Clinical Evolution and Predictors of Chemotherapy-Induced Peripheral Neuropathy

doi: https://doi.org/10.32635/2176-9745.RBC.2019v65n2.392

Evolução Clínica e Preditores da Neuropatia Periférica Induzida por Quimioterapia

Evolución Clínica y Predictores de la Neuropatía Periférica Inducida por Quimioterapia

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Abstract

Introduction: Neurotoxic antineoplastic drugs are frequently associated to chemotherapy-induced peripheral neuropathy (CIPN). **Objective**: To evaluate the clinical evolution of patients exposed to potentially neurotoxic antineoplastic treatment and to identify possible clinical and sociodemographic predictors for the development of CIPN. **Method**: Cohort prospective study with patients with breast, ovary or intestine diagnosis of cancer in chemotherapy treatment with paclitaxel, docetaxel or oxaliplatin. They were assessed before the chemotherapy (T1), in the third month (T2) and 30-60 days after the interruption of the treatment (T3). All the patients responded to the questionnaire of clinical and sociodemographic profiles, were evaluated through neurologic clinical exam, by the performance scale ECOG, by the Hospital Anxiety and Depression Scale - HAD, pain scale of Short-cGuill, self-report of symptoms of CIPN and evaluation with the questionnaire of antineoplastic-induced neurotoxicity (QAIN). **Results:** Through self-report, 75% of the patients presented symptoms of CIPN. The QAIN showed that 90% presented a certain degree of CIPN in T2, while 82.5% still persisted in T3. Neuropathic pain affected 42% of the population (RR = 1.429, $CI_{95\%}$ = 1.130-1.806). Anxiety and depression scores significantly reduced when compared with the beginning of the treatment (reduction of 2.5 points in the scale HAD, $p < 0.05$). The functional capacity of the population did not show any significant change. The school level was considered a predictor of self-report of CIPN symptoms in T2 (OR = 1.314, $CI_{95\%}$ = 1.002-1.723, p = 0.048). **Conclusion:** The low school level may taint the patient capacity to report CIPN symptoms. This study draws attention for the necessity to use specific instruments for early detection of CIPN.

Key word: Neoplasms; Peripheral Nervous System Diseases; Antineoplastic Agents; Neurotoxicity Syndromes; Drug Therapy.

Resumo

Introdução: Drogas antineoplásicas neurotóxicas estão frequentemente associadas à neuropatia periférica induzida por quimioterapia (NPIQ). **Objetivo:** Avaliar a evolução clínica dos pacientes expostos a tratamento antineoplásico potencialmente neurotóxico e identificar possíveis preditores clínicos e sociodemográficos para o desenvolvimento da NPIQ. **Método:** Estudo de coorte prospectiva com pacientes com diagnóstico de câncer de mama, ovário ou intestino em tratamento quimioterápico com paclitaxel, docetaxel ou oxaliplatina. Foram avaliados antes da quimioterapia (T1), no terceiro mês (T2) e 30-60 dias após interrupção do tratamento (T3). Todos responderam ao questionário de perfis sociodemográfico e clínico, foram avaliados por meio de exame clínico neurológico, pela escala de *performance* ECOG, escala hospitalar de ansiedade e depressão (HAD), escala de dor Short-cGuill, autorrelato de sintomas de NPIQ e avaliação com o questionário de neurotoxicidade induzida por antineoplásicos (CINQ). **Resultados:** Por meio de autorrelato, 75% da dos pacientes informaram apresentar sintomas de NPIQ. O CINQ evidenciou que 90% apresentaram algum grau de NPIQ em T2, enquanto 82,5% ainda persistiam em T3. Dor neuropática acometeu 42% da população (RR=1,429; IC95%=1,130-1,806). Os escores de ansiedade e depressão reduziram significativamente quando comparados ao início de tratamento (redução de 2,5 pontos na escala HAD, p<0,05). A capacidade funcional da população não mostrou alterações significativas. No T2, a escolaridade foi considerada preditora para autorrelato de sintomas de NPIQ (OR=1,314, IC95%=1,002-1,723, p=0,048). **Conclusão***:* A baixa escolaridade pode comprometer a capacidade do paciente em relatar os sintomas da NPIQ. Este estudo chama a atenção para a necessidade de utilização de instrumentos específicos para detecção precoce da NPIQ.

