DOI: 10.4274/forbes.galenos.2024.17363
Forbes J Med 2024;5(2):108-15

Original Article / Orijinal Araştırma

View of Perceived Symptoms Associated with Chemotherapy-induced Peripheral Neuropathy in Patients with Breast Cancer: A Cross-sectional Study

Meme Kanseri Hastalarında Kemoterapiye Bağlı Periferik Nöropati ile İlişkili Algılanan Semptomlara Bir Bakış: Kesitsel Bir Çalışma

Alper TUĞRAL[1], Murat AKYOL[2]

[1]İzmir Bakırçay University Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, İzmir, Türkiye
[2]İzmir Bakırçay University Faculty of Medicine, Department of Medical Oncology, İzmir, Türkiye

Cite as: Tuğral A, Akyol M. View of Perceived Symptoms Associated with Chemotherapy-induced Peripheral Neuropathy in Patients with Breast Cancer: A Cross-sectional Study. Forbes J Med. 2024;5(2):108-15

ABSTRACT

Objective: This cross-sectional study aimed to assess the perceived chemotherapy-induced peripheral neuropathy (CIPN) symptoms in patients with breast cancer who received taxane-based chemotherapy.

Methods: A total of 74 patients with breast cancer who underwent taxane-based chemotherapy were screened and invited to participate in this study. Perceived symptoms of CIPN were assessed via the European Organization for Research and Treatment of Cancer-Chemotherapy Induced Peripheral Neuropathy (EORTC-CIPN20) questionnaire after the completion of systemic treatment within a month and a half. Sensory, motor, and autonomic subscale scores were calculated and analyzed for each patient.

Results: This study included 52 patients with breast cancer. The mean total exposure dose was 2093.92±1266.22 mg. The rates of adjuvant and neoadjuvant chemotherapy were similar (n=25 vs. n=27). Most patients underwent breast-conserving surgery (65.4%). The types of chemotherapy regimen were combined anthracycline and paclitaxel (n=28), docetaxel (n=14), and combined anthracycline, pertuzumab, trastuzumab, and docetaxel (n=10). Patients who underwent modified radical mastectomy had significantly higher scores in the perceived symptoms of CIPN motor function subscale of EORTC-CIPN20 (z=-2.838, p=0.005). The autonomic subscale of EORTC-CIPN20 was significantly correlated with age (r=-0.373, p=0.006) and with the total exposure dose of chemotherapy (r=0.295, p=0.034).

Conclusion: The type of surgery, specifically MRM, which has been emphasized as a contributing factor to CIPN, should be taken into consideration for further potential deterioration. By this means, it is reasonable to state that not only ongoing monitoring of the CIPN is of utmost importance, but also potential contributors to the management of the CIPN are of great importance.

Keywords: Breast cancer, chemotherapy, taxane, peripheral neuropathy

ÖZ

Amaç: Bu kesitsel çalışmanın amacı, taksan bazlı kemoterapi uygulanan meme kanserli hastalarda algılanan kemoterapi ilişkili periferik nöropati (CIPN) semptomlarını değerlendirmektir.

Yöntem: Taksan bazlı kemoterapi uygulanan toplam 74 meme kanseri hastası tarandı ve bu çalışmaya katılmaya davet edildi. Algılanan CIPN semptomları, sistemik tedavilerinin bir buçuk ay içinde tamamlanmasının ardından Avrupa Kanser Araştırma ve Tedavi Örgütü-Kemoterapiye Bağlı Periferik Nöropati (EORTC-CIPN20) anketi aracılığıyla değerlendirildi. Her hasta için duyusal, motor ve otonom alt ölçek puanları hesaplandı ve analiz edildi.

Bulgular: Bu çalışma 52 meme kanseri hastası ile tamamlandı. Ortalama maruz kalınan toplam doz 2093,92±1266,22 mg idi. Adjuvan ve neoadjuvan kemoterapi oranı benzerdi (n=25 vs. n=27). Hastaların çoğu meme koruyucu cerrahi geçirmiş idi (%65,4). Kemoterapi rejimi sırasıyla kombine antrasiklin ve

Received/Geliş: 20.03.2024
Accepted/Kabul: 20.05.2024

Corresponding Author/ Sorumlu Yazar:
Alper TUĞRAL PhD,
İzmir Bakırçay University Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, İzmir, Türkiye
Phone: +90 507 442 14 20
✉ alper.tugral@bakircay.edu.tr
ORCID: 0000-0002-8017-2384

Clinical Trials Registration: **NCT06352567**

paklitaksel (n=28), dosetaksel (n=14) ve kombine antrasiklin, pertuzumab, trastuzumab ve dosetaksel (n=10) idi. Modifiye radikal mastektomi (MRM) uygulanan hastalar, EORTC-CIPN20'nin motor fonksiyon alt ölçeğinin algılanan semptomlarında anlamlı derecede daha yüksek skorlar gösterdi (z=-2,838, p=0,005). EORTC-CIPN20'nin otonomik alt ölçeği yaş ile (r=-0,373, p=0,006) ve maruz kalınan toplam kemoterapi dozuyla (r=0,295, p=0,034) anlamlı korelasyon gösterdi.

