İstanbul Med J 2023; 24(4): 334-9
DOI: 10.4274/imj.galenos.2023.59908

The Role of Interleukin-20 in Paclitaxel-Associated Peripheral Neuropathy in Non-Metastatic Breast Cancer Patients Receiving Chemotherapy

Kubilay Karaboyun[1], Eyyüp Çavdar[2], Yakup İriağaç[3], Ahsen Yılmaz[4], Aliye Çelikkol[4], Okan Avcı[1], Erdoğan Selçuk Şeber[1]

[1]Namık Kemal University Faculty of Medicine, Department of Medical Oncology, Tekirdağ, Turkey
[2]Adıyaman Training and Research Hospital, Clinic of Medical Oncology, Adıyaman, Turkey
[3]Atatürk City Hospital, Clinic of Medical Oncology, Balıkesir, Turkey
[4]Namık Kemal University Faculty of Medicine, Department of Biochemistry, Tekirdağ, Turkey

ABSTRACT

Introduction: This study investigated the relationship between serum interleukin-20 (IL-20) levels and paclitaxel-associated neuropathy in patients with non-metastatic breast cancer. Paclitaxel-induced peripheral neuropathy (PIPN) is a significant side effect of paclitaxel chemotherapy, and the exact mechanism underlying PIPN is not fully understood.

Methods: This prospective observational study was conducted with non-metastatic breast cancer patients between January 2022 and November 2022. Neuropathy symptoms were evaluated using the QLQ-CIPN20 questionnaire, and serum IL-20 levels were measured at three time points: before chemotherapy, on the 7th day after the first paclitaxel treatment, and after the last treatment. Univariate and multivariate logistic regression analyses were performed to identify factors predicting PIPN.

Results: This study was completed with 59 female patients. During the study, 47 patients (79.6%) reported any degree of neuropathy, whereas 12 patients (20.4%) had no neuropathy. Univariate analysis to predict neuropathy measured on day 7 after first paclitaxel administration demonstrated that age, body mass index, 7th-day serum IL-20 level, and last cycle serum IL-20 level were predictive for PIPN.

Conclusion: This study demonstrated the relationship between serum IL-20 levels and paclitaxel-related neuropathy in breast cancer patients. Further research targeting the function of IL-20 is needed to investigate potential strategies to prevent and treat PIPN.

Keywords: Paclitaxel, peripheral neuropathy, breast cancer, IL-20, QLQ-CIPN20

Introduction

Paclitaxel is a microtubule-stabilizing agent that has significant therapeutic utility for treating many cancers, including breast cancer. Paclitaxel-induced peripheral neuropathy (PIPN) is a dose-limiting side effect of paclitaxel that could require discontinuation of treatment, and the mechanism has not been fully explained. In clinical practice, PIPN can occur over a period of a few days to several months and mostly causes peripheral sensory neuropathy as well as motor and autonomic neuropathy (1,2). Although the cumulative dose of paclitaxel appears to be the most associated factor with neuropathy, factors such as concomitant medications, comorbidities, older age, and vitamin D levels are also important because PIPN can occur even after the first cycle (3,4).

Many animal studies have shown that the possible neuropathy mechanism induced by paclitaxel includes inflammation, oxidative stress, loss of epidermal nerve fibers, alterations of mitochondrial function, and excitability of neurons, which cause damage to peripheral neurons and the dorsal root ganglion (5-7). Immune upregulation (inducing overexpression of mRNA coding for cytokines such as tumor necrosis factor-alpha, interleukin 1beta (IL-1β), IL-6, CGRP, and substance P) after paclitaxel administration has been shown in previous studies to play an important role in the modulation of cell death (8-10). IL-20 is a proinflammatory and chemoattractant mediator involved in augmenting proinflammatory substances such as IL-6, IL-1, and macrophage inflammatory proteins-1 in astrocytes, monocytes, and epithelial cells (11,12). Previous studies have suggested that IL-20 may function as a proinflammatory mediator in the development of PIPN (13).

In this study, we investigated the relationship between serum IL-20 levels and paclitaxel-related neuropathy.

