A Prospective Study of Risk Factors for Taxane-induced Peripheral Neuropathy in Patients With Breast Cancer

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Abstract

Purpose: The study investigated the clinical risk factors of peripheral neuropathy induced by docetaxel and albumin-bound paclitaxel (AP) in breast cancer patients.

Methods: A prospective observational study was performed in 268 patients from March 2019 to December 2020, related information of patients can be obtained by querying the electronic system, consulting the patient and evaluating the scale, neuropathic symptoms are followed up from the beginning to three months after taxane drug chemotherapy. Univariate and multivariate analysis were used to find the risk factors of overall and severe taxane-induced peripheral neuropathy (TIPN).

Results: The cumulative dose ($OR=3.533$, 95% CI : $1.797\sim6.944$, $p<0.001$), body mass index (BMI) ($OR=2.926$, 95% CI : $1.621\sim5.281$, $p<0.001$), body surface area (BSA) ($OR=1.724$, 95% CI : $1.011\sim2.941$, $p=0.045$), hypocalcemia ($OR=4.899$, 95% CI : $1.518\sim15.811$, $P=0.008$) all increased the risk of TIPN, only cumulative dose ($OR=2.577$, 95% CI : $1.161\sim5.719$, $p=0.020$) and BSA ($OR=2.040$, 95% CI : $1.073\sim3.877$, $p=0.030$) were independent risk factors for severe TIPN.

Conclusion: Cumulative dose, BMI, BSA, and hypocalcemia are risk factors for overall TIPN, while cumulative dose and BSA are risk factors for severe TIPN. Breast cancer patients, those with high BMI and large BSA, hypocalcemia and large cumulative dose can be closely followed by TIPN, preventive intervention measures actively carried out.

Introduction

Breast cancer is a common malignant tumor in women. In the latest global cancer burden data for 2020 released by the World Health Organization's International Agency for Research on Cancer (IARC), breast cancer has surpassed lung cancer as the world's largest cancer. Taxane, which typically include paclitaxel, docetaxel and albumin-bound paclitaxel (AP), play an indispensable role in neoadjuvant, post-operative adjuvant and palliative treatment of breast cancer^[1]. Although docetaxel and AP are dosage forms designed to lower the dose or toxicity of paclitaxel, peripheral neuropathy is a prevalent side effect of all three medications that significantly limits treatment^[2]. Peripheral neuropathy can affect a patient's treatment process by reducing or stopping chemotherapy doses^[3], as well as their quality of life, such as difficulty feeling small objects and walking, which can lead to gait instability and an increased risk of falling^[4], and symptoms may not disappear even if the cancer is expected to be cured^[5]. As cancer survival rates continue to improve, the disease burden of peripheral neuropathy is garnering increased attention.

Many factors may influence the occurrence of Taxane-induced peripheral neuropathy (TIPN), except for the widely recognized significant correlation with dose accumulation, whether other factors such as patient age^[6, 7], body mass index (BMI)^[8, 9], history of diabetes^[10, 11], hypoproteinemia^[12] and concomitant medications^[13, 14] are relevant is debatable, potential predictors of TIPN have not been fully investigated,

and more studies have focused on paclitaxel. In recent years, docetaxel and AP have steadily gained a foothold in the treatment of breast cancer, gradually displacing paclitaxel^[6–14]. There are a few studies on the influencing factors of the two in the treatment of breast cancer leading to peripheral neuropathy. Therefore, this study conducted a prospective observational study to more thoroughly explore the risk factors of peripheral neuropathy in breast cancer patients receiving docetaxel and AP therapy, in order to provide new information that will aid clinicians more accurately predict which patients are at increased risk for peripheral neuropathy.