Palavras-chave: Neoplasias; Doenças do Sistema Nervoso Periférico; Antineoplásicos; Síndromes Neurotóxicas; Tratamento Farmacológico.

Resumen

Introducción: Los fármacos antineoplásicos neurotóxicos a menudo se asocian con neuropatía periférica inducida por quimioterapia (CIPN). **Objetivo:** Evaluar la evolución clínica de pacientes expuestos a tratamientos antineoplásicos potencialmente neurotóxicos e identificar posibles predictores clínicos y sociodemográficos para el desarrollo de CIPN. **Método:** Estudio de cohorte prospectivo con pacientes diagnosticadas con cáncer de mama, ovario o intestino sometidos a quimioterapia con paclitaxel, docetaxel u oxaliplatino. Se evaluaron antes de la quimioterapia (T1), en el tercer mes (T2) y 30-60 días después de la interrupción del tratamiento (T3). Todos respondieron el cuestionario de perfil sociodemográfico y clínico, se evaluaron mediante un examen neurológico clínico, la escala de rendimiento ECOG, la escala de ansiedad y depresión hospitalaria (HAD), la escala de dolor Short-cGuill, el autoinforme de los síntomas de CIPN y la evaluación con el cuestionario de neurotoxicidad inducida por antineoplásicos (CINQ). **Resultados:** Por autoinforme, el 75% de la población informó presentar síntomas de CIPN. El CINQ mostró que el 90% tenía algún grado de NPIQ en T2, mientras que el 82.5% aún persistía en T3. El dolor neuropático afectó al 42% de la población (RR = 1.429; IC del 95% = 1.130-1.806). Las puntuaciones de ansiedad y depresión disminuyeron significativamente en comparación con el valor inicial (reducción de 2.5 puntos HAD, p <0.05). La capacidad funcional de la población no mostró cambios significativos. En T2, la educación se consideró un predictor de síntomas CIPN autoinformados (OR=1.314, IC 95%=1.002-1.723, p=0,048). **Conclusión:** La baja educación puede comprometer la capacidad del paciente para informar los síntomas de CIPN. Este estudio llama la atención sobre la necesidad de utilizar instrumentos específicos para la detección temprana de CIPN.

Palabras clave: Neoplasias; Enfermedades del Sistema Nervioso Periférico; Antineoplásicos; Síndromes de Neurotoxicidad; Tratamiento Farmacológico.

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INTRODUCTION

Neurotoxic antineoplastic drugs as taxanes, derived from platinum, inhibitors of proteosome and vinca alkaloids are frequently associated to chemotherapy-induced peripheral neuropathy (CIPN)[1]. It is characterized by bilateral and distal symmetrical axonopathy with drop of the amplitude of the potential of action and increase of the distal latency. The sensitive nerves are more precociously affected [2].

In general, its symptoms start in the beginning of the chemotherapy treatment, between the first and third cycles and with the peak of severity in the third month of therapy[3,4]. Positive sensitive manifestations (paresthesia, dysesthesia, neuropathic pain) are the most frequent and despite not being associated to higher mortality, have significant impact in the quality of people and influence the adherence and continuation of the treatment[1,4].

There are few evidences about how the clinical parameters can influence the development of CIPN[4-7]. Some authors describe the association of different characteristics of the chemotherapy protocol such as type of neurotoxic drug, interval between the cycles, dose and number of cycles as possible clinical predictors for its development[4-7]. Based in this, the objective of this work is to evaluate the clinical evolution of the patients exposed to a potentially neurotoxic antineoplastic treatment and identify possible clinical and sociodemographic predictors for the development of CIPN.

METHOD

Prospective cohort study that included patients diagnosed with breast, ovary or intestine cancer with curative or palliative intent to treatment who initiated antineoplastic therapy with taxanes (paclitaxel or docetaxel) or oxaliplatin, between January and October 2012 in high complexity oncology unit facility in a public university hospital in Minas Gerais. The Institutional Review Board of Universidade Federal de Minas Gerais (Coep-UFMG) reviewed and approved the study, approval report number 136.463, dated October 31, 2012.