Address for Correspondence: Kubilay Karaboyun MD, Namık Kemal University Faculty of Medicine, Department of Medical Oncology, Tekirdağ, Turkey
Phone: +90 554 291 61 10 **E-mail:** kubilaykaraboyun@gmail.com **ORCID ID:** orcid.org/0000-0002-1783-8075

Cite this article as: Karaboyun K, Çavdar E, İriağaç Y, Yılmaz A, Çelikkol A, Avcı O, Şeber ES. The Role of Interleukin-20 in Paclitaxel-Associated Peripheral Neuropathy in Non-Metastatic Breast Cancer Patients Receiving Chemotherapy. İstanbul Med J 2023; 24(4): 334-9.

Received: 27.09.2023
Accepted: 13.10.2023

Methods

Patients

In this prospective observational study, eligible patients were aged >18 years, with histologically proven breast cancer, and planned (adjuvant or neoadjuvant) to receive 4 cycles of epirubicin plus cyclophosphamide and then weekly paclitaxel (80 mg/m^2 x12 cycles). Patients with human epidermal growth receptor-2 (HER2) expression received HER2-directed therapy concurrently (trastuzumab, 17 cycles of neoadjuvant and/or adjuvant; if pertuzumab received, only 4 cycles in the NACT period). Patients with a prior history of peripheral neuropathy or diabetes mellitus and those with advanced -stage breast cancer were excluded from the study.

In this study, a total of 115 non-metastatic breast cancer patients receiving adjuvant or neoadjuvant chemotherapy between January 2022 and November 2022 were evaluated. Of the 115 patients, 15 patients with diabetes mellitus or preexisting peripheral neuropathy and 39 patients scheduled to receive docetaxel as a taxane were excluded from the study. Patients who had to discontinue treatment because of neuropathy were also excluded from the study. The study was eventually conducted with 59 eligible patients (Figure 1). The study was approved by the Namık Kemal University Local Ethical Committee under the Helsinki Declaration (approval number: 2021.264.11.08, date: 30.11.2021), and informed consent was obtained from all participants. This study was registered on clinicaltrials.gov under NCT05622617.

Questionnaire

Neuropathy symptoms were evaluated with the patients-reported EORTC chemotherapy-induced peripheral neuropathy questionnaire (QLQ-CIPN20) on the 7th day after the first paclitaxel administration and at the last administration of the treatment (Figure 1). QLQ-CIPN20 contains three types of neuropathy: sensory, motor, and autonomic, and consists of 20 questions scaled each 1 to 4 points (1, not at all; 4, very much). Each question is scored, and the sum of the scores ranges between 20 and 80. Because only female patients were recruited for the study, the question regarding autonomic dysfunction (erectile dysfunction) was omitted. Patients were divided into two groups: if patients rated any question as 2, 3 or 4 points, they were assumed to have neuropathy; if they rated all questions as 1 point, they were assumed to have no neuropathy. The Turkish Validation of QLQ-CIPN20 was used in this study.

Measuring Serum IL-20 Levels

Serum IL-20 levels were measured at three time points. Initial IL-20 measurement was performed before chemotherapy. The second IL-20 measurement time point was on the 7th day after the first paclitaxel treatment, and the third measurement time point was after the last paclitaxel treatment (Figure 1).

Serum IL-20 levels were measured by ELISA analysis method. Bio-Techne (R&D SYSTEM Inc., Bio-Techne Corporation Brands, Minneapolis, USA) commercial ELISA kit (catalog no: DL200) of 96 tests was used for this measurement. Blood samples of the subjects included in the study were collected in a red-capped gel tube. These blood tubes were centrifuged at 4000 rpm (revolutions per minute) for 10 min and, the separated serum samples were divided into microcentrifuge tubes and labeled. Collected samples were stored at -80 °C until the day of analysis.

Statistical Analysis

Data were analyzed using SPSS version 26. Descriptive statistics and frequency distributions were calculated for the clinicopathological characteristics of patients. Differences between neuropathy and laboratory, clinical, and pathologic characteristics of patients were evaluated using Independent sample t-tests, chi-square analyses, or Mann-Whitney U tests. Receiver operating characteristic analysis was used to calculate the ideal cut-off value for predicting neuropathy. Logistic regression models, including univariate and multivariate analyses, were established to identify predictors of PIPN. A P-value of ≤0.05 was considered statistically significant.