Materials And Methods

Patients: breast cancer patients receiving taxane (AP or docetaxel) as the base drug for chemotherapy were recruited from March 2019 to December 2020 from tertiary hospital(Fujian Province, China), eligible patients were Asian females, ≥ 18 years of age, with pathologically cytologically confirmed breast cancer and a 21-day chemotherapy regimen cycle, receiving ≥ 2 courses of total chemotherapy, with an expected survival time of ≥ 3 months. Exclusion criteria included the combination of other peripheral neuropathic agents (platinum and vincristine, proteasome inhibitors, thalidomide derivatives) or concomitant use of two taxane drugs during treatment, the presence of prior peripheral neuropathy due to diabetes or any other cause, the use of paclitaxel or other peripheral neuropathic agents prior to the current chemotherapy, the development of brain metastases or death during chemotherapy, and a history of polymyositis, renal failure, and liver failure. This study was approved by the local internal Ethics Review Board, Ethics NO [2020](285).

Clinical data: Before beginning treatment with the taxane, all patients had recorded basic demographic data, including age, height and weight, history of infectious diseases, comorbid diseases, with underwent pathological cytological examination to confirm cancer and immunohistochemical examination to clarify genotyping, recording through the electronic medical record system. Using the laboratory test results query system to record the largest values of abnormal laboratory test indicators from the beginning to the end of taxane chemotherapy, including cytopenia indicators (white blood cells, neutrophils, hemoglobin, lymphocytes), abnormal indexes of liver and kidney functions (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, glutamate transferase, serum creatinine, lactate dehydrogenase), abnormal indexes of electrolytes (calcium, phosphorus, sodium, potassium), abnormal indexes of blood lipids (total serum cholesterol, triglyceride), and concomitant medications during chemotherapy period(glutathione, vitamin B6, statins, beta-blockers, etc.).

Neurotoxicity assessment: Neuropathic symptoms were obtained through in-patient and out-of-hospital telephone follow-up or patient self-reporting from the initial to three months after taxane drug chemotherapy, and then a structured interview was conducted with symptomatic patients, covering eight questions on the FACT/GOG-Ntx(Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity) questionnaire except hearing^[15], with the addition of weakness in limbs or joint stiffness in hands or feet, based on actual situation and referring to the questionnaire evaluation method of Sánchez et al^[16]. The most severe peripheral neuropathy symptoms of all patients were assessed and

graded according to NCI-CTCAE (National Cancer Institute Common Toxicity Criteria for Adverse Events) version 5 grading scale^[17], which defines grade 2 and above neurotoxicity as "Loss of objective sensation or paresthesia ,affecting function, or even affecting daily life and requiring assistive devices". In this study, grade II and above neurotoxicity was defined as severe neurotoxicity(Table.1).

Statistical methods: The data collected were statistical analyzed by SPSS 24.0 software. First, the chi-squared test was used to conduct univariate analysis of the study's counting data. Then the variables that were statistically significant ($P<0.05$) in the univariate analysis were incorporated into binary logistic regression model analysis, screening the risk factors associated with the occurrence of TIPN. Finally, the fitting of the regression model was evaluated using Hosmer-lemeshow test, using area under the curve (AUC) with receiver operating characteristic(ROC) to evaluate predictive effect of the regression model.

Table 1

Taxane-induced peripheral neuropathy characteristics of the 268 patients included in the study

Neuropathy items evaluated	Grade of TIPN		
	Grade1 ^a	Grade 2 ^b	Grade 3 ^c
Numbness, tingling or discomfort in hands or feet (FACT/GOG-Ntx questions 1-4)	43	29	9
Myalgia. Joint pain or muscle cramps (FACT/GOG-Ntx question 5)	17	9	3
Trouble buttoning buttons, feeling shape of objects, or trouble walking (FACT/GOG-Ntx questions8,9,AN6)	20	15	4
Weakness in limbs or joint stiffness in hands or feet (additional questions)	28	12	6
TIPN, Taxane-induced peripheral neuropathy; FACT/GOG-Ntx, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity.			
a:Mild and intermittent symptoms that did not affect activities of daily living (ADL). b:Symptoms did not affect self-care ADL. c:Symptoms affect self-care ADL			

Results

1. Study population.

A total of 268 patients were enrolled in this study (Table.2), with a median age of 49 years, BMI and BSA were 23.04 and 1.60 respectively. Of these, 72 patients were reported other comorbidities(hypertension, diabetes, depression, hyperthyroidism, asymptomatic myocardial ischemia, esophagitis and other diseases). Only two comorbid diseases, hypertension and diabetes, were included in the study because of the high number of patients of combined hypertension and diabetes, while other diseases could not be

analysed due to small number of patients. Thirty-five patients had recorded infectious diseases, the majority of which were hepatitis B, and very few patients had other infectious diseases such as syphilis or HIV, so only hepatitis B was included in the statistical analysis.