To calculate the sample size, it was estimated 60% of the incidence of CIPN in the population exposed[5] and in 10% the presence of peripheral neuropathies in the non-exposed population to antineoplastic agents. It was obtained a population sample of 30 subjects with level of significance of 5% and power of 95%,. However, according to Miot[8], the sample size of longitudinal studies should consider a percent of around 30% of loss of follow up[8]. Therefore, the population size was adjusted to 40 subjects in follow up.

The inclusion criteria were: no treatment cycle of neurotoxic antineoplastic until the first evaluation, older than 18 years and diagnosis of tumor in the breast, ovary or intestine. The exclusion criteria were: presence of cognitive limitations or psychiatric disorders, clinically disabled individuals with performance status PS = ≥3; diagnosis of diabetes or leprosy, injuries or traumas that hampered the evaluation of foot or hands, background of motor or sensitive neurological injury resulting from neurologic diseases such as cerebral metastasis and sequelae of stroke, diagnosis of rheumatoid arthritis, carpal tunnel syndrome or other rheumatoid illnesses; use of antibiotics therapy within four weeks before the first evaluation, use of non-steroid anti-inflammatory or glucocorticoids in the two weeks prior to the first evaluation, intake of alcohol beverages more than three times a week, kidney dysfunction, insufficiency of adrenals or immune system diseases as lupus, deficiency of vitamin B12 not treated, diagnosis of peripheral neuropathy of any origin before chemotherapy.

The patients enrolled were evaluated in three moments: *first evaluation*: in week 0, before initiating the antineoplastic treatment (T1); *second evaluation*: between weeks nine to 12 for protocols occurring at each 21 days (T2). In the specific case of patients with breast cancer that used the protocol known as AC-T (adriamycin/cyclophosphamide four cycles at each 21 days, followed by 12 week sessions of paclitaxel), the second evaluation was done between the weeks six to nine of the treatment with paclitaxel; *third evaluation:* until 60 days after the conclusion of the treatment or in case of palliative care, between weeks 21 to 24 (T3).

These patients were submitted to different evaluations, including the sociodemographic and clinical profiles based in the collection of different variables: age (years), education (years), gender, marital status, tobacco use, alcohol use, type of neurotoxic antineoplastic, antineoplastic protocol, type of cancer, staging, metastasis, chemotherapy obstacle, co-morbidities, use of medication at home.

The measurement of functional capacity was done with the performance status ECOG developed by the *Eastern Cooperative Oncology Group* and validated by the World Health Organization (WHO) in 1982[9].To evaluate the symptoms of anxiety and depression, it was used the *Hospital Anxiety and Depression Scale* – HAD[10,11]. The pain was evaluated with the McGill questionnaire of pain, in its short version – *Short Form McGill Questionnaire* (SF-MPQ)[12,13].

To evaluate CIPN, the following strategies were adopted: symptoms self-reported, neurologic and clinical exam and evaluation using the antineoplastic-induced

neurotoxicity questionnaire (CINQ); a questionnaire validated for the Brazilian population based in a study developed by Simão et al.[13], that reached index Kappa=0,320 (p<0,001) in the attribute agreement analysis and moderate and positive correlation (p= 0.357; p<0.001) when comparing CINQ to the method of Semmes-Weinstein (MSW) monofilaments or estesiometer

During the clinical interview, the first question was: "How are you feeling with chemotherapy?", "have you noticed any side effect?" "do you feel any discomfort in your feet, hands or face?". The responses were logged through a dichotomic variable: presence or absence of CIPN symptoms self-reported of. Next, a systematized clinical neurologic exam was carried out. Finally, the CINQ with 29 items was applied to evaluate 20 symptoms divided in three subscales: symptoms of acute and chronic neuropathy in lower limbs (nine items); symptoms of chronic and acute neuropathy in upper limbs (ten items) and orofacial symptoms of chronic and acute neuropathy (10 items)[6,14]. The results obtained through CINQ are classified in grades from 0 to 4: value 0 – absence of symptoms or without paresthesia; grade 1– symptoms of short duration and that do not interfere in the daily life activities; grade 2 – mild paresthesia that interfere in some functions, but not in the daily life activities; grade 3 – pain or functional commitment that interfere in the daily life activities; and grade 4 – impairing persistent symptoms [6].