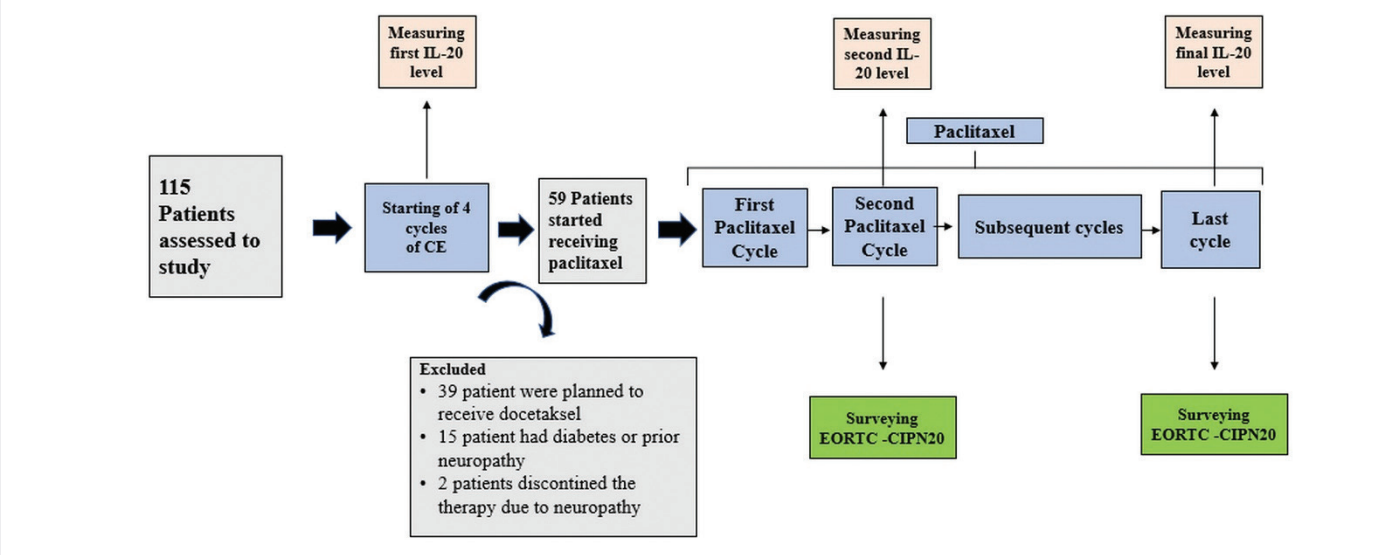

Figure 1. Study flow diagram

IL-20: Interleukin-20, EORTC: European Organization for Research and Treatment of Cancer, CIPN20: Chemotherapy-Induced Peripheral Neuropathy 20-item scale

Results

Fifty-nine female patients with a median age of 52.9 (33-78) years were included in this study. During the study, 47 patients (79.6%) reported any degree of neuropathy, whereas 12 patients (20.4%) had no neuropathy. On the 7th day after the first administration of paclitaxel, a rating score of 2, 3, or 4, which indicates the development of neuropathy, by patients for any of the questions in the QLQ-CIPN20 questionnaire was seen in 38.9% (n=23) patients (Table 1).

In the analysis of factors associated with neuropathy, serum IL-20 levels measured on day 7 (p=0.022), and last cycle serum IL-20 level (p=0.010) were statistically significant regarding the development of neuropathy. The serum IL-20 levels measured on day 7 and on the last cycle day were significantly higher in patients who developed neuropathy on day 7. There were no relationships between neuropathy and, chemotherapy type, estrogen receptor (ER) status, progesterone receptor (PR) status (p=0.670), HER2 expression, tumor size, first IL-20 level, and last serum IL-20 level (Table 1).

In the analysis of the relationship between the 7th-day serum IL-20 level and clinicopathological factors, a significant relationship was observed with the type of chemotherapy. The 7th-day serum IL-20 level was significantly higher in patients receiving adjuvant chemotherapy than in those receiving neoadjuvant settings (p=0.032). No significant difference was observed between the second serum IL-20 level and the following: age, body mass index (BMI), ER status, PR status, HER2 expression, Ki-67 level, and tumor size (Table 2).