Sonuç: CIPN'ye katkıda bulunan bir faktör olarak kendini gösteren ameliyat türünde, özellikle MRM, daha fazla potansiyel kötüleşme için dikkate alınmalıdır. Bu sayede, sadece CIPN'nin sürekli takibinin değil, aynı zamanda CIPN'ye katkıda bulunan potansiyel faktörlerin yönetiminin de büyük önem taşıdığını belirtmek makul olacaktır.

Anahtar Kelimeler: Meme kanseri, kemoterapi, taksanlar, periferal nöropati

INTRODUCTION

Breast cancer (BC) is the most common type of cancer observed in women worldwide. The reported incidence of BC nearly equals 13%.[1] However, the disease-free survival rate of BC has increased to up to 90%, highlighting the utmost need for management strategies regarding the potential side effects of BC treatment to improve survival in BC survivors.[2,3]

Chemotherapy, which has proven efficacious for treating BC, is widely used. However, due to its potential neurotoxic side effects, BC patients who undergo systemic chemotherapy can experience sensory, motor, and autonomic disturbances in the distal part of their extremities, showing themselves as "stock and glove" like sensorial impairments in the initial stages.[4-7] This situation is called Chemotherapy-induced peripheral neuropathy (CIPN), and it is one of the most cumbersome and well-recognized side effects of systemic chemotherapy. The incidence of CIPN can be as high as 30%, even years after the completion of systemic chemotherapy.[4,7] Patients who suffer from CIPN may experience tingling, numbness, pain, and a wide range of symptoms in their hands and feet, which in turn could lead to diminished functional performance, deteriorated gross and fine motor skills, balance loss and so forth.[8-10]

There are well-known risk factors that have been identified in the context of CIPN onset, such as increased dosage, genetic factors, preexisting neuropathy, and so forth.[6,11,12] To the best of our knowledge, there is a gap regarding the potential association between the type of surgery and chemotherapy [adjuvant (ACT) vs. neoadjuvant NACT)] in the context of perceived CIPN, which needs to be addressed further to draw and conclude a sensitive approach in patients with BC who are at risk for CIPN. Therefore, this cross-sectional study aimed to assess the perceived CIPN symptoms in patients with BC who underwent taxane-based chemotherapy.

METHODS

Study Design

This prospective observational study was conducted in the Medical Oncology Unit of İzmir Bakırçay University Faculty of Medicine, according to the 1964 Helsinki Declaration and its later amendments or comparable ethical standards between January 2024 and March 2024. Ethical approval was granted from the İzmir Bakırçay University Ethical Board of Clinical Studies with the following number (decision no: 1414, date: 17.01.2024). The non-probability sampling method was used. This study was conducted according to the Strengthening of the Reporting of Observational Studies in Epidemiology guideline.[13]

Patients

Patients diagnosed with BC and referred to the medical oncology unit for systemic chemotherapy were screened and invited to participate in this study. The inclusion criteria were being a volunteer to participate, being over 18 years old, being female, and being a candidate for systemic chemotherapy. Having distant metastasis, comorbidities that might contribute to or cause sensory and motor deficits, such as multiple sclerosis, diabetes, polyneuropathy, etc., and prolonged surgical (if any) complications (i.e. pain, seroma, etc.) were set as exclusion criteria. Signed informed consent was obtained from each patient.

Assessments

The assessment time frame was set to one month and a half after the completion of systemic chemotherapy.

Data Form

A simple data form was used to gather information about the patients' age, weight, height, marital status, and smoking status. In addition, the clinical features of the patients were gathered and checked based on the current medical examination and systemic chemotherapy reports.

Calculation of Mean Exposure Dose

The mean exposure for chemotherapy drugs was calculated according to the body surface area (BSA) and the Du Bois formulation. The BSA was gathered according to the following formula: BSA [m^2] = Weight [kg]$^{0.425}$ × height (cm)$^{0.725}$ × 0.007184. Universal dose calculations were used to calculate the mean exposure according to the following doses for each patient-specific to their chemotherapy regimen: Four cycles of anthracycline were applied 14 days

apart 60 mg/m^2 intravenous (IV), 12 cycles of paclitaxel were applied seven days apart 80 mg/m^2 IV, and four cycles of docetaxel were applied 21 days apart 75 mg/m^2 IV.