2. Rate of peripheral neuropathy induced by docetaxel and AP

Neurotoxicity during taxane treatment was systematically assessed. 85 patients had signs of neuropathy, including 47 Grade I, 29 Grade II, 9 Grade III, and no Grade IV. There were 211 patients receiving docetaxel chemotherapy, 53(25.12%) patients of TIPN occurred, 9.95% of grade II or higher TIPN, while 57 patients were treated with AP chemotherapy, 32(56.14%) patients of TIPN occurred, 29.82% of grade II or higher TIPN.

3. Univariate and multivariate analysis to determine risk factors of TIPN

The univariate analysis of kinds of variables and rates of TIPN shown in Table. 3, a history of diabetes in co-morbidities, hypocalcemia in laboratory test indicators, and coadministration of COX-2 inhibitors during chemotherapy all showed association with the occurrence of TIPN. The incidence of TIPN was significantly higher in patients with higher BMI, larger BSA, and higher cumulative dose, who had chemotherapy more frequent. Cancer stage and coadministration of beta-blockers during chemotherapy only showed a statistically significant correlation with the occurrence of total TIPN.

In the final binary logistic regression model (Fig. 1), $P < 0.05$ was used as the basis for determining that variables were statistically significant. Cumulative dose (OR=3.533, $p < 0.001$), BMI (OR=2.926, $p < 0.001$), BSA (OR=1.724, $p = 0.045$), and hypocalcemia (OR=4.899, $p = 0.008$) all increased the risk of total TIPN occurrence, and cancer stage (OR = 1.542, $p = 0.062$) had a trend although there was no statistical difference in the logistic regression model. While only cumulative dose (OR=2.577, $p = 0.020$) and BSA (OR=2.040, $p = 0.030$) could increase the incidence of severe TIPN, were independent risk factors of severe TIPN.

4. The fitting and predictive effect of regression model

Using the Hosmer-lemeshow test to evaluate the fitting effect of the logistic regression models employed in the above multifactor analysis, the P values of both the total and severe TIPN binary logistic regression models were much greater than 0.1 (Overall TIPN: $P = 0.77$; Severe TIPN: $P = 0.89$), which proved that the fitting effect of these two regression models was available; using the area under the ROC curve (AUC) similarly to evaluate the prediction effects of the logistic regression models employed in the above multivariate analysis (Fig. 2), the area under the ROC curve (AUC) was higher than 0.5 in both the total and severe TIPN binary logistic regression models, indicating that the prediction models had satisfactory prediction effects.

Table 2
Characteristics of patients (n = 268)

Characteristics		n (%)
Age,median	≥60	37(13.81)
	<60	231(86.19)
Hypertension	with	37(13.81)
	without	231(86.19)
Diabetes	with	30(11.19)
	without	238(88.81)
BMI	<22	175(65.30)
	≥24	93(34.70)
BSA	≤1.5	48(17.91)
	1.5-1.60	85(31.72)
	1.61-1.7	84(31.34)
	>1.7	51(19.03)
Tumor stage	I	53(19.78)
	II	131(48.88)
	III-IV	84(31.34)
Gene type	luminal A	110(41.04)
	luminal B	32(11.94)
	HER-2+(HR-)	50(18.66)
	HER-2+(HR+)	48(17.91)
	Triple-negative	28(10.45)
Chemotherapy treatment	AC-T, AC-TH, AC-THP	200(74.63)
	TAC	22(8.21)
	TC,TCH	30(11.19)
	Others	16(5.97)
A,anthracyclines C:cyclophosphamide T:taxane H:Trastuzumab P:Pertuzumab F: fluorouraci		
AC-T, AC-TH, AC-THP: 3-4 cycles of chemotherapy with anthracycline (doxorubicin,pharmorubicin, pirarubicin) and cyclophosphamide were followed by taxane drugs, with trastuzumab and/or pertuzumab added to patients of HER-2+ genotype		