Univariate and Multivariate Analyses

Univariate analysis to predict neuropathy measured on day 7 after first paclitaxel administration demonstrated that age [odds ratio (OR): 4.58,

Table 1. Relationship between patient' characteristics and neuropathy (n=59)

Variable	7th day survey after the first paclitaxel			During the entire study		
	Neuropathy, yes (n=23)	Neuropathy, no (n=36)	p	Neuropathy, yes (n=47)	Neuropathy, no (n=12)	p
Age	56.29±4.99*	52.46±11.51*	0.062	50.08±2.86*	53.63±1.64*	0.428
BMI	31.29±1.88*	27.99±0.77*	0.077	28.80±0.81*	26.75±1.55*	0.101
Chemotherapy types						
Adjuvant	2 (8.3%)	22 (91.7%)	0.689	19 (79.2%)	5 (20.8%)	0.594
Neoadjuvant	5 (14.3%)	30 (85.7%)		28 (80%)	7 (20%)	
Estrogen receptor						
Positive	4 (9.5%)	38 (90.5%)	0.399	35 (83.3%)	7 (16.7%)	0.299
Negative	3 (17.6%)	14 (82.4%)		12 (70.6%)	5 (29.4%)	
Progesteron receptor						
Positive	4 (10%)	36 (90%)	0.670	32 (80%)	8 (20%)	0.590
Negative	3 (15.8%)	16 (84.2%)		15 (78.9%)	4 (21.1%)	
HER2 status						
Positive	2 (9.5%)	19 (90.5%)	0.516	16 (76.2%)	5 (23.8%)	0.431
Negative	5 (13.2%)	33 (86.8)		31 (71.8%)	7 (18.2%)	
Ki67						
<18	1 (10%)	9 (90%)	0.662	8 (80%)	2 (20%)	0.673
≥18	43 (87.8)	6 (12.2%)		39 (79.6%)	10 (20.4%)	
Tumor size						
≤2 cm	4 (12.1%)	29 (87.9%)	0.635	26 (78.8%)	7 (21.2%)	0.851
>2 cm	3 (11.5%)	23 (88.5%)		21 (80.8%)	5 (19.2%)	
Labaratory paramaters						
White blood cell (10^3/uL)	6.69±2.01*	6.63±1.75*	0.851	6.67±0.27*	6.64±0.41*	0.814
Neutrophil (10^3/uL)	3.71±1.22*	4.07±1.56*	0.582	4.00±0.23*	4.22±0.37*	0.423
Lymphocyte (10^3/ uL)	2.31±0.78*	1.84±0.58*	0.056	1.93±0.08*	1.72±0.21*	0.292
Platelet count (10^3/uL)	259.4±92.9*	279.9±68.6*	0.512	279.1±10.8*	265.7±14.7*	0.553
Hemoglobin (g/dL)	12.31±0.79*	12.16±1.14*	0.618	12.15±0.16	12.33±0.38*	0.564
NLR	1.67±0.46*	2.31±1.23*	0.134	2.18±0.18	2.43±0.26*	0.69
Serum IL-20 levels						
Initial serum IL-20 level	116.62±33.19*	101.41±27.84*	0.289	103.90±4.11	100.90±10.32*	0.194
7th-day serum IL-20 level	134.78±43.97*	107.50±31.20*	0.022	109.95±5.04	114.82±10.64*	0.684
Last cycle serum IL-20 level	134.82±58.55*	104.70±39.09*	0.010	109.79±6.67	103.03±9.10*	0.969

*: Mean ± standart deviation, BMI: Body mass index, HER2: Human epidermal growth receptor-2, NLR: Neutrophil to lymphocyte ratio, IL-20: Interleukin-20

confidence interval (CI): 95%, 1.38-15.20, p=0.013], BMI (OR: 3.21, CI: 95%, 1.03-9.98, p=0.034), Lymphocyte count (OR: 8.33, CI: 95%, 1.43-48.54, p=0.018), 7th-day serum IL-20 level (OR: 10.42, CI: 95%, 1.17-93.20, p=0.036), and last cycle serum IL-20 level (OR: 4.58, CI: 95%, 1.38-15.20, p=0.013) were predictive for PIPN. In the multivariate regression model including predictive markers, age (OR: 3.45, CI: 95%, 0.93-12.80, p=0.064), lymphocyte count (OR: 4.16, CI: 95%, 1.10-15.74, p=0.036), and last cycle serum IL-20 level (OR: 4.79, CI: 95%, 1.24-18.46, p=0.023) were found to be independent predictors for PIPN (Table 3).

