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ORIGINAL ARTICLE

Incidence of taxane-induced peripheral neuropathy receiving treatment and prescription patterns in patients with breast cancer

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Abstract
Purpose Taxane-induced peripheral neuropathy (TIPN) can affect quality of life and treatment outcomes in breast cancer patients. Despite the high incidence, treatment of PN has not been established. This study aimed to evaluate the incidence, risk factors, and prescribing pattern of TIPN receiving pharmacologic treatment in real-world practice.
Methods We conducted a retrospective chart review of 1629 breast cancer patients who received taxanes at the Seoul National University Hospital from July 2012 to June 2014. We determined the incidence and predictors for TIPN treated with anti-neuropathic pain medications during taxane treatment and the 1-year follow-up period after discontinuation of taxanes. The prescribing pattern of anti-neuropathic drugs was also analyzed.
Results A total of 1516 patients with breast cancer were included, and the incidence of TIPN receiving treatment was 21.9% overall, with 42.2% of patients using paclitaxel and 15.8% using docetaxel. The median time to the first anti-neuropathic pain medication prescribed from the start of taxane treatment was 64 days and was significantly earlier in the paclitaxel group. In 21% of patients, TIPN treatment was started after the end of taxane treatment. Identified risk factors for TIPN were paclitaxel use (vs. docetaxel), old age, overweight, metastatic (vs. non-metastatic) breast cancer, and possibly a 3-weekly taxane schedule (vs. weekly). Gabapentin and pregabalin accounted for 71.7 and 24.3% of total use of anti-neuropathic agents, respectively.
Conclusions One-fifth of breast cancer patients who were treated with taxane-based chemotherapy experienced TIPN receiving treatment, and its risk factors were paclitaxel use, old age, overweight, and metastatic cancer.

Keywords Docetaxel · Paclitaxel · Peripheral neuropathy · Breast cancer · Treatment

Introduction

Taxane-based chemotherapy is used in the management of early-stage and metastatic breast cancer, the most common cancer in women. Taxanes (i.e., paclitaxel and docetaxel) have a well-established efficacy and safety profile in the treatment of breast cancer [1].

Peripheral neuropathy (PN) is a common non-hematological side effect of taxanes, which may result in chemotherapy delays, reductions, or discontinuations and poor quality of life (QOL). Taxane-induced peripheral nerve damage can lead to motor and sensory symptoms such as bilateral paresthesia manifested as numbness, tingling, and burning pain [2]. Symptoms of taxane-induced peripheral neuropathy (TIPN) usually improve or resolve spontaneously after discontinuation, whereas severe symptoms may persist for a longer period [3, 4].

The reported overall incidence of TIPN varies, ranging from 57 to 83% for patients treated with paclitaxel and from 11 to 64% for patients treated with docetaxel, according to the National Comprehensive Cancer Network Task Force Report

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[5]. The incidence depends on previously identified risk factors such as chemotherapeutic agents, dose per cycle, cumulative dose, treatment schedule, infusion time, and comorbidities such as diabetes [2, 6].

Despite its common occurrence, physicians tend to underestimate and underreport the severity and frequency of TIPN among patients [7, 8]. Some patients experience painful and persistent PN and these symptoms affect their ability to perform daily activities and reduce overall QOL [4, 9]. Unfortunately, most clinical trials for pharmacological treatment have not demonstrated a meaningful improvement in neuropathic pain [10–13], except a randomized controlled trial showing positive efficacy of duloxetine for the treatment of chemotherapy-induced peripheral neuropathy (CIPN) in 231 patients [14]. Based on the results from this clinical trial, the American Society of Clinical Oncology (ASCO) started recommending duloxetine for CIPN in 2014 [15]. However, physicians considered that there is no established treatment for CIPN until such recommendation was released by ASCO. Therefore, various medications are commonly used for symptom control to alleviate CIPN in clinical practice. Symptomatic pharmacologic treatments include tricyclic antidepressants, anticonvulsants, and serotonin-norepinephrine uptake inhibitors.

