

Prevalence and pattern of chemotherapy-induced peripheral neuropathy among patients with breast cancer: A retrospective study in China

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Abstract: Chemotherapy-induced peripheral neuropathy (CIPN) represents a dose-duration adverse event observed in patients with breast cancer undergoing taxane-based chemotherapy. This condition negatively impacts an individual's quality of life, often leading to limitations in cumulative doses or treatment discontinuation. Therefore, understanding risk factors, including age, sex, treatment duration, treatment agents, and mental state, for Paclitaxel-related neuropathy side effects, which remains a subject of controversy, becomes crucial for patient care. Validation of CIPN measurement is of paramount importance, requiring ongoing improvement for more objective participant descriptions.

The QLQ-CIPN20, a new gold standard CIPN measurement version, has been extensively employed across various trials, assessing three domains: sensory, motor, and autonomic. Comprising 20 self-report items within the EORTC Quality of Life Questionnaire, it evaluates motor (8 items), sensory (9 items), and autonomic symptoms (3 items). Participants rate symptoms on a 4-point Likert scale, indicating the degree of each item's impact. The study explores the association between personal characteristics (age, history of labor pain, BMI, smoking, marital status, history of chronic disease) and disease/treatment (stage, previous and current interventions, combined targeted therapy) with the occurrence and severity of CIPN. Pre-specified hypotheses are tested using appropriate bivariate statistical tests, including independent sample t-tests, Chi-square tests, Pearson's correlation, and linear regression. Multivariate linear regression is employed to analyze the association of age, total paclitaxel dose, and additional chemotherapy agents.

A total of 192 women, with a mean age of 52.11 years (SD 10.92), were surveyed from July 2021 to September 2021 at Tianjin Medical University Cancer Institute and Hospital. The majority were stage I–II (47.91%), stage III (25.52%), and stage IV (26.56%). Chemotherapy regimens included Platinum (23.96%), Anthracycline (7.81%), Cyclophosphamide (9.38%), and Paclitaxel alone (60.42%). The mean cycles of chemotherapy since diagnosis was 3.57 (SD 112.9). QLQ-CIPN20 mean scores for total, sensory, motor, and autonomic

ic subscales were 21.41 (SD 4.88), 10.76 (SD 3.19), 7.61 (SD 1.96), and 3.04 (SD 0.36), respectively. Notably, total CIPN symptoms were not associated with medical history, such as body mass index, diabetes, hypertension, or combined targeted therapy or immunotherapy. However, older age, more accumulated time or cycles of chemotherapy, and treatment with Albumin paclitaxel or additional platinum agents were significantly associated with greater total CIPN symptoms ($P < 0.05$). Similar associations were observed for CIPN sensory impairment, indicating a higher risk in patients with older age, increased accumulated time or cycles of chemotherapy, and those treated with Albumin paclitaxel or additional platinum agents ($P < 0.05$). Furthermore, the relationship between CIPN sensory impairment and risk factors, such as older age, more accumulated time or cycles of chemotherapy, and treatment with albumin paclitaxel, was identified ($P < 0.05$). Specifically, accumulated chemotherapy time (<5 years vs. ≥ 5 years) showed statistical significance in both univariate and multivariate analyses in predicting sensory and motor neuropathy ($P < 0.05$). Given the growing number of older patients developing cancer, older age (>65 years, 25%) in our study appears to be a common and important risk factor for both CIPN sensory and motor impairment.

To conclude, older age, longer duration or more cycles of chemotherapy, and treatment with albumin paclitaxel or additional platinum agents should be recognized as risk factors for CIPN development in paclitaxel-based chemotherapy for patients with breast cancer. Establishing more robust, evidence-based analyses of CIPN in the future is crucial for confirming the clinical impact factors contributing to increased incidence or severity. Identifying high-risk patients becomes easier with a comprehensive understanding of these factors.