Discussion

In this study, we addressed PIPN, a dose-limiting side effect of paclitaxel chemotherapy that is a substantial component of breast cancer treatment management, which can jeopardize breast cancer treatment and quality of life of breast cancer patients. Univariate regression analysis revealed that PIPN detected on day 7 after the first paclitaxel cycle was associated with increased day 7 serum IL-20 levels and last cycle serum IL-20 levels as well as age, lymphocyte count, and BMI. A multivariate regression model investigating PIPN detected on day 7 showed age, lymphocyte count, and last cycle serum IL-20 levels as independent predictors of neuropathy.

The 2012 Early Breast Cancer Trialists' Collaborative Group meta-analysis showed that anthracycline plus taxane chemotherapy resulted in better progression-free survival and overall survival than CMF, which was the standard treatment at that time (14). Since then, taxanes have been an integral component of the management of early or locally advanced breast cancer. However, despite its strong survival effect, taxane-induced neuropathy is an important limiting factor. This may cause patients to discontinue chemotherapy, affect their quality of life, and lead to chronic neuropathic diseases. In our study, 47 patients (79.6%) reported any degree of neuropathy, and two patients who were receiving chemotherapy in neoadjuvant settings discontinued treatment because of peripheral neuropathy and were referred for surgery.

In a study that included female patients receiving paclitaxel as adjuvant therapy, neuropathy started within the first week of paclitaxel treatment, whereas PIPN according to CTCAE v3.0 was observed in 97% of patients during 57 months of long follow-up (15). In another prospective study evaluating patients receiving paclitaxel with QLQ-CIPN-20, neuropathy was observed in 76 of 85 patients (16). In our study, 79.6% of patients developed paclitaxel-associated neuropathy during follow-up, as measured by QLQ-CIPN20. In Chen et al. (13) study, serum IL-20 samples obtained in the first week serially from patients receiving paclitaxel for gynecological cancers showed a positive correlation with patients who developed neuropathy as assessed by QLQ-CIPN-20. They also reported that they regressed paclitaxel-associated neuropathy with IL-20-targeting antibodies in a mouse model (13). Another study in the

Table 2. Analysis of clinicopathologic factors related to 7th-day serum IL-20 levels

Variable	Mean ± SD	Range	p
Age			
≥53	110.67±33.30	60.84-231.90	0.531
<53	105.94±38.69	32.23-177.81	
BMI			
<25	112.38±35.00	68.15-177.81	0.862
≥25	107.09±36.01	32.23-231.90	
Chemotherapy types			
Adjuvant	121.22±43.06	32.23-231.90	**0.032**
Neoadjuvant	99.60±26.34	52.87-177.81	
Estrogen receptor			
Positive	110.11±39.52	32.23-231.90	0.896
Negative	104.47±22.71	74.97-150.49	
Progesteron receptor			
Positive	111.35±40.43	32.23-231.90	0.613
Negative	102.79±22.44	60.84-150.49	
HER2 status			
Positive	103.39±45.91	32.23-231.90	0.147
Negative	111.48±28.42	68.15-177.81	
Ki67			
≤18	121.88±30.34	74.97-170.30	0.143
>18	105.77±36.23	32.23-231.90	
Tumor size			
≤2 cm	108.45±41.52	32.23-231.90	0.626
>2 cm	108.67±26.58	60.84-177.81	

IL-20: Interleukin-20, SD: Standard deviation, BMI: Body mass index, HER2: Human epidermal growth receptor-2

Table 3. Univariate and multivariate analysis to predict neuropathy measured on day 7 after the first paclitaxel