To date, the incidence of TIPN in breast cancer patients is mostly estimated from randomized controlled studies; estimates from real-world practice are usually from surveys or retrospective cohort studies involving a relatively small number of patients. Also, there are limited studies investigating the pharmacological treatment pattern of TIPN in breast cancer patients. Therefore, this study aimed to investigate the incidence and typical pharmacological treatments of TIPN in breast cancer patients.

Methods

This retrospective cohort study was conducted in a single, large-volume tertiary hospital in Korea. This study included adult breast cancer patients treated with taxane-based chemotherapy (docetaxel or paclitaxel) at the Seoul National University Hospital (SNUH) between July 1, 2012, and June 30, 2014. Patients less than 18 years old, foreigners, those having incomplete records, patients who experienced neuropathy before initiating taxane therapy, and those treated with anti-neuropathic drugs for other indications were excluded. The institutional review board of the Seoul National University Hospital approved this study (IRB No. H-1508-139-697).

Data were extracted from electronic medical records. We performed chart reviews for all patients and the following information was collected: demographic characteristics, Eastern Cooperative Oncology Group (ECOG) performance status, comorbidities including diabetes and kidney disease, stage of breast cancer (non-metastatic or metastatic), chemotherapy characteristics such as goal of treatment, duration of treatment, average and cumulative dose, and administration schedule.

The development of TIPN receiving treatment was defined as having newly prescribed anti-neuropathic pain medications during taxane treatment or during the 1-year follow-up period after discontinuation of taxane administration. Onset time was defined as the date of the first prescription for PN after the initiation of taxane treatment. We determined the incidence and predicting factors for TIPN receiving treatment in breast cancer patients. Anti-neuropathic pain medications were defined as anticonvulsants, such as gabapentin, pregabalin, and carbamazepine and antidepressants, such as amitriptyline, nortriptyline, and duloxetine, according to the national guidelines for cancer pain management, sixth edition [16]. Patients were followed until the first year after discontinuation of taxane treatment.

To describe the prescribing pattern of anti-neuropathic pain medications, data regarding the type of anti-neuropathic drugs prescribed, the duration of treatment, and the concomitant analgesic prescriptions were collected. Also, the reasons for discontinuing anti-neuropathic pain medication at 1 month and at 1 year after the treatment starts were obtained from the medical records. For concomitant analgesics, those prescribed for a prophylactic purpose according to institution protocol were excluded.

The cumulative incidence of TIPN receiving treatment is presented with a Kaplan-Meier curve. We used a Cox proportional hazard model to identify the risk factors associated with the development of TIPN and presented an adjusted hazard ratio (aHR) with a corresponding 95% confidence interval (CI). Patients who started another chemotherapeutic regimen, died, or were lost during the follow-up period were censored at the earliest time the event occurred. Descriptive analysis was used for the treatment pattern of anti-neuropathic pain medications. All analyses were performed using SPSS, version 22.0 (SPSS Inc., Chicago, IL, USA). A two-sided $p < 0.05$ was considered statistically significant.

Results

Patient characteristics

Of the 1629 patients screened, 1516 patients were included for the analysis (Fig. 1). More than three quarters of patients ($n = 1165$) received docetaxel while 23.2% of patients were treated with paclitaxel. The study population comprised 70.6% of non-metastatic breast cancer patients and 29.4% of metastatic breast cancer patients. The majority of patients (94.5%) were treated with a 3-weekly taxane schedule. Only

