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ORIGINAL ARTICLE

Occurrence of tinnitus and peripheral sensory neuropathy in women during chemotherapy treatment of breast cancer

Ocorrência de zumbido e neuropatia sensorial periférica em mulheres durante tratamento quimioterápico de câncer de mama

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KEYWORDS

Breast neoplasms
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ABSTRACT

Objective: To analyze the occurrence of tinnitus and peripheral sensory neuropathy in women during breast cancer chemotherapy.
Methods: This is a retrospective analytical study with a quantitative approach, performed in medical records of an oncology outpatient service between February 2014 and February 2015, using the toxicities scores of Common Terminology Criteria for Adverse Events (CTCAE).
Results: Considering 181 patients with breast cancer who met the inclusion criteria, 49.2% reported tinnitus at some point of the treatment, while 65.1% peripheral sensory neuropathy. In both conditions, the predominant severity score was grade 1, with frequencies of 23.8% and 33.1%, respectively. A significant, positive and weak correlation was observed between the severity of tinnitus and peripheral sensory neuropathy ($\rho = 0.325$ and $p = 0.001$), as well as very weak between the number of complete cycles of chemotherapy and tinnitus ($\rho = 0.195$ and $p = 0.009$) and neuropathy peripheral sensory ($\rho = 0.237$ and $p = 0.002$).
Conclusions: Tinnitus and peripheral sensory neuropathy were frequent toxicities during chemotherapy treatment of breast cancer, and both manifested with low severity/functional impact in most participants.

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PALAVRAS-CHAVE

Efeitos colaterais e reações adversas relacionados a medicamentos
Neoplasias da mama
Ototoxicidade
Tratamento farmacológico
Zumbido

RESUMO

Objetivo: Analisar a ocorrência de zumbido e neuropatia sensorial periférica em mulheres durante quimioterapia para câncer de mama.
Métodos: Trata-se de um estudo analítico e retrospectivo com abordagem quantitativa, realizado em prontuários de um serviço ambulatorial de oncologia entre fevereiro de 2014 e fevereiro de 2015, utilizando os escores de toxicidades do *Common Terminology Criteria for Adverse Events* (CTCAE).
Resultados: Das 181 pacientes com câncer de mama que atenderam aos critérios de inclusão, 49.2% relataram zumbido e 65.1% neuropatia sensorial periférica em algum momento do tratamento. Em ambas as condições, o escore de gravidade predominante foi grau 1, com frequências de 23.8% e 33.1%, respectivamente. Foi observada uma correlação significativa, positiva e fraca entre a severidade do zumbido e da neuropatia sensorial periférica (ρ = 0,325 e p = 0,001), bem como muito fraca entre a quantidade de ciclos completos de quimioterapia e zumbido (ρ = 0,195 e p = 0,009) e neuropatia sensorial periférica (ρ = 0,237 e p = 0,002).
Conclusões: Zumbido e neuropatia sensorial periférica foram toxicidades frequentes durante o tratamento quimioterápico do câncer de mama e ambos se manifestaram com baixa gravidade/impacto funcional na maioria das participantes.

INTRODUCTION

Among women, excluding non-melanoma skin cancer, breast cancer is the most common neoplasm worldwide and is also the leading cause of cancer death in women in developing countries and the second in developed countries. In 2020, there were an estimated 66.280 new breast cancer cases in Brazil, corresponding to approximately 29.7% of all cancers' incidence rate, excluding non-melanoma skin cancer. Also, breast cancer was responsible for 17,572 deaths or 16.4% of the total cancer deaths in the country[1,2].

Since cancer treatment is a systemic disease, chemotherapy treatment is indicated for almost all patients. Chemotherapeutic agents act at different stages of the cell cycle, interfering with the proliferation of tumor cells or causing damage that induces the apoptosis of potentially tumor cells, including healthy cells in the body[3]. The ability of tissue penetration gives a high degree of cytotoxicity to chemotherapeutic agents, justifying the systemic harmful effects of chemotherapy on the human body, including the peripheral sensorineural system (PNS) and auditory system[4,5].

Considering the effects on the sensorineural system, chemotherapy-induced peripheral neuropathy (CIPN) occurs in approximately 68% of patients undergoing chemotherapy for one month, 60% in three months, and 30% after six months. The most prevalent symptoms of CIPN are numbness, spontaneous burning, tingling, hyperalgesia, allodynia, and pain. In more severe cases, patients may lose the sensitivity of the affected nerve[5,6].

The chemotherapeutic agents with the highest rates of PNS involvement are platinum salts (cisplatin, carboplatin, and oxaliplatin), vinca alkaloids (vincristine, vinblastine, vinorelbine), bortezomib (a proteasome inhibitor), and taxanes (paclitaxel, docetaxel, cabazitaxel)[7]. The pathophysiology of CIPN, irrespective of the chemotherapeutic agent, can be characterized as a predominantly sensory axonal peripheral neuropathy that manifests as changes in sensitivity in the form of a "glove and a half", affecting primarily longer axons and, therefore, more distal to the central nervous system (CNS)[6].