Assessment of Chemotherapy Induced Peripheral Neuropathy

The European Organization for Research and Treatment of Cancer-Chemotherapy Induced Peripheral Neuropathy (EORTC-CIPN20) was developed to assess potential symptoms associated with CIPN in 2005. The questionnaire has been widely used and reported to be valid and reliable due to its robust psychometric properties.[14] Therefore, EORTC-CIPN20 was used to assess the perceived symptoms of CIPN in this study. The test consists of a total of 20 items each is scored from "1: not at all" to "4: very much" in a 4-point Likert scale. Individuals are requested to fill out the survey by considering their last week. Sensory, motor, and autonomic subscales are reported within the constructs. A total of 9, 8, and 3 items were referred to as sensory, motor, and autonomic disturbances, respectively. The last question of EORTC-CIPN20 evaluates erectile dysfunction that is not suitable for females. Therefore, it should be excluded from women. Raw scores range between 1-36 and 1-32 for the sensory and motor subscales, whereas the range of raw scores of the autonomic subscales is 1-12 for men and 1-8 for women, respectively. When reporting on the EORTC-CIPN20, it is recommended to convert all scores in a 0-100 linear scale. Higher scores indicate worse, and vice versa.[15]

Statistical Analysis

The data are presented as means and standard deviations or numbers and percentages according to the type of data. The normality of the data was checked using the Shapiro-Wilk tests, skewness, and kurtosis as well as graphical representation. Continuous data between groups were analyzed using the independent samples t-test or the Mann-Whitney U test in case of the violation of normality assumptions (i.e. patients with MRM or breast-conserving surgery). Pearson's r or Spearman's rho correlation analyses were performed between parameters according to the assumptions that the distribution met normality. All analyses were two-tailed, and p=0.05 was considered significant. The statistical analysis was performed using IBM Statistical Package for the Social Sciences v.20. (IBM Corp, NY).

RESULTS

Seventy four patients with BC who had completed their systemic treatments (chemotherapy, radiotherapy, surgery) were screened and invited to participate in this study. However, according to the predefined inclusion and exclusion criteria, 22 of them (29.7%) were excluded for various reasons. A detailed participation process is shown in (Figure 1) as a flowchart. Therefore, this study was completed with 52 BC patients [mean age and body mass index (BMI): 48.67±8.21 years and 27.03±4.31 kg/m^2]. ACT was applied in 25 of 52 patients (48.1%), while the rest of the patients underwent NACT (51.9%). Most patients underwent breast-conserving surgery (65.4%). The type of chemotherapy regimen was a combination of anthracycline and paclitaxel (28 out of 52), docetaxel (14 out of 52), or a combination of anthracycline, pertuzumab, trastuzumab, and docetaxel (10 out of 52). The mean total exposure dose was 2093.92±1266.22 mg. Only 13 (25%) reported being an active smoker during the data collection

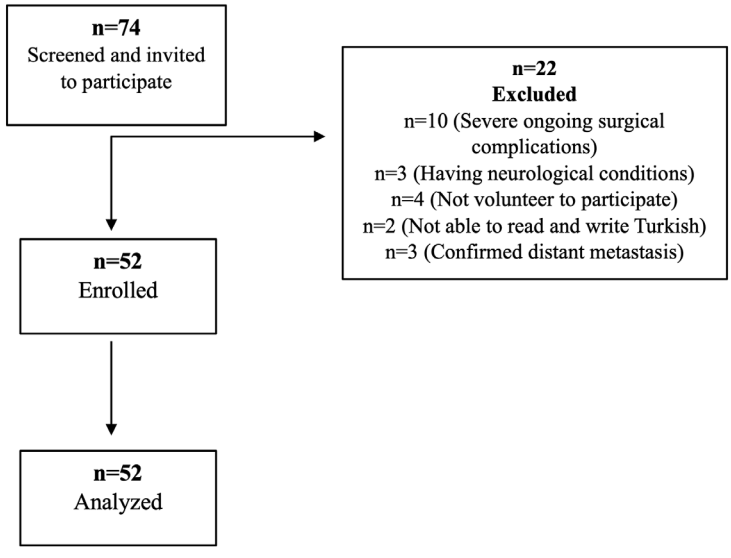

Figure 1. Flow chart of the study participants

period. The clinical and sociodemographic characteristics of patients are shown in (Table 1).