Keywords: Peripheral neuropathy; EORTCQLQ-CIPN20 ;breast cancer

1.Introduction

The incidence of breast cancer exhibits significant variation globally (27 in 100,000 in Africa and East Asia), with a worldwide mortality-to-incidence ratio of 15% ^[1]. Paclitaxel stands out as a major chemotherapeutic agent for both early and metastatic breast cancer, serving as a first-line taxane-based treatment. However, its use is associated with chemotherapy-induced peripheral neuropathy (CIPN), a dose-duration adverse event that adversely affects the quality of life of patients with breast cancer. CIPN often leads to limitations in cumulative doses or even discontinuation of treatment ^[2].

The peripheral neuropathy induced by chemotherapy manifests as sensory loss, paresthesia, dysesthesia, numbness, tingling, and eventual motor function loss, often accompanied by neuropathic pain described as a “stocking and glove” distribution ^[3, 4]. The pathophysiological mechanisms underlying CIPN involve immune-related processes, neuro-inflammatory responses in the nervous system, axonal repair, mitochondrial dysfunction, and DNA damage ^[1, 2, 5]. Efforts to standardize and facilitate the diagnosis and severity evaluation of polyneuropathy

have been made by England JD et al., including the development of a case definition for distal symmetric polyneuropathy ^[6].

Understanding risk factors for Paclitaxel-related neuropathy side effects, a subject of controversy, becomes pivotal for patient management. Factors, such as age, sex, treatment duration, treatment agents, and mental state, are among the major considerations for patients undergoing Paclitaxel-based chemotherapy. The challenge lies in selecting an optimal assessment tool to quantify and compare CIPN symptoms from the patient's perspective. Various measures have been established, including the Cancer-Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-NTX) and the abbreviated version of the Total Neuropathy Score (TNS), though some have shown limitations in treatment response sensitivity in clinical patients ^[7, 9].

One subject/patient-reported outcome measure garnering attention is the European Organization of Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-CIPN twenty-item scale (QLQ-CIPN20) ^[10-12]. Previous research by Postma and colleagues demonstrated promising internal consistency reliability and content validity, with Cronbach's alpha coefficients of 0.82, 0.73, and 0.76 for the sensory, motor, and autonomic scales, respectively ^[13]. However, this study emphasizes the need for expanded evidence across various measurement properties, including construct and convergent validity, responsiveness to change over time, and reliability, when applied to diverse populations.

Given the limited evidence from Postma et al.'s paper, this secondary data analysis aims to contribute to the empirical evidence concerning the QLQ-CIPN20's internal consistency reliability, construct and convergent validity, and responsiveness to change over time. Such efforts are crucial for enhancing the understanding of CIPN measurement tools and their application in diverse patient populations.

2. Materials and Methods

2.1 Study design, setting, and patient data collection

The patient characteristics like age, body mass index (BMI), initial metastasis status, medical history, and present medical conditions, such as diabetes and hypertension were included. The association between the personal characteristics (age) history of labor pain, body mass index [BMI], smoker, marital status, history of chronic disease) and disease/treatment (stage, previous and current treatment interventions, combined target therapy), occurrence and severity of CIPN were assessed.

The QLQ-CIPN20 QLQ-BR23 questionnaire

The CIPN20 is a 20-item self-report questionnaire of EORTC Quality of Life

The CIPN20 is a 20-item self-report questionnaire within the EORTC Quality of Life Questionnaire and is designed to assess motor (8 items), sensory (9

items), and autonomic symptoms (3 items). Respondents rate their experiences on a 4-point Likert scale (1 = “not at all,” 2 = “a little,” 3 = “quite a bit,” and 4 = “very much”), providing a numerical representation of the degree of each item. The sensory subscale scores range from 1 to 36, motor subscale scores range from 1 to 32, and autonomic sensory subscale scores range from 1 to 12 for men and 1 to 8 for women (excluding the erectile function item). Additionally, summary scores, termed CIPN20 sum1-19, are calculated on a scale from 0 to 76 ^[1].