Normality tests were performed, obtaining variables with non-parametric distribution, being necessary, therefore, to choose non-parametric tests for discrete variables. Friedman Test for numerical variables and Cochran test for categorical variables were performed to verify whether significant differences occurred along the time. In this case, analyzes comparing T1xT2, T1xT3 and T2xT3 were conducted with Wilcoxon tests for numerical variables, McNemar for dichotomic categorical variables and marginal homogeneity test for ordinal dichotomic variables. For multiple comparisons, it was adopted the value of p=0.029 (correction of Bonferroni).

For the analysis of CIPN development predictors, comparative analyzes between the clinical and sociodemographic characteristics were performed in relation to the presence of CIPN at each timing (T1, T2 and T3) comparing the analyzes to the findings of CIPN identified through self-reports and CINQ. In this case, it were utilized the exact test of Fisher for categorical variables and the Mann-Whitney test for numerical variables. Binary logistic regression was performed in T2 and T3. It was utilized the test of Hosmer-Lemeshow with backward strategy (CI 95%). The co-variables with p < 0.20 were included in the logistic regression model.

RESULTS

During the 18 months of enrollment, 262 patients met the inclusion criteria of the study. After evaluation of the criteria, it was necessary to exclude 207 (79% of the patients eligible), resulting in a population of 55 patients for follow up, 27.3% were lost to follow up because they abandoned the study soon after baseline evaluation, which ended up in a final population of 40 patients (Figure 1).

The total population (n = 55) consisted of patients with ages ranging from 32 to 80 years (median 54 years). Females were predominant (83.6%), overall, married (45.5%) and had until three children (67.3%). The level of education was low, since the majority had less than 11 years of study and, therefore, failed to complete high school (72.7%). The majority (50.9%) self-claimed they were catholic and reported they went to church once a week or more. In regard to the use of tobacco and alcohol, there was a predominance of those who never smoked (49.1%) and never consumed alcohol (45.5%).

In relation to clinical profile, the majority would initiate treatment with paclitaxel (63.6%), adjuvant, being breast cancer predominant in the population (60.4%). Protocol ACT, which corresponds to the regimen adriamycin (A) and cyclophosphamide (C) combined, being four cycles of AC with 21 days interval, followed by

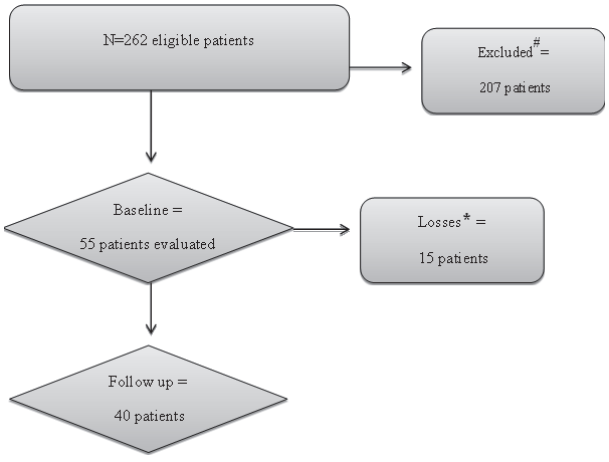

Figure 1. Flowchart of the eligible and excluded patients and follow up in the prospective cohort of evaluation of CIPN

Captions: # Arthritis arthrosis (7 cases), diabetes (44 cases), difficulty of locomotion (2 cases), neurological disease (4 cases), chronic alcoholism (12 cases), urgent beginning of chemotherapy (26 cases), injury in lower limbs with plaster (1 case), nephropathy (1 case), previous peripheral neuropathy (7 cases), important cognitive deficit (9 cases), PS>3 (55 cases), refused to participate (12 cases), no contact telephone number (23 cases), previous treatment of leprosy (1 case), use of corticoids, non-steroid anti-inflammatory or antibiotics until 15 days before the evaluation (3 cases). *Loss of follow up due to abandonment of the clinical trial because of progression of the disease (n=7), death (n=3), change of antineoplastic protocol (n=3), transference (n=1), diagnosis of arthritis and arthrosis post-evaluation of baseline (n=1).