According to the linear converted scale scores of CIPN (0-100), the mean sensory, motor, and autonomic scores of CIPN were 21.50±18.68, 22.02±19.27 and 24.67±22.01, respectively. The total cumulative scores of the same subscales were 14.80±5.04, 12.69±4.27, and 3.48±1.32, respectively. Setting threshold 35 as discriminative of potential CIPN presence in the total score, 16 out of 52 patients (30.7%) had scores higher than this threshold. Patients who underwent MRM showed higher scores in the perceived symptoms of CIPN in all subscales compared with patients who underwent breast-conserving surgery; however, a significant result was only obtained in the motor function subscales of EORTC-CIPN20 (z=-2.838, p=0.005). When the mean scores of these subscales were compared between patients with ACT and NACT, the autonomic subscale of EORTC-CIPN20 was significantly higher in patients with NACT (z=-2.238, p=0.025). Although age and BMI were seen as lower in the NACT group compared with those with ACT, remarkably higher means were observed in both motor (27.06 vs. 16.56) and sensory subscales (24.00 vs. 18.81) of EORTC-CIPN20 in the NACT group compared with the ACT, yet those did not reach statistical significance (p>0.05). Yet, the mean exposure of chemotherapy was nearly two-fold higher in patients with NACT compared with the patients with ACT (2792.26 mg vs. 1339.72 mg) (z=-3.315, p=0.001). The detailed mean scores and comparisons of EORTC-CIPN20 between groups (MRM vs. breast-conserving surgery or ACT vs. NACT) are shown in (Table 2). Thirteen patients (25%) who were active smokers showed higher mean scores in the sensory and autonomic subscales of EORTC-CIPN20 compared with non-smokers; however, between-group comparisons

Table 1. Clinical and sociodemographic characteristics of patients

Marital status	**n (%)**
Married	39 (75)
Single or divorced	13 (25)
Smoking	
Yes	13 (25)
No	39 (75)
Alcohol consumption	
Yes	4 (7.7)
No	48 (92.3)
Type of chemotherapy	
ACT	25 (48.1)
NACT	27 (51.9)
Type of surgery	
BCS	28 (66.7)
MRM	14 (33.3)
Type of chemotherapy regimen	
AC+PAXL	28 (53.8)
Docetaxel	14 (26.9)
AC+docetaxel+pertuzumab+trastuzumab	10 (19.3)

BCS: Breast-conserving surgery, MRM: Modified radical mastectomy, ACT: Adjuvant chemotherapy, NACT: Neoadjuvant chemotherapy

Table 2. Detailed scores and comparisons of EORTC-CIPN20

EORTC-CIPN20				
Total score	**n (%)**			
<35	36 (69.3)			
>35	16 (30.7)			
	Median (IQR$^{25-75}$)	**Median (IQR$^{25-75}$)**		
EORTC-CIPN20	**MRM**	**BCS**	**z**	**p**
Sensory	25.92 (11.11, 41.66)	14.81 (3.70, 26.84)	-1.468	0.142
Motor	33.33 (13.83, 43.74)	12.5 (4.16, 23.80)	-2.838	0.005
Autonomic	33.33 (12.49, 50.00)	16.66 (0.00, 33.33)	-1.418	0.156
EORTC-CIPN20	**ACT**	**NACT**		
Sensory	14.81 (5.55, 25.92)	18.51 (3.70, 44.44)	-0.717	0.473
Motor	12.50 (4.16, 27.08)	20.83 (8.33, 41.66)	-1.884	0.060
Autonomic	16.66 (0.00, 24.99)	33.33 (16.66, 50.00)	-2.238	0.025
Mean exposure time (mg)	618.15 (516.71, 2245.20)	2213.01 (1935.98, 4087.66)	-3.315	0.001

p<0.05.

EORTC-CIPN20: European Organization for Research and Treatment of Cancer-Chemotherapy Induced Peripheral Neuropathy (EORTC-CIPN20) questionnaire, BCS: Breast-conserving surgery, MRM: Modified radical mastectomy, ACT: Adjuvant chemotherapy, NACT: Neodjuvant chemotherapy, mg: Milligram, z: Mann-Whitney U test, IQR: Interquartile range

showed no significant difference (p>0.05). When floor and ceiling effects were analyzed, 13.4% and 94.2% of patients scored "1=not at all" in 10th item (Did you have difficulty distinguishing between hot and cold water?) and "4=very much" in 13th item (Did you have difficulty opening a jar or bottle because of weakness in your hands?) in EORTC-CIPN20, respectively.