Characteristics	n (%)
TAC: Anthracyclines+cyclophosphamide and taxane are used in the same chemotherapy cycle, Cyclophosphamide and taxane are used in the same chemotherapy cycle, with trastuzumab and/or pertuzumab added to patients of HER-2+ genotype	
Other chemotherapy regimens: TA regimen (taxane and anthracyclines), TX(H) regimen (taxane,capecitabine and/or trastuzumab), TH(P) regimen (taxane, trastuzumab and/or pertuzumab), FEC-T regimen (3-4 cycles of chemotherapy with cyclophosphamide, anthracyclines and fluorouracil were followed by taxane drugs)	

Table 3
univariate analysis of between variables and risk of TIPN

Variables		Overall TIPN(%)	P	Severe TIPN(%)	P
Age	≥60	16(18.8)	0.105	4(10.5)	0.527
	<60	69(81.2)		34(89.5)	
Hypertension		16(18.8)	0.105	7(18.4)	0.373
Diabetes		15(17.6)	0.022	9(23.7)	0.018
Hepatitis B		9(10.6)	0.482	3(7.9)	0.487
BMI	<22	7(8.2)	<0.001	2(5.3)	<0.001
	22-24	24(28.2)		11(28.9)	
	≥24	54(63.5)		25(65.8)	
BSA	≤1.5	3(3.5)	<0.001	1(2.6)	<0.001
	1.5-1.60	13(15.3)		4(10.5)	
	1.61-1.7	33(38.8)		13(34.2)	
	>1.7	36(42.4)		20(52.6)	
Cancer stage	I	15(17.6)	0.038	5(13.2)	0.111
	II	38(44.7)		17(44.7)	
	III	23(27.1)		11(28.9)	
	IV	9(10.6)		5(13.2)	
Chemotherapy cycles	>4	21(24.7)	<0.001	10(26.3)	0.016
	≤ 4	64(75.3)		28(73.7)	
Gene type	lunimal A	36(42.4)	0.653	15(39.5)	0.987
	lunimal B	10(11.8)		4(10.5)	
	HER-2+(HR-)	14(16.5)		7(18.4)	
	HER-2+(HR+)	13(15.3)		8(21.1)	
	triple-negative	12(14.1)		4(10.5)	
Docetaxel cumulative dose	<500	2(3.8)	<0.001	1(4.8)	<0.001
	500-610	29(54.7)		10(47.6)	
	>610	22(41.5)		10(47.6)	

Variables		Overall TIPN(%)	P	Severe TIPN(%)	P
AP cumulative dose	<1800	17(53.1)	0.014	8(47.1)	0.041
	≥ 1800	15(46.9)		9(52.9)	
Hypoleucocytosis		40(47.1)	0.173	19(50.0)	0.226
Neutropenia		40(47.1)	0.395	19(50.0)	0.367
Hemoglobin decreased		23(27.1)	0.142	10(26.3)	0.450
Lymphocytopenia		42(49.4)	0.384	17(44.7)	0.916
ALT goes up		38(44.7)	0.879	21(55.3)	0.132
AST goes up		34(40.0)	0.377	18(47.4)	0.122
ALP goes up		25(29.4)	0.097	11(28.9)	0.359
γ-GGP goes up		29(34.1)	0.104	15(39.5)	0.077
LDH goes up		29(34.1)	0.154	11(28.9)	0.931
Cr goes down		19(22.4)	0.196	9(23.7)	0.316
Hypocalcemia		16(18.8)	0.001	8(21.1)	0.033
Hyperphosphatemia		26(30.6)	0.518	14(36.8)	0.189
Hyponatremia		4(4.7)	0.994	3(7.9)	0.407