		Univariate analysis		Multivariate analysis	
Variables	**Category**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p****
Age	<58.5 vs. >58.5*	4.58 (1.38-15.20)	**0.013**	3.45 (0.93-12.80)	**0.064**
BMI	<30 vs. >30*	3.21(1.03-9.98)	**0.034**		
Chemotherapy types	Adjuvant vs. neoadjuvant	1.83 (0.33-10.34)	0.492		
Estrogen receptor	Positive vs. negative	0.49 (0.98-2.48)	0.389		
Progesteron receptor	Positive vs. negative	0.59 (0.12-2.96)	0.524		
HER2	Positive vs. negative	0.70 (0.12-3.94)	0.681		
Ki67	Low vs. high	1.01 (0.98-1.05)	0.477		
Tumor size	≤2 cm vs. >2 cm	0.28 (0.04-1.73)	0.169		
Labaratory paramaters					
White blood cell (10^3/uL)	<6600 vs. >6600	1.20 (0.24-5.93)	0.823		
Neutrophil (10^3/uL)	<4050 vs. >4050	0.27 (0.03-2.38)	0.237		
Lymphocyte (10^3/uL)	>2.2 vs. <2.2*	8.33 (1.43-48.54)	**0.018**	4.16 (1.10-15.74)	**0.036**
Platelet count (10^3/uL)	>276 vs. <276	0.95 (0.19-4.66)	0.512		
Hemoglobin (g/dL)	>12 vs. <12	2.91 (0.33-26.17)	0.340		
NLR	>2.23 vs. <2.23	0.18 (0.02-1.60)	0.124		
Serum IL-20 levels					
Initial serum IL-20 level	>101.57 vs. <102.57	2.52 (0.51-12.50)	0.259		
7^{th}-day serum IL-20 level	>111.40 vs. <111.40*	10.42 (1.17-93.20)	**0.036**		
Last cycle serum IL-20 level	>126.44 vs. <126.44*	4.58 (1.38-15.20)	**0.013**	4.79 (1.24-18.46)	**0.023**

*The ideal cut-off value was calculated by the ROC curve, **Forward LR method was used, OR: Odds ratio, CI: Confidence interval, BMI: Body mass index, HER2: Human epidermal growth receptor-2, NLR: Neutrophil to lymphocyte ratio, IL-20: Interleukin-20

literature investigating paclitaxel neuropathy using the QLQ-CIPN-20 questionnaire showed that the highest neuropathy score was observed in the first 7 days after the first cycle of paclitaxel. Higher pain scores in the first chemotherapy cycle did not predict higher neuropathy scores in subsequent cycles (17). In accordance with the hypothesis of our study, IL-20 increases with paclitaxel administration and may contribute to the development of neuropathy by probably regulating chemoattractants. The fact that serum IL-20 measured before paclitaxel treatment was not associated with neuropathy and that IL-20 measured on day 7 after treatment and the last cycle of paclitaxel treatment was associated with neuropathy suggests that IL-20 may be one of the mediators contributing to the development of PIPN.

The association of PIPN with older age, lymphocyte count, and BMI in our study is consistent with the studies investigating PIPN in the literature. Ghoreishi et al. (18) showed that age, BMI, and PR positivity were predictive of PIPN in their study investigating PIPN in 56 breast cancer patients receiving paclitaxel. In another study exploring chemotherapy-associated neuropathy in patients who had received cisplatin or paclitaxel, older age was found to be predictive for chemotherapy-associated neuropathy (19). Mizrahi et al. (20) demonstrated that patients receiving paclitaxel or oxaliplatin, low hemoglobin before treatment, high body mass index, advanced age, and female gender were more likely to develop paclitaxel- or oxaliplatin-induced CIPN after treatment. It is very valuable for clinicians to identify markers that predict PIPN. In this study, we identified predictive markers in a well-selected (excluding diseases that may cause neuropathy) patient population with early-stage breast cancer. However, nevertheless, the key significance of this study is the insight into the relationship between IL-20 and PIPN, which can be an important marker in the future for the prevention or treatment of neuropathy.

Although the exact mechanism of paclitaxel-induced neuropathy is not clearly understood, treatments for possible causes have been investigated. Several studies have reported that approved therapies such as duloxetine, melatonin, minoxidil, N-acetylcysteine, or statins may diminish PIPN because of their anti-inflammatory, anti-oxidative, or neuroprotective effects (21-23). However, these studies appear to be experimental and mostly empirically applied treatments, and these treatments do not provide a standard treatment approach to prevent or treat PIPN. Moreover, studies with other and/or the same medications with similar mechanisms have shown that these agents do not prevent or reduce PIPN (24-26). These findings suggest that a lack of a clear understanding of the pathophysiology of paclitaxel-associated neuropathy makes an effective prevention or treatment option impossible. The association between neuropathy and IL-20 obtained from our study can be interpreted as the detection of an amplifier signal that triggers multiple mechanisms in the pathogenesis of the disease and may be the target of future therapies.