12 consecutive weeks of paclitaxel (T), would be initiated in 45.5% (n = 25) of the patients. The presence of other co-morbidities was identified in 74.1% (n = 431) of the patients, with systemic arterial hypertension standing out. The predominant functional capacity was index 0 (zero) of ECOG, where the patient is completely active without evidence of oncologic disease symptoms (56.4%).

Depression or anxiety conditions were considered improbable for the majority of the population. The presence of pain of different types, except neuropathic pain, seven days before the first evaluation was noticed in 60% of the population, located in the tumor region associated or not to bone, articular, muscle pain and headache.

In a comparative analysis performed between the group follow up and the group loss it were not encountered statistically significant differences for the sociodemographic variables. However, for the clinical variables, the patients of the group loss presented worst functional capacity according to performance scale ECOG (p=0.002) and felt pain more frequently (p – 0.013) when compared to the group follow up.

The sociodemographic and clinical characteristics of the population follow up (n = 40) are detailed in Table 1. There was predominance of females (n = 32, 80%) with low education level and grade 0 (zero) of ECOG functional capacity where the individual is completely active (67.5%). It is observed that the majority would initiate the treatment with paclitaxel (55%), adjuvant, being breast cancer the predominant in the population (60.4%). Depression or anxiety disorders were considered unlikely for the majority of the population.

The analysis of the clinical evolution included functional capacity, pain, symptoms of anxiety and depression, self-report of CIPN and evaluation of CIPN with CINQ (tables 2, 3 and 4). The results of the neurologic clinical exam did not indicate significant clinical alterations along the time, except for the reduction of the perception of the right bicipital reflection (T1xT3 p= 0.020).

However, through self-report, it was observed that, both in T2 and T3, 75% (n = 30) of the population informed to have symptoms of CIPN (Table 2), while 82.5% (n=33) still persisted with some degree of the syndrome in T3, regardless of the type of antineoplastic (Table 2). Despite three patients (75%) had improved their CIPN condition after the end of the treatment, it was noticed that, for the others, the symptoms listed in the subscale of lower and upper limbs of CINQ had worsened, which reflects the increase of intensity and frequency of symptoms in upper and lower limbs with consequential and progressive impact in the daily life activities, even after the interruption of the exposure to the antineoplastic (Table 2).

It was noticed also that during the treatment, it was identified significant increase of the presence of neuropathic pain (Table 2). Analyzes have identified that, despite the pain of other types have evolved throughout the treatment, 17 (42%) patients developed neuropathic pain in some moment during the study. In T2, it was found a risk of 43% of development of neuropathic pain in patients who presented any symptom of CIPN (RR = 1.429; CI 95% = 1.130 – 1.806). There was no significant modifications of neuropathic pain between T2 and T3, which demonstrates the persistent nature of the condition.

The anxiety and depression scores reduced significantly when compared with the beginning of the treatment. The functional capacity of the population evaluated by the scale ECOG did not show significant alterations (Table 2).

In T2, education was the only variable considered predictive of self-report of symptoms of CIPN (OR=1.314, CI 95%=1.002- 1.723, p=0.048) (Table 3). In this model of regression, it were included the variables: gender, labor status, education, weight, number of antineoplastic drugs, time of diagnosis, use of medications at home, functional capacity, presence and intensity of the pain (Table 3).

It was observed association between the syndrome identified by the CINQ and the depression score in T3 (p=0.018) (Table 3). There was no relation between CIPN with different characteristics of the protocol adopted such as type of neurotoxic drug, interval between the cycles, dose and number of cycles. In the model of regression utilized, it were included the variables gender, labor status, weight, staging, use of medications at home, functional capacity, depression score, presence and intensity of pain (Table 4). However, none of the co-variables remained in the model, which suggests that, while utilizing the proper medication, clinical and sociodemographic variables did not influence the presence of symptoms of CIPN in the population evaluated.

DISCUSSION

The results of this research confirm that CIPN is a problem which affects patients exposed to taxanes and oxaliplatin either during or after the treatment as already evidenced in other studies [1,3,7].