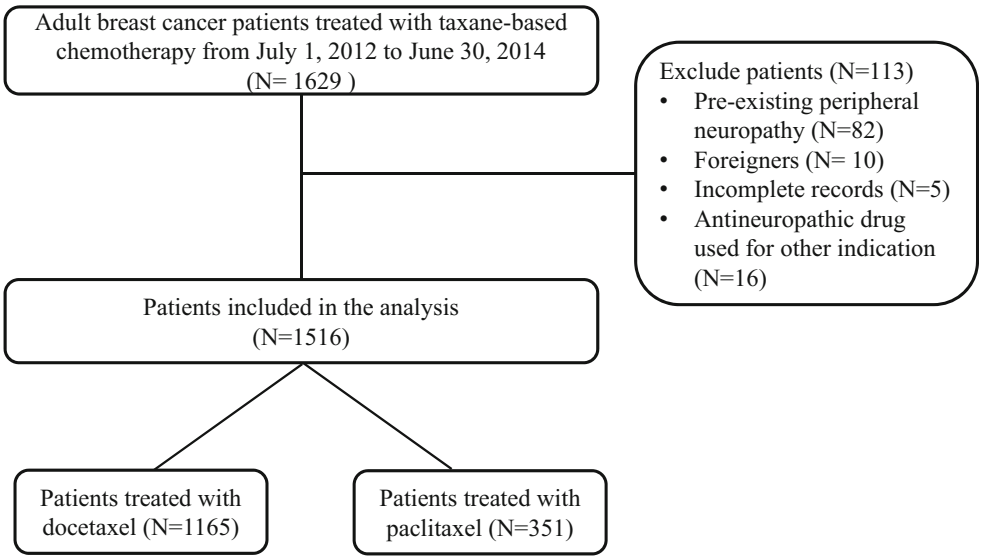

Fig. 1 Patient selection process

6.6 and 0.9% of patients had comorbid diabetes and kidney disease, respectively (Table 1).

Incidence and risk factors for TIPN

Overall, 332 of 1516 patients (21.9%) received pharmacological treatment for TIPN; among them, 33 patients (9.9%) discontinued taxane treatment due to peripheral neuropathy.

A significantly high incidence of TIPN receiving treatment was observed in patients who received paclitaxel compared with docetaxel (42.2 vs. 15.8%, $p < 0.001$) (Fig. 2). The median onset time of PN was 64 days (1–468 days), with a significantly earlier onset time in the paclitaxel group (median, 49 vs. 71 days, $p < 0.001$). Non-metastatic cancer patients showed significant earlier onset compared with metastatic cancer patients (median, 63 vs. 68 days, $p = 0.037$). Onset was not significantly different between a 3-weekly and weekly taxane regimen (63 vs. 82 days, $p = 0.212$).

While 89.9% (133 patients) in the paclitaxel group and 69.0% (127 patients) in the docetaxel group received the first anti-neuropathic agents during taxane treatment, 10.1 and 31.0% of patients in the respective groups started them after the end of taxane treatment. The mean cumulative dose until the start of pharmacologic treatment for TIPN was 254.6 ± 145.0 mg/m^2 for docetaxel and 527.7 ± 434.3 mg/m^2 for paclitaxel.

The identified risk factors for TIPN treatment were paclitaxel use (aHR 2.28, CI 1.72–3.01 compared with docetaxel), age (41–60 years, aHR 2.08 [CI 1.44–3.00], ≥61 years, aHR 2.66 [CI 1.71–4.15], compared with age ≤40 years), overweight (BMI ≥25 kg/m^2, aHR 1.34, CI 1.05–1.70), metastatic breast cancer (aHR 2.13, CI 1.60–2.82 compared with non-metastatic breast cancer), and a 3-weekly taxane schedule (aHR 2.00, CI 1.26–3.19, compared with a weekly schedule) (Table 2).