Study Limitations

This study is not without limitations. First, although the QLQ-CIPN-20 is a questionnaire with high sensitivity and specificity for neuropathy, it includes subjective assessment because it is self-administered. Second, the fact that IL-20 level measurement and neuropathy questionnaire could not be performed in every paclitaxel cycle is an important

limitation. In addition, the lack of long-term follow-up neuropathy results on the patients is another limitation. The lack of long-term follow-up neuropathy results in the patients and small population are other limitations. The strength of our study is its prospective design and the exclusion of patients with neuropathy and those with diseases that may affect neuropathy, such as diabetes.

Conclusion

In conclusion, with this study, we showed that age, BMI, and lymphocyte count may be predictors for the development of PIPN in patients receiving paclitaxel with curative intent for treating breast cancer. We also demonstrated the relationship between IL-20 and the pathophysiology of paclitaxel-associated neuropathy for treating breast cancer. Future studies targeting the significance of IL-20 in the development of neuropathy are needed to prevent and treat neuropathy in larger patient populations.

Ethics Committee Approval: The study was approved by the Namık Kemal University Local Ethical Committee under the Helsinki Declaration (approval number: 2021.264.11.08, date: 30.11.2021).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept - K.K., E.Ç., O.A.; Design - Y.İ., A.Y., A.Ç.; Data Collection or Processing - K.K., E.Ç.; Analysis or Interpretation - E.Ç., O.A.; Literature Search - E.Ç., O.A.; Writing - K.K., E.S.S.