CIPN can have several impacts on the quality of life of patients with cancer, beyond signifying a challenge to cancer professionals regarding its diagnosis and treatment, mainly when there is a previous involvement of the PNS[8], such as diabetes mellitus, which contributes to the development of CIPN and worsening neurological sequelae that persist after the end of anticancer therapy[6]. Besides, clinical and sociodemographic variables can influence the manifestation of CIPN, including age, diagnosis time, race, and associated drugs[9,10]. Several studies have been conducted to understand the genetic, functional, and pharmacological aspects of CIPN in patients[11-14].

Considering the systemic toxicities of chemotherapeutic agents beyond CIPN, the literature indicates that several drugs are associated with reports of patients who developed hearing loss after antineoplastic treatment[15,16]. The pathophysiological bases for ototoxicity or neurotoxicity are not yet fully understood, although there is evidence that the formation of reactive oxygen and nitric oxide species can cause lipid peroxidation and induce apoptosis of hair cells and vascular stria by mechanisms that involve the p53 protein and caspases[16-18]. Similarly, DNA damage, ion channel blocking[16], and other mechanisms are observed and can directly affect type 1 neurons in the spiral ganglion, resulting in apoptosis of the myelin sheath[17].

However, there is a significant limitation when verifying each chemotherapeutic agent's real ototoxic effect since the treatment protocols often include their combination with supportive drugs, such as aminoglycosides and loop diuretics, which have ototoxic potential[4]. Therefore, even if a single chemotherapeutic agent does not have a significant ototoxic effect, there may be synergism between drugs, which in the long term may trigger damage to the auditory system. This outcome may depend on the dosage, time of exposure, patient age, and genetic susceptibility[19].

The signs and symptoms of ototoxicity include hearing loss, tinnitus, changes in balance, and vertigo[20,21]. Tinnitus is the most common symptom,

which can signal that the inner ear or vestibulocochlear nerve structures are affected by treatment. Hearing loss and tinnitus are usually sensorineural, bilateral, and of symmetrical degree, manifesting alone or together[15,21-23]. The literature reports a high degree of ototoxicity to platinum chemotherapy group[4,17,19], followed by vincristine sulfate, doxorubicin hydrochloride, and epirubicin[19]. Cyclophosphamide's potential to affect the auditory system has been reported, both in the isolated form at low dosages[18] and along with other drugs[23].

Other chemotherapeutics, such as 5-fluorouracil (5FU) and taxanes, have shown a low degree of ototoxicity[24-27], and evidence of hearing disorders after treatment with taxanes is always along with other antineoplastic drugs[28,29]. However, experimental studies showed that systemic treatment with 5FU leads to late destruction of the myelin sheath in the central nervous system[30] and treatment with paclitaxel in P3 mice treated with different concentrations (10, 20 and 30 μM) by 48 h showed a degenerative process and a decrease in the number of cells in the neurons of the spiral ganglion resulting from caspase-mediated apoptosis[31], indicating a neurotoxic effect of these drugs in the auditory pathway.

Regarding radiotherapy, although most studies indicate a strong relationship of ototoxicity to head and neck tumors[32-34], simultaneous administration to chemotherapeutic agents can potentiate the effects of cell apoptosis in the cochlea[35]. Previous investigations that have verified the effect of treatment with chemotherapy and radiotherapy on breast, cervical and uterine neoplasms in the auditory system report the presence of hearing loss in both treatments[23]. Therefore, this study analyzed the occurrence of tinnitus and peripheral sensory neuropathy in women during chemotherapy for breast cancer.

METHODS

This is a retrospective analytical study with a quantitative approach, conducted from the medical records of an oncology outpatient service located in northeastern Brazil. The service evaluated was chosen due to the availability of data access and the number of patients undergoing chemotherapy treatment before data collection after nonsystematic observations. In this service, 560 medical records were available, being previously tracked and evaluated to identify and include all patients who met the proposed inclusion criteria (non-probabilistic sample).

Breast cancer patients over 18 years-old, with cyto or histopathological diagnosis, with a minimum diagnosis time of six months (excluding women who recently started cancer treatment) and undergoing chemotherapy between February 2014 and February 2015 (data collection period) were selected. As the oncology service team manually filled out the medical records during treatment, clarity, legibility, and complete filling of all variables being studied on the medical records were adopted as secondary inclusion criteria. The inadequacies of patients and medical records led to exclusion.