Table 1 Baseline characteristics of the study cohort (n = 1516)

Variables	Number (%)
Sex (female)	1512 (99.7)
Age (years), median [range]	49 [22–84]
20–40	295 (19.5)
41–60	1033 (68.1)
>60	188 (12.4)
Body mass index (kg/m^2, mean ± SD)	23.3 ± 3.4
<25	1106 (72.9)
≥25	410 (27.0)
ECOG performance score	
<1	748 (49.3)
≥1	729 (48.1)
Unknown	39 (2.6)
Comorbid disease	
Diabetes	100 (6.6)
Kidney disease	13 (0.9)
Cancer stage	
I–III	1070 (70.6)
IV	446 (29.4)
Taxane received	
Docetaxel	1165 (76.8)
Paclitaxel	351 (23.2)
Treatment Setting	
Neo-adjuvant	554 (36.6)
Adjuvant	522 (34.4)
Palliative	440 (29.0)
Administration schedule	
Weekly	83 (5.5)
3-weekly	1433 (94.5)
Treatment duration (days, mean ± SD)	98.5 ± 90.0

ECOG Eastern Cooperative Oncology Group, *SD* standard deviation

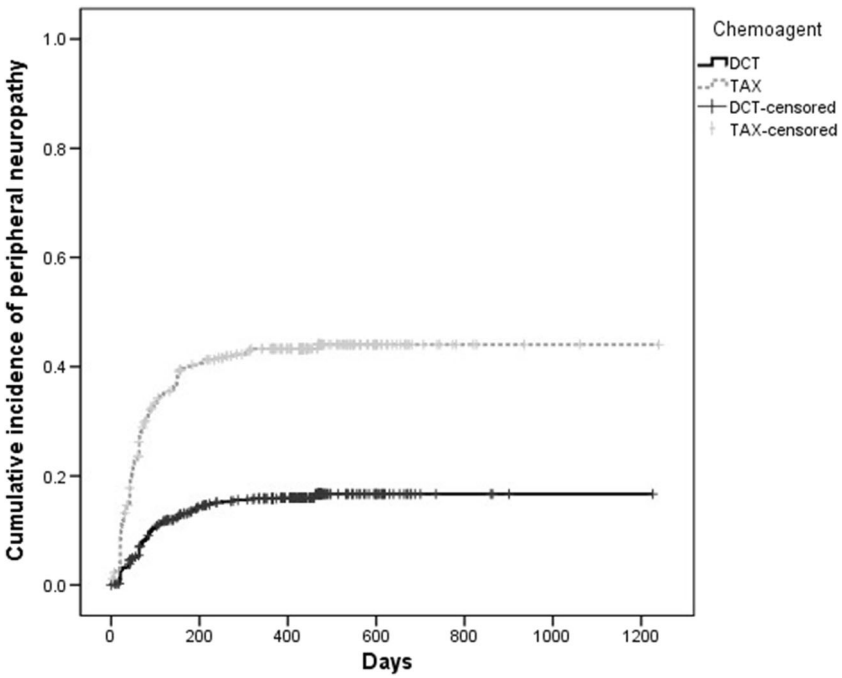

Fig. 2 Cumulative incidence of taxane-induced peripheral neuropathy in patients starting anti-neuropathic pain medications. *DCT* docetaxel, *TAX* paclitaxel

Treatment with anti-neuropathic pain medications

Gabapentin (74.4%) was most commonly chosen as an initial treatment for TIPN, followed by pregabalin (22.3%). Five patients (1.5%) started with combination therapy. The median number of days that anti-neuropathic agents were in use per patient was 49 days, ranging from 1 to 636 days. During the follow-up period, a total of 35,108 patient days of anti-neuropathic agents were prescribed and gabapentin and pregabalin accounted for 71.7 and 24.3% of the total use of anti-neuropathic agents, respectively. The average number of anti-neuropathic pain medication used per patient during the

Table 2 Risk factors for peripheral neuropathic pain treatment related to taxane (n = 1516)