Item 20, related to male erectile function, was initially included in the CIPN20 sum1-19 score. However, due to the inclusion of only female patients in our dataset and a zero response rate for this question, item 20 was eventually excluded from the CIPN20 sum1-19 score for the analysis. It is noteworthy that despite its exclusion from the analysis, the rationale for this decision is explicitly acknowledged.

2.2 Statistic analysis

Pre-specified hypotheses were tested using appropriate bivariate statistical tests, including independent sample t-tests, Chi-square tests, Pearson’s correlation, and linear regression. Analysis of the association of age, total dose of paclitaxel, and addition of chemotherapy agents was conducted using Multivariate linear regression. A p value less than 0.05 was considered statistically significant.

3. Results

3.1 General Characteristics of patients(N=192)

One hundred ninety-six women with a mean age of 52.11 years (SD 10.92) were in stages I–II (47.91%), III (25.52%), and IV(26.56%)at the time of the survey in Tianjin Medical University Cancer Institute and Hospital since July 2021 to September 2021. About 23.96% underwent chemotherapy combined with Platinum (7.81%), Anthracycline (9.38%), and Cyclophosphamide, while 60.42% received Paclitaxel alone. The mean cycle needed for patients to be diagnosed was 3.57 (SD 112.9). QLQ–CIPN20 mean scores for the total, sensory, motor, and autonomic scales were 21.41 (SD 4.88), 10.76 (SD 3.19), and 7.61 (SD 1.96), and 3.04 (SD 0.36) respectively.

Table1. Baseline of breast cancer patients receiving medical treatment

General situation			Pathology and Molecular Type		
Characteristic	N	%	Characteristic	N	%
Age			ER status		
≤35	19	9.9	Positive	120	62.5
36-60	125	65.1	Negative	60	31.3
>60	48	25	Unknown	12	6.2
BMI			PR status		
<25	117	60.9	Positive	96	50.0

25-30	60	31.3	Negative	88	45.8
>30	15	7.8	Unknown	9	4.7
Menstrual status			Her-2 status		
Premenopause	32	16.7	Positive	66	34.4
Postmenopause	160	83.3	Negative	96	50.0
Smoke			Unknown	30	15.6
No	188	97.9	Ki-67 Index		
Yes	4	2.1	≤14%	10	5.2
Alcohol			>14%	162	84.4
No	2	1.0	Unknown	20	10.4
Yes	190	99.0	TNM Stage		
Hypertension			I	25	13.0
No	173	90.1	II	67	34.9
Yes	19	9.9	III	49	25.5
Diabetes Mellitus			IV	51	26.6
No	178	92.7			
Yes	14	7.3			

Type Of Medications			Duration Of Therapy		
Characteristic	N	%	Characteristic	N	%
Additional agent			ATC		
Platinum-based	46	24.0	≤5 years	187	97.4
Anthracycline	15	7.8	>5 years	5	2.6
Cyclophosphamide	18	9.4	Cycles of chemotherapy		
Paclitaxel alone	113	58.9	1	53	27.6
Paclitaxel regimen			2-3	48	30.2
Albumin paclitaxel	68	35.4	4-5	42	21.9
Paclitaxel	33	17.2	more than 5	39	20.3
Docetaxel	91	47.4	ITC		
Targeted therapy			1 week	8	4.2
Yes	69	35.9	2 week	13	6.8
No	123	64.1	3 week	171	89.1

3.2



Numbness in the toes or feet and in the fingers or hands were the most frequently symptoms in our study. Specifically, no patients reported not experiencing cramp in feet, difficulty hearing, or blurred vision. Shooting or burning pain in toes or feet and difficulty climbing chairs or getting up out of a chair was reported infrequently, with on less than 10% of participants scoring a mean greater than 1. All items spanned the full score range of 1 to 4. The response distributions are illustrated in Fig. 2.