Continue Table 3 univariate analysis of between variables and risk of TIPN

Variables	Overall TIPN(%)	P	Severe TIPN(%)	P
Total cholesterol goes up	45(52.9)	0.795	20(52.6)	0.844
Triglycerides	43(50.6)	0.119	19(50.0)	0.395
Estazolam	18(21.2)	0.152	9(23.7)	0.192
Cox-2 inhibitors	23(27.1)	0.002	11(28.9)	0.030
Antibiotics	4(4.7)	0.994	3(7.9)	0.407
Glutathione	29(34.1)	0.448	15(39.5)	0.221
Glycyrrhizic acid glycosides	32(37.6)	0.604	17(44.7)	0.513
Polyene phosphatidyl choline	35(41.2)	0.154	17(44.7)	0.178
Vitamin B6	4(4.7)	0.194	3(7.9)	1.000
β-blocker	10(11.8)	0.013	3(7.9)	0.717
Statins	8(9.4)	0.858	3(7.9)	1.000
Fibrates	5(5.9)	1.000	3(7.9)	0.776
CCB	10(11.8)	0.103	5(13.2)	0.321
ACEI/ARB	9(10.6)	0.128	5(13.2)	0.218

Discussion

This study assessed the clinical risk factors for peripheral neuropathy caused by the progressively more widely used but less explored taxane drugs (AP and docetaxel) in breast cancer treatment through a prospective observational design study that extensively explored controversial and potential predictors. The results of univariate and multivariate analyses showed that cumulative dose, BMI, BSA, and hypocalcemia all increased the risk of overall TIPN, while only cumulative dose and BSA were independent risk factors of severe TIPN. After the area under the ROC curve and the Hosmer-lemeshow test respectively, the regression model showed favourable prediction and fitting effect.

Consistent with the findings of many studies^[8,16,18–21], cumulative dose is an independent risk factor for the development of TIPN. The incidence of TIPN has been significantly increased at cumulative doses of docetaxel ≥ 500 mg and AP ≥ 1800 mg, suggesting that special attention should be paid to the prevention and treatment of TIPN when reaching this dose during clinical use. Another study by Molassiotis et al^[22] showed that the number of chemotherapy cycles received was correlated with the occurrence of peripheral neuropathy, thus peripheral neuropathy was time-dependent rather than dose-dependent, which was inconsistent with traditional literature reports. In the present study, the number of

chemotherapy cycles received only showed an association in univariate analysis, and considering that the dosing regimens and doses given to patients vary in clinical use, it is considered that determining the occurrence of TIPN based on the number of chemotherapy treatments is somewhat inadequate, the cumulative dose is more appropriate as a predictor.

Both in univariate and multivariate analyses, high BMI and BSA of patients were significantly different than low BMI and BSA. In particular, BSA was an independent predictor of the occurrence of severe TIPN in this study, which supported the results of previous studies^[7,18-20] that high BMI and BSA were good predictors of the occurrence of TIPN. In general, as the patient's BSA increases, the dose increases accordingly, because taxane are administered referring to BSA that the higher the single dose administered, the higher the cumulative dose from each time, therefore the higher the risk of TIPN occurrence. The link between high BMI and the nervous system is complex, obesity has been found to cause microvascular injury and peripheral nerve dysfunction in animal models^[23], and there is other literature supporting obesity as a risk factor for other types of neuropathy, such as oxaliplatin-induced peripheral neuropathy^[24], diabetic neurological disease^[25], and ulnar neuropathy-like symptoms^[26], but further research is needed to determine how high BMI specifically affects the development of TIPN.