Informed Consent Form was waived due to the documental nature of the data collection, which did not directly involve the participants. Data acquisition on medical records was performed continuously over one year, according to the oncology service's availability to receive the researchers and give access to the medical records. Each patient included in the sample had his medical record in a single moment, without longitudinal monitoring of the data collected.

The main variables of this study, tinnitus and peripheral sensory neuropathy, were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) in its fourth version (v4.03) published by the National Cancer Institute in 2009. Conceptually, we also adopted the CTCAE definition of tinnitus, described as a disorder characterized by noise in the ears, such as ringing, buzzing, roaring, or clicking. Likewise, PNS was conceptually defined as a disorder characterized by inflammation or degeneration of peripheral sensory nerves[36].

The oncology service professionals performed the identification and registration of each toxicity and variable studied in the medical records evaluated, later analyzed in this study for our researchers. Two oncology researchers conducted data collection, assigning the CTCAE classification to the toxicities and variables studied according to the manifestations described in the medical records. The data collected by both researchers were crossed to minimize divergences and reduce the risk of bias.

The CTCAE classification for tinnitus adopted considers the severity of symptoms and the need for intervention according to the limitation of activities of daily living (ADL), established in grade 1 (mild symptoms; intervention not indicated), grade 2 (moderate symptoms; limiting instrumental ADLs) and grade 3 (severe symptoms; limiting self-care ADLs). We assign grade 0 to patients who did not manifest tinnitus (for statistical purposes), whereas grades 4 and 5 do not exist for this adverse event according to the CTCAE classification[36].

The CTCAE classification for peripheral sensory neuropathy also considers the same criteria involving severity and the need for intervention according to the impact on ADLs, established in grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia), grade 2 (moderate symptoms; limiting instrumental ADLs), grade 3 (severe symptoms; limiting self-care ADL), grade 4 (risk of life; an indication of urgent intervention) and grade 5 (death). We also assign grade 0 to patients who did not manifest this disorder[36].

The sociodemographic variables collected from medical records, previously registered by the service studied, were age (in years-old), state (all Brazilian federal units and the Federal District), housing area (urban or rural), race/ethnicity (white, yellow, and black/mixed), religion (catholic, evangelical, spiritist or other), partner status (with or without a partner), number of children, schooling (without schooling, elementary school, high school or higher education), occupation, occupational situation (with or without a job) and family income (in minimum wages).

According to the most prevalent data or status, these variables were evaluated with their respective occurrences and stratified into two groups for later

comparison. In contrast, an extensive description of each subgroup does not contribute significantly to the objective, while verifying whether the most prevalent subgroup has an association with the variables can expand the state of the art regarding the occurrence of tinnitus and peripheral sensory neuropathy.

The clinical variables collected from the medical records were diagnosis of breast cancer, histopathological subtype, time of diagnosis (less than six months, between six and 12, and more than 12 months), stage of breast cancer (I, II, III, or IV) and cancer treatment, including surgical procedures (only biopsy, lumpectomy (partial mastectomy) or radical mastectomy), radiotherapy (less or equal than 20 sessions or more than 20) and chemotherapy protocols. Chemotherapeutic agents and complete cycles of chemotherapy (CCC) were also counted and evaluated in the sample.

Also, the presence of comorbidities described in the medical records of each patient was assessed. However, we included in the statistical analyses only comorbidities with ten or more patients (hearing loss, systemic arterial hypertension, diabetes mellitus, arthritis or osteoarthritis, and osteoporosis), but CTCAE accessed only hearing loss symptomatic/functional severity. Moreover, the main signs and symptoms associated with cancer treatment were also included: pain, fatigue, nausea and vomiting, anxiety, and depressive symptoms. These variables were evaluated concerning the occurrence of tinnitus and peripheral sensory neuropathy.

The collected data were tabulated in Google Sheets™ spreadsheets, using numeric codes to designate the presence or absence of variables and scoring when necessary. The statistical procedures developed adopted 95% significance, with descriptive operations to verify and analyze the frequencies (absolute and relative) and inferential/analytic operations to verify the differences between variables. The software chosen to perform these operations was PAST (version 4.0, Oslo, Norway, 1999).

Lilliefors test (L) was used to verify the normality of the data sets, while comparisons of the contingency tables were performed using Pearson's chi-square test (X^2) and Fisher's exact test (†; when the expected values in the contingency table were less than five), followed by the odds ratio (OR) with a 95% confidence interval (95% CI) for significant values (p-value < 0.05). The comparison between means in non-parametric sets was performed using the Kruskal-Wallis (H) test with the Dunn-Bonferroni post hoc test, while non-parametric correlations were operated using the Spearman correlation test (ρ coefficient).

The Research Ethics Committee of the Ribeirão Preto School of Nursing (University of São Paulo) approved all the data collection procedures described above, under number 531.146 (CAAE: 20834513.0.0000.5393), guided by resolution 466/12 for human beings from the National Council of Health Institute of Brazil, maintaining the reliability and confidentiality of all data collected and presented.