The higher incidence of symptoms of CIPN occurred in T2 evaluation, confirming previous studies that showed peaks of symptoms of neuropathy around the third cycle of treatment [4]. The symptoms of CIPN kept stable between weeks 6 and 12 without any significant reduction at last until 30 days after the conclusion of the chemotherapy, which is in line with the chronic aspect of the neuropathic

Table 1. Sociodemographic and clinical characteristics of the population of patients with cancer before the beginning of the antineoplastic potentially neurotoxic treatment (n=40)

Parameters		Follow up (n=40) n (%)
Age (years) [median (P25-P75)]		53.5 (33-80)
Education (years) [median (P25-P75)]		8 (2-20)
Gender	Female	32 (80.0%)
	Male	8 (20.0%)
Marital status	Single	7 (17.5%)
	Married	20 (50.0%)
	Separated	8 (20.0%)
Tobacco use	Never smoked	21(52.5%)
	Smoked in the past	13 (32.5%)
	Smokes	6 (15.0%)
Alcohol use	Never drank	19 (47.5%)
	Drank in the past	15 (37.5%)
	Drinks	6 (15.0%)
Neurotoxic antineoplastic type	Paclitaxel	24 (60.0%)
	Oxaliplatin	13 (32.5%)
	Docetaxel	3 (7.5%)
Antineoplastic protocol	AC-T[a]	19 (47.5%)
	Carbo/paclitaxel[b]	3 (7.5%)
	b-FOL[c] ou FLOX[d]	8 (20.0%)
	Docetaxel/CTX[e]	2 (5.0%)
	Other regimens	2 (5.0%)
Type of cancer	Breast	24 (60.0%)
	Colon/rectum	13 (34.2%)
	Others	1 (2.6%)
Staging	II	10 (25.0%)
	III	17 (42.5%)
	IV	13 (32.5%)
Metastasis	Present	13 (32.5%)
	Absent	27 (67.5%)
Chemotherapy objective	Adjuvant	20 (50.0%)
	Palliative	10 (25.0%)
	Neoadjuvant	10 (25.0%)
Co-morbidities	Present	26 (65.0%)
	Absent	14 (35.0%)
Use of medications at home	Yes	26 (65.0%)
	No	14 (35.0%)
Index of daily performance (PS ECOG 0-4)	0	27 (67.5%)
	1	11 (27.5%)
	2	2 (5.0%)
Anxiety (scale HAD)	Unlikely	33 (82.5%)
	Likely	7 (17.5%
Depression (scale HAD)	Unlikely	32 (80.0%)
	Likely	8 (20.0%)
Pain	Present	20 (50.0%)
	Absent	20 (50.0%)
Intensity of the pain	Mild	8 (20.0%)
	Moderate	9 (22.5%)
	Acute	3 (7.5%)

Captions: [a] AC-T: adriamycin 60 mg/m²/cyclophosphamide 600 mg/m², per 4 cycle, at each 21 days, followed by paclitaxel 80 mg/m², weekly during 12 weeks (1 cycle at each 3 doses). [b] Carbo/Taxol: carboplatin AUC 6/paclitaxel 175 mg/m² at each 3 weeks. [c b]-FOL: oxaliplatin 85 mg/m D1 and D15/folic acid 20 mg/m² D1, D8 and D15/5-fluorouracil 500 mg/m² D1, D8, D15, at each 28 days. [d] Flox nordic: oxaliplatin 85 mg/m² d1/folic acid 60 mg/m² D1 and D2/5- fluorouracil 500 mg/m² D1 and D2, interval at each 15 days. [e] Docetaxel/CTX: docetaxel 75 mg/m²/ cyclophosphamide 600 mg/m²,at each 21 days for 4 cycles.