This study showed that the incidence of TIPN in patients with hypocalcemia during the application of taxane drugs was 4.899 times higher than patients without hypocalcemia, which is a new finding in this study. Regarding the study of how blood calcium affects the occurrence of TIPN, it has been reported in the literature that it may be related to voltage-gated calcium channels^[27]. Increased expression of a T-type calcium channel, Cav3.2, was observed in a rodent model of paclitaxel-induced peripheral neuropathy, meanwhile, inhibition of N-type and $\alpha_2\delta$ calcium channels was found to minimize or reverse peripheral neuropathy in a rat model of paclitaxel- and oxaliplatin-induced peripheral neuropathy, and also clinical trials^[28-30] showing that calcium-magnesium supplements can reduce the incidence of peripheral neuropathy. Therefore, the use of taxane in breast cancer patients with hypocalcemia should be noted for the occurrence of TIPN.

In a multivariate analysis of the overall TIPN incidence, there was a trend ($p=0.062$) for cancer stage to influence the occurrence of TIPN, although not statistically different. In a large retrospective cohort study conducted by Song et al^[19], The risk of TIPN was considerably raised in patients with metastatic compared to non-metastatic breast cancer. The reason may be due to the fact that as the cancer stage becomes more advanced, the heavier the tumor burden, the greater the consumption of the organism, the less tolerable the patient to chemotherapy. Conversely, the less therapeutic intensity needs to be in the earlier stage of the cancer, the less therapeutic drugs need to be used, and the dose and cycle of taxane administration are relatively less, thus TIPN should be considered when taxanes are used in patients with advanced cancer stages. In addition, the combination of COX-2 inhibitors or β -blockers may be a risk factor for TIPN in the univariate analysis that supports the findings of Sánchez et al^[17]. Unfortunately, the findings of these two variables did not sustained in the multivariate logistic regression model, probably

on account of the small number of patients taking both drugs in the sample of this study influencing the conclusions. It is hoped that further research and exploration can be carried out in the future.

There are some shortcomings in this study. On the one hand, history of smoking^[31] and alcohol consumption^[32] are potential factors in the development of TIPN. However, it was impossible to statistically analyze such contributing factors thanks to the small number of females with alcohol addiction in the included area. On the other hand, most of the population eligible to requirements for this study were postoperative adjuvant and neoadjuvant patients, and fewer patients were palliative care. According to this and other studies, the risk of TIPN is higher in the later stages of cancer, and it is worthwhile to investigate the risk factors. Notwithstanding, given that patients undergoing postoperative adjuvant and neoadjuvant therapy have a longer survival rate, if the specific population can be screened for active and effective TIPN prevention and treatment, it will improve the quality of life of patients in the future.

In conclusion, this study confirmed that cumulative dose, BMI, BSA, and hypocalcemia are risk factors for the development of TIPN. Therefore, these factors can be taken into account when starting chemotherapy for breast cancer patients in the future. Patients with higher BMI, BSA and hypocalcemia can be considered as candidates for treatment regimens with lower TIPN occurrence, weighing the pros and cons in larger cumulative dose choose whether to switch to other solutions, and patients also can be better educated about the symptoms, then preventive interventions can be taken to improve their quality of life.

Declarations

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Conflicts of interest/Competing interests: The authors declare no competing interests.

Availability of data and material: Not applicable

Code availability: SPSS, version 23.0 (IBM Corp, Armonk, NY) was used for all analyses.

Authors' contributions: All authors contributed to the study conception and design. Data collection and analysis, paper writing and interpretation, manuscript preparation were performed by Cuilv Liang. Study design, data analysis, paper proofreading were performed by Zhang Yin. Data analysis, paper interpretation were performed by Qiying Chen, Wenfa Chen, mingzhu Chen. All authors contributed to this manuscript and have consented to the submission of this paper.

Ethics approval: The work was approved and registered as a observational study by the Ethics Review Board of Sencond Affiliated Hospital of Fujian Medical University (Ethics NO [2020](285).

Consent to participate: This was an observational study, but all treatment plans, diagnoses, and treatment measures had obtained the informed consent of patients and their families.

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Figures

Figure 1

Multivariate analysis of between variables and risk of overall and severe TIPN

Figure 2

ROC Curve for overall TIPN and severe TIPN binary logistic regression models