RESULTS

After the medical records tracking and analysis, 181 women met the proposed inclusion criteria and were included in these results (N = 181), with a mean age of 52.5 ± 10.9 years, with a minimum of 26 and a maximum of 81 years. Considering sociodemographic variables, most of them were from Sergipe state (143/79%), residents of the urban housing area (148/81.8%), black or mixed (125/69.1%), Catholic (125/69.1%), married (86/47.5%), with a partner (102/56.4%) and two children (115/63.5%). Besides, most of them did not complete higher education (152/84%), were jobless (78/43.1%) and had a family income less than or equal to three minimum wages (156/86.2%). The main occupations identified were housewive (44/24.3%), rural worker (39/21.5%), pedagog or educator or teacher (17/9.4%), administrative assistant (11/6.1%), housemaid (10/5.5%), and general services assistant (9/5%).

Considering clinical variables, most of the sample was diagnosed with breast cancer more than a year ago (114/63%), and the most frequent histopathological subtype was invasive ductal carcinoma in at least one breast (154/85.1%). At the point of data collection, 14 patients were in stage IV (7.7%), 83 in stage III (45.9%), 66 in stage II (36.5%), and 18 in stage I (9.9%). Moreover, most of them underwent radical mastectomy (122/67.4%), and only 56 (30.9%) underwent more than 20 radiotherapy sessions. Lastly, 102 (56.4%) practiced physical activity before the diagnosis of breast cancer. Table 1 shows the general occurrence of tinnitus and peripheral sensory neuropathy in the sample, while Table 2 compares these toxicities to the sample's main sociodemographic and clinical characteristics.

Women with a diagnostic time less than 12 months were less likely to present tinnitus (OR: 0.46; 95% CI: 0.25 — 0.86) and peripheral sensory neuropathy (OR: 0.45; 95% CI: 0.24 — 0.85). Likewise, women who underwent less than 20 radiotherapy sessions or never underwent this therapeutic modality were less likely to present tinnitus (OR: 0.51; 95% CI: 0.27 — 0.97) and peripheral sensory neuropathy (OR: 0.40; 95% CI: 0.19 — 0.93).

Table 1 — Occurrence of tinnitus and peripheral sensory neuropathy in women undergoing breast cancer chemotherapy, according to the Common Terminology Criteria for Adverse Events classification (N = 181).

Classification	Tinnitus	Peripheral sensory neuropathy
	n (%)	n (%)
Grade 0	92 (50.8)	63 (34.8)
Grade 1	43 (23.8)	60 (33.2)
Grade 2	36 (19.9)	56 (30.9)
Grade 3	10 (5.5)	2 (1.1)
Grade 4	N/A	0 (0)
Grade 5	N/A	0 (0)
Total	181(100)	181(100)

N/A: not applicable.

Table 2 — Occurrence of tinnitus and peripheral sensory neuropathy in women undergoing breast cancer chemotherapy according to the main sociodemographic and clinical characteristics.

Variables	Tinnitus			Peripheral sensory neuropathy		
	With n / %	Without n / %	*P*-value (X^2)	With n / %	Without n / %	*P*-value (X^2)
Age						
≤ 49 years	42/23.2	32/17.7	0.089	51/28.2	23/12.7	0.381
> 49 years	47/26	60/33.1		67/37	40/22.1	
Race						
Black or mixed	63/34.8	62/34.3	0.621	81/44.8	44/24.3	0.868
Others	26/14.4	30/16.6		37/20.4	19/10.5	
Partner						
With	47/26	55/30.4	0.344	64/35.4	38/21	0.432
Without	42/23.2	37/20.4		54/29.8	25/13.8	
Occupation						
With job	48/26.5	55/30.4	0.426	63/34.8	40/22.1	0.191
Without job	41/22.7	37/20.4		55/30.4	23/12.7	
Schooling						
With higher education	14/7.7	15/8.3	0.916	19/10.5	10/5.5	0.968
Without higher education	75/41.4	77/42.5		99/54.7	53/29.3	
Family income						
≤ 3 minimum wages	78/43.1	78/43.1	0.577	103/56.9	53/29.3	0.557
> 3 minimum wages	11/6.1	14/7.7		15/8.3	10/5.5	
Physical activity						
Yes	51/28.2	51/28.2	0.799	72/39.8	30/16.6	0.083
No	38/21	41/22.7		46/25.4	33/18.2	
Housing area						
Urban	71/39.2	77/42.5	0.494	96/53	52/28.7	0.844
Rural	18/9.9	15/8.3		22/12.2	11/6.1	
Religion						
Catholic	62/34.3	63/34.8	0.863	83/45.9	42/23.2	0.610
Others	27/14.9	29/16		35/19.3	21/11.6	
Diagnosis time						
≥ 6 and ≤ 12 months	25/13.8	42/23.2	0.014*	36/19.9	31/17.1	0.013*
> 12 months	64/35.4	50/27.6		82/45.3	32/17.7	
Stage						
I or II	38/21	46/25.4	0.324	59/32.6	25/13.8	0.184
III or IV	51/28.2	46/25.4		59/32.6	38/21	
Radiotherapy						
≤ 20 sessions	55/30.4	70/38.7	0.037*	74/40.9	51/28.2	0.011*
> 20 sessions	34/18.8	22/12.2		44/24.3	12/6.6	
Surgical procedures						
Radical mastectomy	65/35.9	57/31.5	0.111	82/45.3	40/22.1	0.412
Others	24/13.3	35/19.3		36/19.9	23/12.7	