There were also significant correlations, which should be discussed in detail. Age was significantly correlated with the mean scores of the autonomic subscale of EORTC-CIPN20 (r=-0.373, p=0.006). The total exposure dose of chemotherapy was also significantly correlated with the autonomic subscale of EORTC-CIPN20 (r=0.295, p=0.034). No significant differences were observed between the sensory and motor subscales as well as age, BMI, and exposed dose, respectively (p>0.05).

DISCUSSION

There is no standardized consensus or gold standard for diagnosing and evaluating CIPN. Patient-reported outcomes, such as EORTC-QLQ-CIPN20, are reported to be useful and reliable for assessing the general picture of patients who suffer from or are at risk for CIPN, especially in the context of potential functional limitations.[14] In addition, when considering the total cumulative score, the sensory scale had higher mean scores than the motor and autonomic subscales. This result was expected because CIPN frequently presents with a sensory-dominant impairment. Other studies have also found higher means of sensory subscale scores compared to the others.[9,16] Yeo et al.[17] reported the highest mean changes in the sensory subscale in patients receiving taxane-based chemotherapy during the chemotherapy treatment trajectory. On the other hand, the effect of the type of surgery, especially on the motor subscale, deserves further study due to the fear avoidance attitude, ongoing pain, and/or pain catastrophizing that might contribute more to perceived CIPN symptoms in patients with MRM. In line with the literature findings, higher exposure doses of chemotherapy were significantly associated with increased perceived autonomic symptoms of CIPN. In this regard, it should be noted that the timing of measurement might also act as a major contributing factor in the context of perceived CIPN symptoms according to the patient-reported outcome(s).

Studies indicated that the prevalence of CIPN gradually decreases from nearly 70% to 30% within the first month and after six months of completion of chemotherapy.[4] Although we assessed our patients within a month and a half, our results seem parallel and comparable with the findings of Seretny et al's.[4] study in which nearly the same rate of prevalence was reported in a six-month or more time frame (30.7% vs 30%) according to the setting of threshold as 35 in the total cumulative score of EORTC-CIPN20 in our study. However, we found this rate earlier than those reported in six months or more. This can be attributable to the timing of measurements in our study, which corresponded nearly to two months after the completion of chemotherapy. In parallel with this, the onset and severity of CIPN were reported to be highest during and after the completion of systemic chemotherapy.[18] Though there have been no reports of useful cut-off values or thresholds for EORTC-CIPN20, we set this threshold as 35 in the total score according to the study of Alberti et al.[9], in which scores above 35 relatively correspond to grades two or more in the Total Neuropathy Score (TNSc) classification. Other studies also indicated significant correlations between clinician-assessed and patient-reported outcomes in the context of perceived CIPN.[18] For instance, Zhi et al.[5] reported diminished tactile and vibration perception in the Quantitative Sensory Testing (QST) method in patients with mild to moderate CIPN according to patient-reported outcomes. However, available methods in the literature on the assessment of CIPN do not show any superiority. By way of instance, QST evaluates large, myelinated fibers,[19] associated with sensory input, which is a predominant loss, especially in the initial stages of CIPN, which can be accounted for as an advantage. However, focusing only on sensory disturbance(s) using the QST may fail to detect and/or interpret potential motor disturbances. Thus, previous studies have indicated that using combined measurement methods is preferable for detecting and interpreting the potential consequences of CIPN.[10]

Not only the primary symptoms but also the associated consequences of perceived CIPN, such as falls, balance loss, increased energy expenditure, depression and anxiety, and sleep disorders, during functional abilities can significantly cause a deteriorated quality of life for patients undergoing taxane-based CT.[4,6,20] Moreover, some clinical and individual factors are known to have affected CIPN, such as the presence of comorbidities, nutrition, previous psychological status, obesity, the level of physical activity, as well as the amount of exposed dose, and so forth.[21-24] The main risk factor for CIPN is the cumulative dosage of chemotherapy.[6,11] We also found that patients who underwent NACT with higher doses showed higher but insignificant scores in each subscale of EORTC-CIPN20 compared to the ones who underwent ACT with significantly lower doses exposed. This might be relatively expected because all our patients with NACT underwent a combination of chemotherapy including HER2 antibodies such as pertuzumab and/or trastuzumab, which further contribute to an increased exposure dose of chemotherapy. Candelario et al.[25] reported a two-fold higher risk of experiencing CIPN in patients with HER2 positivity (odds

