.03, p=0.85$
Cold allodynia	108, 15.1	69, 13.9	39, 17.9	$\chi^2=1.9, p=0.16$
General allodynia	100, 14.0	61, 12.2	39, 17.9	$\chi^2=4.0, p=0.04$
Pinprick hypoesthesia	60, 8.4	35, 7.0	25, 11.5	$\chi^2=3.8, p=0.06$
<i>Pain distribution<sup>b</sup></i>				
Unidentified	39, 5.8	38, 8.5	1, 0.4	$\chi^2=339.9, p<0.001$
Glove/Stocking	192, 28.4	25, 5.6	167, 72.9	
Surgery site	77, 11.4	66, 14.8	11, 4.8	
Tumor site	201, 29.7	173, 38.7	28, 12.2	
Other	167, 24.7	144, 32.4	22, 9.6	
	Mean, S.D.	Mean, S.D.	Mean, S.D.	
DN4 score <sup>c</sup>	2.8, 2.2	2.6, 2.2	3.3, 2.2	$t=-3.7, p<0.001$

Notes: <sup>a</sup>n=716, <sup>b</sup>n=676, <sup>c</sup>n=715.

Although this side effect has been consistently found in several studies<sup>5</sup> and is considered to be of the utmost importance as it can impede an adequate treatment<sup>8</sup> or induce other complications such as depression, insomnia or falls,<sup>16</sup> it is commonly overlooked. Furthermore, reliable statistics about this side effect in Mexico are scarce making it harder for decision makers to develop strategies to address CINP as a public health problem. Taking this into account, the aim of this study was to describe for the first time for our country the incidence of CINP treated in Mexico's National Institute of Cancer (INCAN) pain clinic and compare it with other cancer-related pain patients.

Initially, it is important to highlight some of the difficulties we encountered that may have had an impact on our results. Such a complication was the fact that some of the clinical charts showed the use of some hormonal chemotherapeutic agents that were used only once or for reasons other than cancer treatment. All such molecules were included as other in our results section (Table 2.) since the number of different molecules may have made adequate analyses impossible. Another obstacle we

encountered was that some medical charts did not have enough information about patients' clinical condition. The source of this predicament is not easy to assert as it may be related to several different factors such as the number of clinicians involved in the treatment of a single patient or the lack of communication between related departments. It is important to mention that INCAN is a highly specialized center dedicated to research, education and treatment of patients with oncologic conditions, thus, effective communication may sometimes be difficult among the overwhelming number of patients.

About our results, we describe for the first time in our country the incidence of CINP in cancer patients treated with at least one chemotherapeutic agent. We found that patients included in this protocol were more susceptible to present CINP if they were treated with paclitaxel and platins such as oxaliplatin and cisplatin. Moreover, CINP appeared to be highly prevalent as 30.9% of our patients had it as one of their primary diagnoses. The fact that the patients with the highest risk of developing CINP were those treated with paclitaxel agrees with several other reports.<sup>4,8</sup> However, some other results could be

**Table 3** Pain perception and management during a year attending the Pain Management Clinic

	<b>Total sample n=752 n, %</b>	<b>OSNP group n=519 n, %</b>	<b>CINP group n=233 n, %</b>	<b>Statistics</b>
<i>Tramadol</i> Admission 1-year	290, 38.6 219, 29.2	184, 35.5 147, 71.7	106, 45.5 72, 31.0	$\chi^2=6.8, p=0.009$ $\chi^2=0.5, p=0.45$
<i>Tapentadol</i> Admission 1-year	2, 0.3 6, 0.8	2, 0.4 5, 1.0	– 1, 0.4	$\chi^2=0.9, p=0.34$ $\chi^2=0.5, p=0.44$
<i>Morphine</i> Admission 1-year	204, 27.1 259, 34.5	147, 28.3 169, 32.6	57, 24.5 90, 38.8	$\chi^2=1.2, p=0.27$ $\chi^2=2.7, p=0.09$
<i>Oxycodone</i> Admission 1-year	23, 3.1 23, 3.1	14, 2.7 14, 2.7	9, 3.9 9, 3.9	$\chi^2=0.7, p=0.39$ $\chi^2=0.7, p=0.39$
<i>Buprenorphine</i> Admission 1-year	25, 3.3 29, 3.9	20, 3.9 23, 4.4	5, 2.1 6, 2.6	$\chi^2=1.4, p=0.22$ $\chi^2=1.4, p=0.22$
<i>Fentanyl</i> Admission 1-year	23, 3.1 39, 5.2	17, 3.3 30, 5.8	6, 2.6 9, 3.9	$\chi^2=0.2, p=0.60$ $\chi^2=1.1, p=0.27$
<i>Methadone</i> Admission 1-year	2, 0.3 8, 1.1	2, 0.4 8, 1.5	– –	$\chi^2=0.9, p=0.34$ $\chi^2=3.6, p=0.06$
<i>Paracetamol</i> Admission 1-year	453, 60.2 429, 57.1	298, 57.4 291, 56.1	155, 66.5 138, 59.5	$\chi^2=5.5, p=0.01$ $\chi^2=0.7, p=0.38$
<i>Celecoxib</i> Admission 1-year	99, 13.2 79, 10.5	73, 14.1 51, 9.8	26, 11.2 28, 12.1	$\chi^2=1.1, p=0.27$ $\chi^2=0.8, p=0.35$
<i>NSAID</i> Admission 1-year	79, 10.5 55, 7.3	55, 10.6 33, 6.4	24, 10.3 22, 9.5	$\chi^2=0.01, p=0.90$ $\chi^2=2.3, p=0.12$
<i>Steroid</i> Admission 1-year	25, 3.3 29, 3.9	16, 3.1 17, 3.3	9, 3.9 12, 5.2	$\chi^2=0.3, p=0.58$ $\chi^2=1.5, p=0.21$
<i>Carbamazepine</i> Admission 1-year	2, 0.3 5, 0.7	2, 0.4 3, 0.6	– 2, 0.9	$\chi^2=0.9, p=0.34$ $\chi^2=0.1, p=0.65$
<i>Neuromodulator</i> Admission 1-year	382, 50.8 393, 52.3	245, 47.2 255, 49.1	137, 58.8 138, 59.5	$\chi^2=8.6, p=0.003$ $\chi^2=6.8, p=0.009$
<i>Antidepressants</i> Admission 1-year	46, 6.1 61, 8.1	33, 6.4 37, 7.1	13, 5.6 24, 10.3	$\chi^2=0.1, p=0.68$ $\chi^2=2.2, p=0.13$