X^2: Pearson's chi-square test; *: *p*-value < 0.05.

Considering the chemotherapy protocols, most of the patients underwent a combination of doxorubicin and cyclophosphamide (102/56.4%), 21 (20.6%) without subsequent taxane (AC), and 81 (79.4%) with a subsequent taxane (AC-T), either paclitaxel (79/97.5%) or docetaxel (2/2.5%). Also, 47 patients were exposed to multiprotocol (26%), 13 patients to protocol involving 5FU (7.2%), and 19 patients to other protocols (less than ten), being grouped in a unique protocol (10.5%). Table 3 shows the occurrence of tinnitus and peripheral sensory neuropathy according to the chemotherapy protocols experienced.

Table 3 — Occurrence of tinnitus and peripheral sensory neuropathy in women undergoing breast cancer chemotherapy according to chemotherapy protocol.

Chemotherapy protocols	Tinnitus			Peripheral sensory neuropathy		
	With n / %	Without n / %	*P*-value (X^2)	With n / %	Without n / %	*P*-value (X^2)
AC protocol	9/5	12/6.6	0.538	9/5	12/6.6	0.028*†
AC-T protocol	42/23.2	39/21.5	0.516	57/31.5	24/13.3	0.188
Multiprotocol	25/13.8	22/12.2	0.521	35/19.3	12/6.6	0.120
5FU protocols	2/1.1	11/6.1	0.018*†	5/2.8	8/4.4	0.065†
Others	11/6.1	8/4.4	0.629†	12/6.6	7/3.9	0.799†
AC *versus* AC-T	-	-	0.462	-	-	0.023*†
AC *versus* Multiprotocol	-	-	0.431	-	-	0.015*†
AC *versus* 5FU	-	-	0.139†	-	-	1†
AC *versus* Others	-	-	0.527†	-	-	0.224†
AC-T *versus* Multiprotocol	-	-	0.883	-	-	0.619
AC-T *versus* 5FU	-	-	0.017*†	-	-	0.031*†
AC-T *versus* Others	-	-	0.799†	-	-	0.586†
Multiprotocol *versus* 5FU	-	-	0.025*†	-	-	0.021*†
Multiprotocol *versus* Others	-	-	0.789†	-	-	0.381†
5FU *versus* Others	-	-	0.027*†	-	-	0.280†
Complete cycles of chemotherapy						
≥ 10 cycles	49/27.1	40/22.1	0.119	70/38.8	19/10.5	0.000*†
< 10 cycles	40/22.1	52/28.7		48/26.5	44/24.3	

X^2: Pearson's chi-square test; *: *p*-value < 0,05. †: Fisher's exact test.

Women exposed to 5FU protocols were less likely to present tinnitus compared to the rest of the sample (OR: 0.17; 95% CI: 0.04 — 0.79). Women exposed to the AC protocol were less likely to present peripheral sensory neuropathy (OR: 0.35; 95% CI: 0.14 — 0.89). Also, women exposed to the AC-T protocol were more likely to present tinnitus than women exposed to 5FU protocols (OR: 5.92; 95% CI: 1.23 — 28.43), women exposed to multiprotocol were more likely to present tinnitus than women exposed to 5FU protocols (OR: 6.25; 95% CI: 1.25 — 31.33), as well as women exposed to 5FU protocols were less likely to present tinnitus than women exposed to other protocols (OR: 0.13; 95% CI: 0.02 — 0.77).