ratio: 2.11). The same authors also reported a nearly threefold increased risk of CIPN in patients who received paclitaxel compared with that in patients who received docetaxel alone (odds ratio: 2.89). The current literature also supports this hypothesis that patients who underwent paclitaxel are much more likely to experience CIPN.[7,12] Although the chemotherapy regimen was combined with anthracycline and paclitaxel in nearly half of our sample, we did not find any significant difference in terms of sensory and motor subscales except for the autonomic subscale of EORTC-CIPN20, which was significantly higher compared with patients who underwent docetaxel only. Although higher mean scores were observed for each subscale, the results were insignificant except for the autonomic subscale. These findings may be attributed to the highly skewed results of EORTC-CIPN20, which was also reported in other studies.[26] In addition, other uncontrollable factors might also cause these insignificant results, such as EORTC-CIPN20, to be filled out by considering the last week, which is relatively narrow and vulnerable to detect a complete picture of potential CIPN. On the other hand, we also found a weak but significant correlation between the autonomic subscale of EORTC-CIPN20 and the exposure dose. The motor and sensory subscales did not significantly correlate with EORTC-CIPN20. However, this finding should be thoroughly interpreted because of the relatively lower levels of reliability and validity of the autonomic subscale of EORTC-CIPN20 compared with other subscales.[26,27] Besides, there is only a set of three items associated with autonomic disturbance in EORTC-CIPN20 (i.e. blurred vision, hypotension, and erectile dysfunction), and we could not evaluate the last item as it is only for males. Studies have also indicated that experiencing hypotension and/or blurred vision can also originate from prolonged side effects of systemic chemotherapy.[27] Furthermore, Rattanakrong et al.[16] reported no significant difference in the autonomic scale scores between patients with BC and healthy controls. Yet, a weak but significant correlation between the autonomic subscale of EORTC-CIPN20 and age should be considered, especially for older patients who are expected to be more vulnerable to neurotoxic chemotherapy and thereby suffer more from CIPN. Indeed, secondary complications, such as increased fall risk[8], should be seriously considered in these older patients since they might cause devastating complications for functionality.[26] Bao et al.[8] reported a nearly two-fold increased risk of CIPN in patients with obesity. Yet, controversial results were also reported in which individual (i.e. age, race, smoking, alcohol) and clinical factors (i.e. diabetes, renal disease) were not found as significant factors in the context of the severity of CIPN.[25] In parallel with the previous findings of Candelario et al.[25], we also did not find any significant correlation between BMI and each subscale of EORTC-CIPN20. This insignificant finding can be attributed to the timing of our measurement, and it might be reasonable to conclude that the cumulative effects of neurotoxic chemotherapy might not have occurred at the time of data collection. On the other hand, the most prominent finding of our study was that patients who underwent MRM showed significantly higher scores on the motor subscale of EORTC-CIPN20 compared with those who underwent breast-conserving surgery. MRM can be accounted for in more extensive surgery not only by losing the breast but also by experiencing ongoing surgical complaints (i.e. pain in the surgical incision) might have contributed to this result. Lavoie Smith et al.[27] reported that those with a more proximal extension of CIPN associated with upper extremity dysfunction were prone to have higher CIPN scores. Therefore, patients who underwent MRM should be closely monitored due to worsening CIPN symptoms by aggravating both sensory and motor disturbances, which in turn might result in a remarkable decrease in functionality. Notably, patients with MRM are particularly prone to avoid their affected upper extremities due to false beliefs upon the manifestation of lymphedema, which ultimately results in fear avoidance patterns.[28] Nonetheless, a ceiling effect was also found at a rate of 94.2% in the 13th item of EORTC-CIPN20 ("Did you have difficulty opening a jar or bottle because of weakness in your hands") which might also be considered to have originated from the relatively notable number of patients with MRM (~35%) in our study. Mols et al.[26] reported that the most frequent symptom was the same item in the EORTC-CIPN20. This finding carries a noticeable importance because patients with BC might likely face problems associated with gross and fine motor skills of the upper extremity, which can end in loss of work and devastating financial toxicity.[29] Therefore, not only the perception of CIPN but also secondary consequences, such as diminished fine motor ability, should be integrated into the trajectory of survivorship.[10] We were also able to report a decrease in handgrip and peripheral muscle strengths as well as diminished fine motor ability in the trajectory of systemic chemotherapy in patients with BC.[30] In our study, we also found higher mean scores of the EORTC-CIPN20 motor and autonomic subscales in patients who presented themselves as active smokers compared with non-smokers during data collection, yet the difference did not reach statistical significance for each subscale. However, we only asked respondents whether they were smoker or not and did not collect the cumulative amount of smoking in a day or duration. However, we think that this finding is worthy of future study because the mean exposure dose of chemotherapy (1908 mg vs. 2155 mg) and age (45 vs. 50) were lower in smokers.