3.3 Risk factors of CIPN20 scale in univariate and multivariate analysis

Patients with older age, longer duration or more cycles of chemotherapy, and those treated with albumin paclitaxel or with additional platinum agents were significantly associated with greater total CIPN symptoms ($P < 0.05$). CIPN sensory impairment was also significantly greater for patients with older age, longer duration or more cycles of chemotherapy, and those treated with albumin paclitaxel or with additional platinum agents ($P < 0.05$). The relationship between CIPN sensory impairment and the risk factors, such as older age, longer duration or more cycles of chemotherapy, and with albumin paclitaxel, was also identified ($P < 0.05$). In particular, accumulation chemotherapy time (< 5 years vs. ≥ 5 years) was either statistically significant in univariate and multivariate analyses, in its ability to predict sensory neuropathy and motor neuropathy ($P < 0.05$). Since there is supporting clinical evidence for a growing number of older patients developing cancer, older age (> 65 years, 25%) in our research seems to be more common and an important risk factor for both CIPN sensory and motor impairment.

Table 3. Risk factors of total CIPN20 scale in univariate and multivariate analysis

Patient (n=192)	N	Univariate		Multivariate
		P	β	P
Age				
≤35	19	0.004*	0.172	0.041*
36-60	125			
>60	48			
Additional agent		<0.033*	0.043	0.432
Platinum-based	46			
Anthracycline	15			
Cyclophosphamide	18			
Paclitaxel alone	113			
Paclitaxel regimen		<0.0001*	-0.259	0.143
Paclitaxel	117			
Docetaxel	60			
Albumin paclitaxel	15			
Accumulation time of chemotherapy		0.0062*	0.122	0.0432*
≤5 years	184			
>5 years	8			
Cycles of chemotherapy		0.0019*	0.227	0.30
1-5	153			
6-10	34			
>10	5			
Interval time of chemotherapy		0.7195		
1 week	8			
2 week	13			
3 week	171			
Immunotherapy		0.1631		
Yes	19			
No	173			
BMI		0.2283		
<25				
25-30				
>30				
Menstrual status		0.0728		
Premenstrual				
Postmenopausal				
Targeted therapy		0.2174		
Transtuzumab	16			
Transtuzumab+pertuzumab	33			
Bev	20			
None	123			

Table 4. Risk factors of sense scale in univariate and multivariate analysis

	Sense scale		
	N	Univariate	Multivariate
Age			
≤35	19	0.0206*	0.026*
36-60	125		
>60	48		
Additional agent		0.0163*	0.367
Platinum-based	46		
Anthracycline	15		
Cyclophosphamide	18		
Paclitaxel alone	113		
Paclitaxel regimen		<0.0001*	0.012
Paclitaxel	117		
Docetaxel	60		
Albumin paclitaxel	15		
Accumulation time of chemotherapy		0.0031*	0.047*
≤5 years	184		
>5 years	8		
Cycles of chemotherapy		0.0001*	0.143
1-5	153		
6-10	34		
>10	5		
Interval time of chemotherapy		0.6656	
1 week	8		
2 week	13		
3 week	171		
Immunotherapy		0.1608	
Yes	19		
No	173		
BMI		0.1733	
<25			
25-30			
>30			
Menstrual status		0.0857	
Premenstrual			
Postmenopausal			
Targeted therapy		0.3571	
Transtuzumab	16		
Transtuzumab+pertuzumab	33		
Bev	20		
None	123		

Table 5. Risk factors of motor scale in univariate and multivariate analysis

	N	Motor scale	
		Univariate	Multivariate
Age			
≤35	19	0.0016	0.196
36-60	125		
>60	48		
Additional agent		0.2577	0.604
Platinum-based	46		
Anthracycline	15		
Cyclophosphamide	18		
Paclitaxel alone	113		
Paclitaxel regimen		0.0034	0.992
Paclitaxel	117		
Docetaxel	60		
Albumin paclitaxel	15		
Accumulation time of chemotherapy		0.0401*	0.042*
≤5 years	184		
>5 years	8		
Cycles of chemotherapy		0.3307	0.534
1-5	153		
6-10	34		
>10	5		
Interval time of chemotherapy		0.8928	
1 week	8		
2 week	13		
3 week	171		
Immunotherapy		0.2044	
Yes	19		
No	173		
BMI		0.4369	
<25			
25-30			
>30			
Menstrual status		0.1224	
Premenstrual			
Postmenopausal			
Targeted therapy		0.2937	
Transtuzumab	16		
Transtuzumab+pertuzumab	33		
Bev	20		
None	123		