Table 2. Clinical evolution of patients in neurotoxic drugs (n=40)

Parameters		T1 (n=40) N (%)	T2 (n=40) N (%)	T3 (n=40) N (%)	Value p (<0.05) T1xT2xT3	Value p* (<0.029)* T1xT2	Value p* (<0.029) T1xT3	Value p* (<0.029) T2xT3
Status of daily performance (performance ECOG)	0	27 (67.5%)	21(52.5%)	20 (64.5%)	0.262##	-	-	-
	1	11 (27.5%)	17 (42.5%)	8 (25.8%)				
	2	2 (05.0%)	1 (2.5%)	3 (9.7%)				
Neuropathic pain	Present	0 (0.0%)	09(22.5%)	15 (37.5%)	<0.001**	0.004†	<0.001†	0.109†
	Absent	40 (100.0%)	31(77.5%)	25 (62.5%)				
Pain (all types)	Total pain index (0-45)	0	0	0	0.308#	-	-	-
	Median (min.-máx.)	(0-33)	(0-28)	(0-26)				
Intensity of the pain present	EVA (0-10)	0	0	0	0.868#	-	-	-
	Median (min.-máx.)	(0-10)	(0-10)	(0-8)				
Anxiety and depression (Scale HAD)	Total score (0-42)	9	6	6,5	0.008#	0.137■	0.009■	0.057■
	Median (min.-máx.)	(1-25)	(0-36)	(0-25)				
	Anxiety score (0-21)	5	3	3,5	0.001#	0.070■	0.012■	0.126■
	Median (min.-máx.)	(0-13)	(0-15)	(0-14)				
	Depression score (0-21)	4	3	3	0.210#	-	-	-
	Median (min.-máx.)	(0-15)	(0-14)	(0-13)				
Self-reported symptoms of CIPN	Present	2 (05.0%)	30 (75.0%)	30 (75.0%)	<0.001**	<.001†	<0.001†	1.000†
	Absent	38 (95.0%)	10 (25.0%)	10 (25.0%)				
Total score CINQ (0-190) Median (min.-max.)		3 (0-90)	14 (0-91)	18.5 (0-78)	<0.001	<0.001	<0.001	0.249
Score CINQ subscale for lower limbs (0-90) Median (min.-max.)		0 (0-45)	6 (0-48)	9.5 (0-41)	<0.001	0,001	<0.001	0.095
Score CINQ subscale for upper limbs Median (min.-max.)		0 (0-22)	3 (0-32)	2 (0-46)	<0.001	<0.001	<0.001	0.746
Score CINQ orofacial subscale (0-100) Median (min.-max.)		0 (0-40)	3 (0-34)	2 (0-42)	0.097	-	-	-

Captions: *Value p<0.29 (correction of Bonferroni), ** Test of Cochran, #Test of Friedman, ## Test of Kendall, †Test of McNemar, • Test of Wilcoxon.

conditions [6]. The results indicate also that the symptoms of CIPN usually initiate in the lower limbs, become more severe and persist for more time compared to the upper limb symptoms. The orofacial symptoms did not evolve significantly in the population evaluated.

It stands out in the findings of this work the non-determination of association among different characteristics of the protocol adopted, such as type of neurotoxic drug, interval between the cycles, dose and number of cycles, predictors frequently cited by different authors[4,7,14]. In the present study, the presence of CIPN resulted exclusively from the exposure of the individual to the neurotoxic drug, being this an imminent risk factor for the syndrome.

Among the sociodemographic characteristics, only education was predictor of self-reported symptoms of CIPN, since as poor the education level is, less chances has the patient of spontaneously reporting CIPN symptoms. The prevalence of patients enrolled in this study with mean education of eight years approaches the profile identified in studies that indicate the expansion of the access of the low education population to the oncology healthcare services and to the National Health System in Brazil, specially between 1998 and 2013[15,16]. In this context, the findings of this study reinforce the necessity of clearer and more objective interventions for early detection of CIPN symptoms in low education groups, thus preventing severe neural damages from the antineoplastic therapeutic.

Table 3. Possible sociodemographic and clinical predictors for development of CIPN according to CINQ and self-report in Time 2 (T2) and Time 3 (T3)