Study Limitations

This study has some strengths and limitations. Establishing a real-time environment for patient-reported outcomes, a homogeneous sample of BC, and using non-biased clinical data (i.e. the cumulative dose, surgery, chemotherapy regimen, etc.) to compare patients with ACT and NACT in terms of discriminating surgical effects can be considered the strengths of this study. However, the relatively small sample size and the cross-sectional nature of the design of this study, which hampered us from comparing before and after, can be considered limitations of this study. In addition, since this study was conducted in a single outpatient clinic and relatively included Caucasian women, the generalizability of our results might be arguable. Besides, since we included only female patients with BC, the last item of EORTC-CIPN20 could not be calculated because it directly evaluates erectile dysfunction. Our results need to be clarified in further studies, especially when combined with objective assessments of motor and sensory disturbances.

CONCLUSION

The findings of this study highlighted the need for further and ongoing evaluation of perceived CIPN symptoms, particularly in patients who received higher doses of chemotherapy and/or were older. However, the autonomic reflections of potential CIPN should be carefully interpreted in terms of their clinical implications. The type of surgery, specifically MRM, which has been emphasized as a contributing factor to CIPN, should be taken into consideration for further potential deterioration. By this means, it is reasonable to state that not only ongoing monitoring of the CIPN is of utmost importance, but also potential contributors to the management of the CIPN are of great importance.

Ethics

Ethics Committee Approval: Ethical approval was granted from the İzmir Bakırçay University Ethical Board of Clinical Studies with the following number (decision no: 1414, date: 17.01.2024).

Informed Consent: Written informed consent was obtained from each patient.

Authorship Contributions

Surgical and Medical Practices: M.A., Concept: M.A., Design: A.T., M.A., Data collection or Processing: A.T., M.A., Analysis or interpretation: A.T., M.A., Literature Search: A.T., Writing: A.T., M.A.,

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Giaquinto AN, Sung H, Miller KD, et al. Breast cancer statistics, 2022. CA Cancer J Clin. 2022;72:524-41.
2. Wang LZ, Li JF, Wang TF, et al. Long-term recurrence rate and survival in different aged patients with breast cancer undergoing breast conserving therapy. Zhonghua Wai Ke Za Zhi. 2021;59:127-33.
3. Nardin S, Mora E, Varughese FM, et al. Breast cancer survivorship, quality of life, and late toxicities. Front Oncol. 2020;10:864.
4. Seretny M, Currie GL, Sena ES, et al. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. Pain. 2014;155:2461-70.
5. Zhi WI, Chen P, Kwon A, et al. Chemotherapy-induced peripheral neuropathy (CIPN) in breast cancer survivors: a comparison of patient-reported outcomes and quantitative sensory testing. Breast Cancer Res Treat. 2019;178:587-95.
6. Molinares D, Kurtevski S, Zhu Y. Chemotherapy-Induced Peripheral Neuropathy: Diagnosis, Agents, General Clinical Presentation, and Treatments. Curr Oncol Rep. 2023;25:1227-35.
7. Song SJ, Min J, Suh SY, et al. Incidence of taxane-induced peripheral neuropathy receiving treatment and prescription patterns in patients with breast cancer. Support Care Cancer. 2017;25:2241-8.
8. Bao T, Basal C, Seluzicki C, Li SQ, Seidman AD, Mao JJ. Long-term chemotherapy-induced peripheral neuropathy among breast cancer survivors: prevalence, risk factors, and fall risk. Breast Cancer Res Treat. 2016;159:327-33.
9. Alberti P, Rossi E, Cornblath DR, et al. Physician-assessed and patient-reported outcome measures in chemotherapy-induced sensory peripheral neurotoxicity: two sides of the same coin. Ann Oncol. 2014;25:257-64.
10. Stoller S, Capozza S, Alberti P, Lustberg M, Kleckner IR. Framework to leverage physical therapists for the assessment and treatment of chemotherapy-induced peripheral neurotoxicity (CIPN). Support Care Cancer. 2023;31:293.
11. Ghoreishi Z, Keshavarz S, Asghari Jafarabadi M, Fathifar Z, Goodman KA, Esfahani A. Risk factors for paclitaxel-induced peripheral neuropathy in patients with breast cancer. BMC Cancer. 2018;18:958.
12. Engvall K, Gréen H, Fredriksson M, Åvall-Lundqvist E. Persistent neuropathy among early-stage breast cancer survivors in a population-based cohort. Br J Cancer. 2021;125:445-57.
13. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 2007;147:573-7.
14. Li T, Park SB, Battaglini E, et al. Assessing chemotherapy-induced peripheral neuropathy with patient reported outcome measures: a systematic review of measurement properties and considerations for future use. Qual Life Res. 2022;31:3091-107.
15. Postma TJ, Aaronson NK, Heimans JJ, et al. The development of an EORTC quality of life questionnaire to assess chemotherapy-induced peripheral neuropathy: the QLQ-CIPN20. Eur J Cancer. 2005;41:1135-9.
16. Rattanakrong N, Thipprasopchock S, Siriphorn A, Boonyong S. Reliability and Validity of the EORTC QLQ-CIPN20 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Chemotherapy-Induced Peripheral