		Auto scale	
	N	Univariate	Multivariate
Age			
≤35	19	0.5627	
36-60	125		
>60	48		
Additional agent		0.7140	
Platinum-based	46		
Anthracycline	15		
Cyclophosphamide	18		
Paclitaxel alone	113		
Paclitaxel regimen		0.7392	
Paclitaxel	117		
Docetaxel	60		
Albumin paclitaxel	15		
Accumulation time of chemotherapy		0.7706	
≤5 years	184		
>5 years	8		
Cycles of chemotherapy		0.076	
1-5	153		
6-10	34		
>10	5		
Interval time of chemotherapy		0.8871	
1 week	8		
2 week	13		
3 week	171		
Immunotherapy		0.6431	
Yes	19		
No	173		
BMI		0.7131	
<25			
25-30			
>30			
Menstrual status		0.5316	
Premenstrual			
Postmenopausal			
Targeted therapy		0.1897	
Transtuzumab	16		
Transtuzumab+pertuzumab	33		
Bev	20		
None	123		

Discussion

The validity of CIPN measurement is critically important and requires enhancement in the future for objective participant descriptions. The new gold standard CIPN measurement version, QLQ-CIPN20^[10, 11], has been extensively utilized in multiple previous trials across three domains: sensory, motor, and autonomic. Alternatively, future intervention trials should adopt a gold standard CIPN measurement approach involving only the best items, facilitating comparisons with trials that used QLQ-CIPN20^{[12] [13]}.

The internal consistency reliability of each QLQ-CIPN20 item was assessed, revealing that dizziness, blurred vision, and erectile dysfunction may present as non-CIPN-related problems. The EORTC QLQ-CIPN20, a 20-item CIPN measure, generally covers three domains: sensory, motor, and autonomic. The FACT/GOG-Ntx subscale^[14] includes 11 items covering four main domains, including motor, sensory, hearing, and dysfunction.

The association between personal characteristics (age, history of labor pain, BMI, smoking status, marital status, career, history of chronic disease) and disease/treatment factors (stage, previous and current treatment interventions, combined target therapy) with the occurrence and severity of CIPN was recorded. Previous studies suggest that older age patients with cancer are more at risk of paclitaxel-induced neuropathy^[15, 16]. However, CALGB 40101 demonstrated that older age is not an independent risk factor for paclitaxel-induced peripheral neuropathy, with obesity and a 2-week paclitaxel regimen showing significant contrary associations^[5, 8]. A high BMI is significantly associated with the occurrence of chronic neurotoxicity in patients with colon cancer receiving capecitabine and oxaliplatin^[17, 18].

Novel genetic predictors involved in paclitaxel-induced peripheral neuropathy, such as FGD4^[19], have been identified in genome-wide association studies. The 2020 ASCO guideline recommends prevention and treatment approaches for managing chemotherapy-induced peripheral neuropathy (CIPN) in adult cancer survivors. The use of preventive treatment for CIPN in patients with malignant tumors should be actively discouraged. Furthermore, clinicians and researchers adopt several approaches to assess appropriateness, including dose reduction, treatment alternatives, or stopping chemotherapy, in patients already experiencing CIPN^[20]. Further clinical and preclinical studies are necessary to clarify the molecular mechanisms underlying the involvement of altered estrogen levels in CIPN.

Conclusion:

In conclusion, older age, longer duration or more cycles of chemotherapy, and treatment with albumin paclitaxel or with additional platinum agents should be considered as risk factors for CIPN development in paclitaxel-based chemo-

therapy of patients with breast cancer. It will be important to establish more robust, evidence-based analyses of CIPN in the future to verify supporting clinical evidence for the impact factors in the increased incidence or severity of CIPN, which can easily be identified as high-risk patients.

Supplementary Materials:

Author Contributions:

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