(Continued)

**Table 3** (Continued).

	<b>Total sample n=752 n, %</b>	<b>OSNP group n=519 n, %</b>	<b>CINP group n=233 n, %</b>	<b>Statistics</b>
	Mean, SD	Mean, SD	Mean, SD	
<i>Pain perception</i>				
Admission	2.5, 2.6	2.5, 2.7	2.3, 2.4	Time F=0.2, p=0.60
1-year	2.3, 2.5	2.3, 2.6	2.4, 2.5	TimexGroup F=1.4, p=0.23
<i>Maximum pain perception</i>				
Admission	5.5, 3.1	5.5, 3.2	5.3, 3.0	Time F=10.8, p=0.001
1-year	4.9, 3.3	4.7, 3.3	5.2, 3.1	TimexGroup F=4.4, p=0.03

interpreted as divergent such as the fact that we did not find any correlation with either clinical comorbidities in our CINP group such as those reported by other groups.<sup>17</sup> This fact could be related to the number of charts included in this study and, as we continue with this line of research, we expect to find a correlation similar to other reports.

Another finding, we believe to be relevant, is the lack of difference in the maximum pain perception in our CINP group after being treated in our pain clinic for a year. Although the use of neuromodulators such as pregabalin was highly prevalent as shown in Table 3, and that international standards include anticonvulsants,<sup>18</sup> this apparent inefficacy may be related to low availability of other treatments such as topical lidocaine or antidepressants such as duloxetine.<sup>19</sup> Moreover, although several agents have been proved to be effective as treatment of CINP,<sup>3</sup> it is currently considered by The American Society of Clinical Oncology that there are no agents that can be recommended for prevention of this side effect.<sup>20</sup> Other explanation may be that the number of comorbidities present in our general population made treatment particularly difficult. Other authors have also encountered similar results as this fact appears to be directly related to the incidence of cancer pain.<sup>21</sup>

It is important to highlight the high percentage of breast cancer patients that were attended in our clinic. This could be related to the type of CT agent most commonly used to treat this type of cancer. Also, other authors have found similar results regarding breast cancer finding other comorbidities to be important such as obesity, psychological status or even low physical activity.<sup>16,22</sup> However, this should not be interpreted lightly as it can be related to the fact that there is currently a national campaign of awareness to diagnose breast cancer which

may alter the number of patients that are treated for cancer. Other findings included the fact that most of our patients were in stage 3 or 4 when treated in our pain clinic. This could point toward either an increased probability of pain in more advanced processes or the fact that a more aggressive treatment may be related to an altered pain state. In fact, our findings also show a significant relation between metastases and increased pain, a fact that had previously been pointed out.<sup>23,24</sup>

Furthermore, our findings show that patients included in this protocol were more susceptible to present CINP if they were treated with paclitaxel and platins such as oxaliplatin and cisplatin. Moreover, CINP appeared to be highly prevalent as 30.9% of our patients fit the criteria for them to be diagnosed with this pathology. The fact that the patients with the highest risk of developing CINP were those treated with paclitaxel agrees with several other reports.<sup>4,8</sup> However, it is important to point out that other chemotherapeutic agents were also found to importantly induce CINP.

Even though our study opens a wide area of opportunity for further research as, to our knowledge, it is the first to highlight this particular situation in our country which is a leap forward in our knowledge on CINP in Mexico, there are several areas of opportunity that should be addressed as we encountered some critical limitations for in study. For example, the fact that we were unable to present CTCAE grading as it is not currently being used in our institution. This was an important setback as having it would have given us a wider perspective on the importance of CINP in our group.

Moreover, there was no information regarding neurophysiological studies due to the lack of availability of specialized equipment or technicians to answer as high

a demand as we face in our institute. Furthermore, one of the most important obstacles we need to report was the fact that some crucial information such as the descriptions about the physical distribution of CINP were depthless or unspecific, thus making it impossible for us to report certain well-known facts as present in our study. This may have come as a result of a clinical bias due to a lack of information about the importance of CINP and its high prevalence in our institute. Therefore, new working standards are being implemented in our clinic in order to prevent further inaccuracy and to ensure proper medical care for our patients.

These results bring CINP into a focal point for decision makers in our country and other countries in Latin America about the importance of this condition. We expect that broadening our data will bring about reliable information that may help clinicians to better diagnose and treat CINP.

## Conclusion

The amount of CINP was similar to previous reports; however, the number of variables related to this type of pain in our cohort may open a new line of research and highlight the importance of this particular issue to our health system. It is necessary to develop a mechanism to predict the risk of patients to suffer CINP and to search the mechanism to control and reduce the suffering related to the current treatments.

## Data availability statement

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

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## Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

## Disclosure

The authors declare no conflicts of interest in this work.

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