In this same perspective, women exposed to the AC protocol were less likely to present peripheral sensory neuropathy than those exposed to AC-T (OR: 0.36; 95% CI: 0.12 — 0.85) or multiprotocol protocols (OR: 0.26; 95% CI: 0.09 — 0.76). Women exposed to the AC-T protocol (OR: 3.80; 95% CI: 1.13 — 12.81) and multiprotocol (OR: 4.66; 95% CI: 1.28 —17.05) were more likely to present peripheral sensory neuropathy than women exposed to 5FU protocols. Lastly, women exposed to ten or more CCC were more likely to present peripheral sensory neuropathy than women exposed to less than ten CCC (OR: 3.07; 95% CI: 1.59 — 5.93). One thousand nine hundred and twenty CCC were identified in women (average 10.6 ± 5.9 per individual); 75 CCC in the AC protocol (39%; avg. 3.6 ± 0.7); 1,041 CCC (54.2%; avg. 12.9 ± 4.2) in the AC-T protocol; 626 CCC (32.6%; avg. 13.3 ± 6.5) in multiprotocol; 51 CCC (2.7%; avg. 3.9 ± 2.1) in 5FU protocols; and 127 CCC (6.6%; avg. 6.7 ± 3.4) in other protocols. Spearman's correlation coefficient (ρ) verified whether the severity of tinnitus and peripheral neuropathy was related to the number of CCC experienced by patients and whether the severity of these toxicities was associated with each other. Significant, positive, and weak correlations were observed between the occurrence of tinnitus and peripheral sensory neuropathy (ρ = 0.325 and $p = 0.001$) and very weak between the number of CCC and tinnitus (ρ = 0.195 and $p = 0.009$) and the number of CCC and neuropathy peripheral sensory (ρ = 0.237 and $p = 0.002$).

The Kruskal-Wallis *H* test verified whether the average number of CCC varied between chemotherapy protocols, indicating that they differ significantly from each other ($p < 0.001$). The Dunn-Bonferroni post hoc test showed that the AC-T and multiprotocol groups had a higher CCC than the others ($p < 0.05$) and did not differ from each other ($p > 0.05$). Also, no differences were observed between the mean CCC of the AC and 5FU groups ($p > 0.05$) and 5FU and other protocols ($p > 0.05$), while the AC group differed from the group with other protocols ($p < 0.05$). Table 4 shows the occurrence of tinnitus and peripheral sensory neuropathy according to the identified comorbidities and other signs and symptoms associated with breast cancer treatment.

Women with tinnitus were more likely to present hearing loss (OR: 7.01; 95% CI: 1.52 — 32.31), while women with peripheral sensory neuropathy were more likely to present arthritis or arthrosis (OR: 3.19; 95% CI: 1.05 — 9.76) and osteoporosis (OR: 4.33; 95% CI: 1.24 — 15.14). Besides, Spearman's correlation test identified

that the number of simultaneous comorbidities (0 to 5) was not associated with the severity of tinnitus (p = 0.084) or peripheral sensory neuropathy (p = 0.058). Lastly, the symptomatic/functional severity of hearing loss accessed by CTCAE was not correlated with the severity of tinnitus by Spearman's correlation (p = 0.198).

Moreover, women with tinnitus were more likely to present anxiety symptoms (OR: 2.54; 95% CI: 1.33 — 4.85) and depressive symptoms (OR: 2.79; 95% CI: 1.53 — 5.12), while women with peripheral sensory neuropathy were more likely to present pain (OR: 3.31; 95% CI: 1.43 — 7.68) and depressive symptoms (OR: 1.94; 95% CI: 1.046 — 3.613).Spearman's correlation test identified that the number of simultaneous comorbidities (0 to 5) showed a significant, positive, and very weak correlation with tinnitus (ρ = 0.258 and p = 0.004) and peripheral sensory neuropathy severities (ρ = 0.153 and p = 0.034).

Table 4 — Occurrence of tinnitus and peripheral sensory neuropathy according to comorbidities and other signs and symptoms of breast cancer treatment.

Variables	Tinnitus			Peripheral sensory neuropathy		
	With n / %	Without n / %	*P*-value (X^2)	With n / %	Without n / %	*P*-value (X^2)
Comorbidities						
Hearing loss	12/6.6	2/1.1	0.004*†	10/5.5	4/2.2	0.773†
Systemic arterial hypertension	40/22.1	34/18.8	0.274	47/26	27/14.9	0.693
Diabetes mellitus	15/8.3	8/4.4	0.099	16/8.8	7/3.9	0.815†
Arthritis/arthrosis	11/6.1	14/7.7	0.577	21/11.6	4/2.2	0.041*†
Osteoporosis	13/7.2	11/6.1	0.599	21/11.6	3/1.7	0.019*†
Signs or symptoms						
Pain	78/43.1	76/42	0.342	107/59.1	47/26	0.007*†
Fatigue	67/37	60/33.1	0.139	87/48.1	40/22.1	0.151
Nausea and vomiting	40/22.1	31/17.1	0.121	45/24.9	26/14.4	0.680
Anxiety symptoms	69/38.1	53/29.3	0.004*	82/45.3	40/22.1	0.412
Depressive symptoms	59/32.6	38/21	0.000*	70/38.8	27/14.9	0.034*

X^2: Pearson's chi-square test; *: p-value < 0,05. †: Fisher's exact test.