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. Velasco-González R, Coffeen U. Neurophysiopathological Aspects of Paclitaxel-induced Peripheral Neuropathy. Neurotox Res 2022; 40: 1673-89.
2. Hershman DL, Weimer LH, Wang A, Kranwinkel G, Brafman L, Fuentes D, et al. Association between patient reported outcomes and quantitative sensory tests for measuring long-term neurotoxicity in breast cancer survivors treated with adjuvant paclitaxel chemotherapy. Breast Cancer Res Treat 2011; 125: 767-74.
3. Freilich RJ, Balmaceda C, Seidman AD, Rubin M, DeAngelis LM. Motor neuropathy due to docetaxel and paclitaxel. Neurology 1996; 47: 115-8.
4. Vermeer CJC, Hiensch AE, Cleenewerk L, May AM, Eijkelkamp N. Neuro-immune interactions in paclitaxel-induced peripheral neuropathy. Acta Oncol 2021; 60: 1369-82.
5. Miao H, Xu J, Xu D, Ma X, Zhao X, Liu L. Nociceptive behavior induced by chemotherapeutic paclitaxel and beneficial role of antioxidative pathways. Physiol Res 2019; 68: 491-500.
6. Yilmaz E, Watkins SC, Gold MS. Paclitaxel-induced increase in mitochondrial volume mediates dysregulation of intracellular Ca2+ in putative nociceptive glabrous skin neurons from the rat. Cell Calcium 2017; 62: 16-28.
7. Flatters SJL, Bennett GJ. Studies of peripheral sensory nerves in paclitaxel-induced painful peripheral neuropathy: evidence for mitochondrial dysfunction. Pain 2006; 122: 245-57.
8. Gao M, Yan X, Weng HR. Inhibition of glycogen synthase kinase 3β activity with lithium prevents and attenuates paclitaxel-induced neuropathic pain. Neuroscience 2013; 254: 301-11.
9. Ullah R, Ali G, Subhan F, Naveed M, Khan A, Khan J, et al. Attenuation of nociceptive and paclitaxel-induced neuropathic pain by targeting inflammatory, CGRP and substance P signaling using 3-Hydroxyflavone. Neurochem Int 2021; 144: 104981.
10. Huang ZZ, Li D, Liu CC, Cui Y, Zhu HQ, Zhang WW, et al. CX3CL1-mediated macrophage activation contributed to paclitaxel-induced DRG neuronal apoptosis and painful peripheral neuropathy. Brain Behav Immun 2014; 40: 155-65.
11. Chiu YS, Wei CC, Lin YJ, Hsu YH, Chang MS. IL-20 and IL-20R1 antibodies protect against liver fibrosis. Hepatology 2014; 60: 1003-14.
12. Chen WY, Chang MS. IL-20 is regulated by hypoxia-inducible factor and up-regulated after experimental ischemic stroke. J Immunol 2009; 182: 5003-12.
13. Chen LH, Yeh YM, Chen YF, Hsu YH, Wang HH, Lin PC, et al. Targeting interleukin-20 alleviates paclitaxel-induced peripheral neuropathy. Pain 2020; 161: 1237-54.
14. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Electronic address: bc.overview@ctsu.ox.ac.uk; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Anthracycline-containing and taxane-containing chemotherapy for early-stage operable breast cancer: a patient-level meta-analysis of 100 000 women from 86 randomised trials. Lancet 2023; 401: 1277-92.
15. Tanabe Y, Hashimoto K, Shimizu C, Hirakawa A, Harano K, Yunokawa M, et al. Paclitaxel-induced peripheral neuropathy in patients receiving adjuvant chemotherapy for breast cancer. Int J Clin Oncol 2013; 18: 132-8.
16. George AM, Arya MA, Joseph SK, Philip A, Reghu R, Sam KM. A Prospective Study on the Incidence and Severity of Paclitaxel-induced Peripheral Neuropathy in the Indian Population. Current Cancer Therapy Reviews 2022; 18: 278-84.
17. Loprinzi CL, Reeves BN, Dakhil SR, Sloan JA, Wolf SL, Burger KN, et al. Natural history of paclitaxel-associated acute pain syndrome: prospective cohort study NCCTG N08C1. J Clin Oncol 2011; 29: 1472-8.
18. 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.
19. Argyriou AA, Polychronopoulos P, Koutras A, Iconomou G, Gourzis P, Assimakopoulos K, et al. Is advanced age associated with increased incidence and severity of chemotherapy-induced peripheral neuropathy? Support Care Cancer 2006; 14: 223-9.
20. Mizrahi D, Park SB, Li T, Timmins HC, Trinh T, Au K, et al. Hemoglobin, Body Mass Index, and Age as Risk Factors for Paclitaxel- and Oxaliplatin-Induced Peripheral Neuropathy. JAMA Netw Open 2021; 4: e2036695.
21. Salehifar E, Janbabaei G, Hendouei N, Alipour A, Tabrizi N, Avan R. Comparison of the Efficacy and Safety of Pregabalin and Duloxetine in Taxane-Induced Sensory Neuropathy: A Randomized Controlled Trial. Clin Drug Investig 2020; 40: 249-57.
22. Lu Y, Zhang P, Zhang Q, Yang C, Qian Y, Suo J, et al. Duloxetine Attenuates Paclitaxel-Induced Peripheral Nerve Injury by Inhibiting p53-Related Pathways. J Pharmacol Exp Ther 2020; 373: 453-62.
23. Khalefa HG, Shawki MA, Aboelhassan R, El Wakeel LM. Evaluation of the effect of N-acetylcysteine on the prevention and amelioration of paclitaxel-induced peripheral neuropathy in breast cancer patients: a randomized controlled study. Breast Cancer Res Treat 2020; 183: 117-25.
24. Ruddy KJ, Le-Rademacher J, Lacouture ME, Wilkinson M, Onitilo AA, Vander Woude AC, et al. Randomized controlled trial of cryotherapy to prevent paclitaxel-induced peripheral neuropathy (RU221511I); an ACCRU trial. Breast 2019; 48: 89-97.
25. Shinde SS, Seisler D, Soori G, Atherton PJ, Pachman DR, Lafky J, et al. Can pregabalin prevent paclitaxel-associated neuropathy?--An ACCRU pilot trial. Support Care Cancer 2016; 24: 547-53.
26. Kochan DC, Novotny PJ, Cathcart-Rake EJ, Orme JJ, Tevaarwerk AJ, Ruddy KJ, et al. An evaluation of the effect of lithium on taxane-induced neuropathy. Support Care Cancer 2023; 31: 299.