Neuropathy 20-Item Scale) among Thai Women with Breast Cancer Undergoing Taxane-Based Chemotherapy. Asian Pac J Cancer Prev. 2022;23:1547-53.

17. Yeo F, Ng CC, Loh KWJ, et al. Minimal clinically important difference of the EORTC QLQ-CIPN20 for worsening peripheral neuropathy in patients receiving neurotoxic chemotherapy. Support Care Cancer. 2019;27: 4753-62.
18. Wang YJ, Chan YN, Jheng YW, et al. Chemotherapy-induced peripheral neuropathy in newly diagnosed breast cancer survivors treated with taxane: a prospective longitudinal study. Support Care Cancer. 2021;29:2959-71.
19. Backonja MM, Walk D, Edwards RR, et al. Quantitative sensory testing in measurement of neuropathic pain phenomena and other sensory abnormalities. Clin J Pain. 2009;25:641-7.
20. Jheng YW, Chan YN, Wu CJ, et al. Neuropathic Pain Affects Quality of Life in Breast Cancer Survivors with Chemotherapy-Induced Peripheral Neuropathy. Pain Manag Nurs. 2024;25:308-15.
21. Ellikçi R, Arslan S. Peripheral neuropathy and lifestyle factors in women with breast cancer receiving taxane-based chemotherapy: Pathway analysis. Eur J Oncol Nurs. 2023;66:102415.
22. Lee KM, Jung D, Hwang H, et al. Pre-treatment anxiety is associated with persistent chemotherapy-induced peripheral neuropathy in women treated with neoadjuvant chemotherapy for breast cancer. J Psychosom Res. 2018;108:14-9.
23. Schwab L, Visovsky C. Psychological distress and quality of life in breast cancer survivors with taxane-induced peripheral neuropathy: A scoping review. Front Oncol 2023;12:1005083.
24. Timmins HC, Mizrahi D, Li T, Kiernan MC, Goldstein D, Park SB. Metabolic and lifestyle risk factors for chemotherapy-induced peripheral neuropathy in taxane and platinum-treated patients: a systematic review. J Cancer Surviv. 2021;17:222-36.
25. Candelario N, Wongrakpanich S, Morginstin MS. Predictors of chemotherapy-induced peripheral neuropathy among breast cancer patients treated with taxanes. J Clin Oncol. 2015;33:(Suppl 28). Available from: https://ascopubs.org/doi/10.1200/jco.2015.33.28_suppl.90
26. Mols F, van de Poll-Franse LV, Vreugdenhil G, et al. Reference data of the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-CIPN20 Questionnaire in the general Dutch population. Eur J Cancer. 2016;69:28-38.
27. Lavoie Smith EM, Barton DL, Qin R, Steen PD, Aaronson NK, Loprinzi CL. Assessing patient-reported peripheral neuropathy: the reliability and validity of the European Organization for Research and Treatment of Cancer QLQ-CIPN20 Questionnaire. Qual Life Res. 2013;22:2787-99.
28. Gutiérrez-Sánchez D, Pajares-Hachero BI, Trinidad-Fernández M, et al. The benefits of a therapeutic exercise and educational intervention program on central sensitization symptoms and pain-related fear avoidance in breast cancer survivors. Pain Manag Nurs. 2022;23:467-72.
29. Kuang Y, Yuan X, Zhu Z, Xing W. Financial toxicity among breast cancer patients: A scoping review of risk factors and outcomes. Cancer Nurs. 2023.
30. Tuğral A, Arıbaş Z, Akyol M, Bakar Y. Assessment of sensorimotor and strength related function of breast cancer patients during systemic drug therapy: a prospective observational study. BMC Cancer. 2023;23:981.