DISCUSSION

Before the interpretation and application of these results, the limitations of this investigation must be highlighted. First, professional calibrations to record toxicities were not performed, implying a possible bias in data collection, although medical records filled inappropriately have been excluded. Second, our results were collected in a single oncology service, without probabilistic sampling, as well as an accurate temporal analysis was not performed between the manifestation of toxicities during treatment. However, the time factor was partially circumvented when patients at the beginning of treatment were excluded.

Auditory symptoms and CIPN are frequently reported by individuals undergoing cancer treatment. Sensory-type CIPNs are most often be accompanied by motor and autonomic changes. Auditory symptoms can manifest in different ways, from tinnitus, which can indicate aggression to the auditory system, signifying, in most cases, the precursor of a sensory or neural hearing loss. Although chemotherapeutic agents have different effects on target cells, the occurrence of CIPN and hearing symptoms by these agents is related to the class of drugs and the dose administered (punctual or cumulative), considering the potential of chemotherapeutic agents to cause damage to the cochlea and peripheral nervous system structures[5,6,20].

However, the occurrence and severity of CIPN are dose-dependent and increase proportionately[6]. Our results contemplate and corroborate this statement when we assess the number of CCC associated with the occurrence and severity of tinnitus and peripheral sensory neuropathy by CTCAE score, showing that in both conditions the symptoms can manifest more severely as patients are exposed to a more significant number of CCC (more than ten) during cancer treatment.

Also, the onset of peripheral neuropathies can often occur weeks or months after the start of chemotherapy. Despite this, the acute occurrence is also reported, especially when the chemotherapeutic agents are oxaliplatin or paclitaxel[5,6]. Our results demonstrate that women with less than twelve months of treatment may have a lower occurrence of peripheral sensory neuropathy and tinnitus, reinforcing previously evidence reported of tinnitus as a commonly late manifestation after the start of chemotherapy[37].

Other factors such as advanced age and diabetes mellitus can contribute to the appearance of auditory symptoms and peripheral neuropathies[8,9,38]. Besides, African American descent and low income are risk factors related to the development of peripheral neuropathies[8,9]. However, none of these were associated with the occurrence of these conditions in our results.

Alternatively, the presence of anxiety and depression were associated with the occurrence of tinnitus. Furthermore, a higher cumulative dose of chemotherapy, the presence of comorbidities, and depression were associated with the occurrence of CIPN, an outcome described by other studies concerning CIPN[8,9].

Moreover, while our findings suggest that the presence of arthritis or osteoarthritis was associated with a higher occurrence of CIPN, patients with autoimmune diseases from another investigation were less likely to develop this condition. Nevertheless, similar to our findings, investigation reported that systemic arterial hypertension was not associated with CIPN[10]. Given the significance of CIPN, understanding these risk factors becomes essential for developing prevention and treatment strategies[9].

Considering our findings and the available literature about chemotherapeutic agents related to the occurrence of CIPN, taxane agents (paclitaxel and docetaxel) have frequently been associated. The incidence of this condition in patients exposed to taxanes can vary from 11% to 83%, while in patients with breast cancer it can reach up to 70.8%[12]. The exact mechanisms by which taxane agents trigger neurotoxicity are still poorly understood. Nevertheless, as they act in connection with beta-tubulin in microtubules and lead to apoptosis of target cells, disrupting the function of microtubules in axons, leading to the emergence of neuropathies[11].

Chemotherapy with paclitaxel or docetaxel in breast cancer is frequent and is indicated in the early phases or with metastatic tumors, showing the importance of these agents in this type of cancer[11,12]. In our findings, the presence of a taxane after the AC protocol (AC-T protocol) was associated with a more significant peripheral sensory neuropathy occurrence when these two protocols were compared. In contrast, the absence of the taxane (AC protocol) was associated with a lower incidence than the multiprotocol group. Peripheral neuropathies associated with taxanes can manifest as bilateral paresthesias in the form of tingling, numbness, and pain associated with the burning sensation[12]. In contrast, those caused specifically by paclitaxel (predominant taxane agent in our sample) is associated with reduced quality of life and functional capacity of cancer survivors[11], and restriction of daily activities[12].

Another investigation related to taxane chemotherapeutic agents in patients older than 65 years indicated that paclitaxel was associated with a greater chance of manifesting neuropathies than docetaxel[10]. Moreover, another investigation involving docetaxel indicated that the AC-T protocol might be associated with more severe peripheral neuropathies in the long term[13].