Parameters	QNIA (value p<0.05)		Self-report (value p<0.05)	
	T2 (n=40)	T3 (n=40)	T2 (n=40)	T3 (n=40)
Age	0.551*	0.225*	0.866*	0.724*
Gender	0.563#	0.172#	0.361#	0.068†
Education (in years)	0.843*	0.983*	0.033*	0.301*
Marital status	0.525#	0.884#	0.465†	0.325#
Tobacco use	0.326#	0.257#	0.890#	0.684#
Alcohol use	1.000#	0.635#	0.888#	0.534#
Type of neurotoxic antineoplastic	0.760#	0.712#	0.747#	0.633#
Antineoplastic Protocol	1.000#	0.539#	0.588#	0.588#
Number of doses	0.589*	0.712*	0.187*	0.860*
Number of cycles	0.627*	0.744*	0.724*	0.820*
Type of cancer	0.692#	0.630#	0.778#	0.778#
Staging	0.186#	0.437#	0.338#	1.000#
Metastasis	1.000#	1.000#	0.845†	0.845#
Comorbidities	1.000#	1.000†	0.251†	0.702†
Use of medication at home	0.023#	0.631†	0.908†	0.088†
Daily performance rate (PS ECOG 0-4)	0.437†	0.142#	0.336#	0.086†
Anxiety (Scale HAD)	0.228*	0.811*	1.000*	0.363 *
Depression (Scale HAD)	0.018*	0.083*	1.000*	0.988 *
Pain	0.061#	0.114#	0.271†	0.097
Intensity of the pain	0.449*	0.112*	0.469*	0.145*

Captions: *Test of Mann Whitney; #Exact test of Fisher; † Chi-square test .

Table 4. Grades of peripheral neuropathy detected by CINQ in patients exposed to antineoplastic treatment potentially neurotoxic in different times (n=40)

Parameters		T1 (n=40) n %		T2 (n=40) n %		T3 (n=40) n %		Value p# (<0.05) T1xT2xT3	Value p† (<0.029) T1 x T2	Value p† (<0.029) T1x T3	Value p† (<0.029) T2x T3
Grades of neuropathy								0.005	0.006*	0.013*	0.900*
	0	16	40.0	04	10.0	07	17.5				
	1	11	27.5	16	40.0	11	27.5				
	2	03	07.5	07	17.5	08	20.0				
	3	04	10.0	05	12.5	07	17.5				
	4	05	12.5	08	20.0	07	17.5				

Captions: *Value p <0.029 (correction of Bonferroni), #Test of Kendall, †Test of marginal homogeneity.

The strictness of the exclusion criteria of the population of this study may have circumvented the inclusion of individuals with neuropathic status from other origins that could impact the results, but, on the other hand, it restrained the follow up population to 55 individuals, among whose, 27% were considered losses. A recent meta-analysis that evaluated the possible clinical predictors for CIPN evidenced the lack of uniformity of the pain evaluation methods in addition to the sample size-related problems, which can hamper the comparison of this study with other epidemiological conducted formerly [17].

This was the first national, single-center study that evaluated CIPN in adults as opposed to international studies, usually multicenter.

CONCLUSION

Concluding, CIPN is a prevalent problem in patients exposed to taxanes and oxaliplatin either during or after the therapeutics with major incidence between six and nine weeks of antineoplastic treatment. The education of the patients treated in the ward unit of a public hospital in

Brazil showed to be predictive of self-reported symptoms of CIPN, as it was evidenced that as low the education, less chances for the patient to spontaneously report symptoms of CIPN, which may suggest the necessity of implementing specific instruments with objectives validated for such evaluation.

CONTRIBUTIONS

Delma Aurélia da Silva Simão contributed for the conception and planning of the study, data collection, analysis and interpretation, wording of the manuscript and final approval of the version published. Mery Natali Silva Abreu contributed for the conception and planning of the study, data analysis and interpretation, critical review and final approval of the version published. Rodrigo Santiago Gomez contributed for the conception and planning of the study, collection of data, critical review and final approval of the version published. Leonardo Dornas de Oliveira e Raissa Silva Souza contributed for the planning of the study, data collection, critical review and final approval of the published version. Tércia Moreira Ribeiro da Silva contributed for the interpretation of the data, critical review and final approval of the version published. Antônio Lúcio Teixeira contribute for the study planning, data analysis and interpretation, critical review and final approval of the version published.

DECLARATION OF CONFLICT OF INTERESTS

There are no conflict of interests to declare.

FUNDING SOURCES

"Fundação de Amparo à Pesquisa de Minas Gerais (Fapemig)".

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Recebido em 21/1/2019
Aprovado em 13/6/2019