Although we have not found any other studies involving multiprotocol in the statistical analysis, the combination of antineoplastic agents in different protocols, in addition to the high dose of chemotherapeutic agents, may justify a greater risk of peripheral sensory neuropathy compared to protocols without taxanes or involving 5FU (which did not involve taxanes). However, the number of protocols with taxanes included in the multiprotocol has not been systematically investigated, denoting a critical limitation in interpreting the results. Finally, while the literature reports evidence of CIPN related to platinum, especially oxaliplatin[14], the use of this chemotherapeutic agent was small and included in the multiprotocol or other protocols.

Considering our findings related to the occurrence of auditory symptoms and chemotherapy, most women underwent doxorubicin and cyclophosphamide combination (AC protocol; 102/56.4%), being 81 (79.4%) with subsequent administration of a taxane agent (AC-T protocol). Although taxanes have a low degree of toxicity[24-27], our findings demonstrated that patients who received sequential administration of taxanes and multiprotocol were more likely to develop tinnitus than treatment with 5FU, which proved to be the least harmful to the auditory system.

When taxanes were administered, 97.5% of women received paclitaxel as medication, and 2.5% received docetaxel. Generally, taxanes demonstrated a positive effect on the occurrence of tinnitus, demonstrating ototoxicity or neurotoxic effect related to a probable synergism between the medications used in this protocol, corroborating with the literature that also suggests harmful effects on hearing only when associated with other treatments[28,29].

The effect of tinnitus on multiprotocol therapy may be related to the use of platinum, which has high ototoxicity and neurotoxic effect[4,17,19,39]. However, although 5FU has not demonstrated an effect on the occurrence of tinnitus, an influence on the occurrence of hearing disorders cannot be ruled out late since, in addition to its ototoxic effect[19], the literature also shows late destruction of the myelin sheath in the central nervous system in animals that received systemic treatment[28,29].

Considering the relationship between peripheral sensory neuropathy and tinnitus, there is evidence that neurotoxic chemotherapy frequently causes both conditions in patients with cancer. The literature reports that stress, associated with cancer treatment, may be one of the predisposing factors for the manifestation of both conditions, although ototoxicity is less studied than CIPN[40]. In contrast, our results demonstrate a correlation between both conditions in the sample studied, suggesting that the severity of tinnitus and CIPN increases concomitantly in these patients. Thus, in our opinion, an effect on cranial pairs cannot be ruled out since tinnitus has been investigated as an effect associated with hearing, and this symptom is usually also present in hearing alterations resulting from retrocochlear damage, as auditory neuropathy.

The correlation between tinnitus and peripheral neuropathy in this study may indicate that the treatment of breast cancer has also injured the auditory nerve since the chemotherapeutic agent paclitaxel, which has shown an association with tinnitus, also causes changes in the portion of the spiral ganglion and the auditory nerve in experimental studies in animals[31]. However, given the cross-sectional nature of our findings, it is only possible to establish associations between the variables, which still lack prospective and longitudinal approaches to establish a consistent cause-effect relationship.

Other investigations regarding chemotherapy toxicity that involved neuropathies, tinnitus, and hearing loss simultaneously found that 14.1% of the patients manifested the three conditions, most of whom were older with a more significant number of comorbidities, in addition to greater functional impairment, lower quality of life and higher levels of depressive symptoms[41]. Likewise, corroborating with our findings, there is evidence of an association between depression and the manifestation of peripheral neuropathy in patients with cancer, so that psychological suffering influences its severity[42].

Concerning the radiotherapy treatment, our findings showed a significant association with the occurrence of tinnitus, corroborating with Oliveira et al. (2016), who also found toxic effects on the hearing of women who received the same treatment for ovarian, cervical, and uterine cancer[23]. Breast cancer treatment showed tinnitus (49.2%) as the main symptom of sequelae of the auditory system, with few occurrences of hearing loss (7.7%). However, when present, it demonstrated a significant association with tinnitus, suggesting that this may have been the first sign of alteration in the auditory system, serving as a potential precursor for both cochlear and retrocochlear hearing loss due to auditory neuropathy.

Thus, women undergoing treatment must be accompanied by clinical examinations to monitor the auditory system, both in its peripheral and central parts. Furthermore, we suggest prospective studies monitoring the cochlear amplifier through otoacoustic emissions and the auditory nerve, through electrophysiological procedures such as short-latency auditory evoked potentials, to guide the understanding of the ototoxic or neurotoxic effect of these treatments.

CONCLUSION

Tinnitus and peripheral sensory neuropathy in women with breast cancer were considered significant for both conditions. No associations were identified between these conditions and sociodemographic factors. Alternatively, the associated clinical data suggest that both conditions can manifest as late toxicities and are directly dependent on the chemotherapeutic agents administered. However, limitations do not allow to establish with certainty a cause-and-effect relationship. The relationship between tinnitus and peripheral sensory neuropathy in patients with breast cancer still needs to be unraveled, while hearing loss, radiation therapy, and depressive symptoms should be better explored in new prospective studies to expand these associations.

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