		With TIPN (n = 332) N (%)	Without TIPN (n = 1184) N (%)	Multivariate analysis		
				aHR	95% CI	p value
Sex	Female	330 (99.4)	1182 (99.8)	0.44	0.11–1.78	0.248
Age (years)	20–40	34 (10.2)	261 (22.0)	1.00		
	41–60	231 (69.6)	802 (67.7)	2.08	1.44–3.00	<0.001
	>60	67 (20.2)	121 (10.2)	2.66	1.71–4.15	<0.001
BMI (kg/m^2)	<25	225 (67.8)	877 (74.1)	1.00		
	≥25	107 (32.2)	307 (25.9)	1.34	1.05–1.70	0.019
PS	0	131 (39.5)	617 (52.1)	1.00		
	≥1	195 (58.7)	534 (45.1)	1.07	0.84–1.38	0.571
	Unknown	6 (1.8)	33 (2.8)			
Diabetes		29 (8.7)	71 (6.0)	0.93	0.71–1.39	0.714
Kidney disease		6 (1.8)	7 (0.6)	1.98	0.88–4.45	0.101
Taxane	Docetaxel	184 (55.4)	981 (82.9)	1.00		
	Paclitaxel	148 (44.6)	203 (17.1)	2.28	1.72–3.01	<0.001
Stage	I–III	159 (47.9)	911 (76.9)	1.00		
	IV	173 (52.1)	273 (23.1)	2.13	1.60–2.82	<0.001
Schedule	Weekly	25 (7.5)	58 (4.9)	1.00		
	3-weekly	307 (92.5)	1126 (95.1)	2.00	1.26–3.19	0.004

aHR adjusted hazard ratio, *BMI* body mass index, *TIPN* taxane-induced peripheral neuropathy, *PS* performance score

follow-up period was 1.1 ± 0.4. The majority of patients (n = 291) were prescribed only one kind of anti-neuropathic agent. After starting the treatment, 25 patients changed to other agents and 12 patients added other agents. During the treatment, 67.6% of patients did not receive any other analgesics. Non-steroidal anti-inflammatory drugs (NSAIDs), tramadol, codeine, and strong opioids were prescribed in 12.6, 9.7, 3.2, and 4.9% of patients, respectively (Table 3).

Treatment duration was less than 1 month in 39.2% of patients, while 4.8% remained on treatment more than 1 year. In 130 patients who discontinued their anti-neuropathic pain medications within 1 month after starting the treatment, the reasons for discontinuation were "improved symptom" (52 patients, 40.0%), "lack of efficacy" (42 patients, 32.3%), "adverse effect" (4 patients, 3.1%), and "no record" (31 patients, 23.8%). Among these patients, 79 (60.8%) discontinued taxane treatment prior to or at the same time as discontinuation of the anti-neuropathic pain medication. At 1 year from the start of treatment, 316 patients discontinued all anti-neuropathic pain medications, 50.0% for improved symptom and 26.3% for lack of efficacy. Only 20.6% of patients continued taxane treatment after stopping the anti-neuropathic pain medication (Table 4).

Table 3 Anti-neuropathic pain medication treatment characteristics in taxane-treated patients

Variables	Number (%)
Initially chosen medication[a]	
Gabapentin	250 (74.4)
Pregabalin	78 (22.3)
Nortriptyline	4 (1.2)
Amitriptyline	3 (0.9)
Carbamazepine	1 (0.3)
Duloxetine	1 (0.3)
Total prescribed days (patient days, %)	35,108 (100)
Gabapentin	25,186 (71.7)
Pregabalin	8536 (24.3)
Nortriptyline	743 (2.1)
Amitriptyline	273 (0.8)
Carbamazepine	258 (0.7)
Duloxetine	112 (0.3)
Treatment duration	
≤1 month	130 (39.2)
1–2 months	60 (18.1)
2–6 months	91 (27.4)
6 months–1 year	35 (10.5)
>1 year	16 (4.8)
Co-medication	
No analgesics	167 (67.6)
Acetaminophen only	11 (2.0)
NSAID	76 (12.6)
Weak opioid: tramadol	35 (9.7)
Weak opioid: codeine	14 (3.2)
Strong opioids	12 (4.9)

[a] Five patients used a combination therapy of anti-neuropathic pain medication

NSAID non-steroidal anti-inflammatory drug

Discussion

This retrospective cohort study described the incidence and risk factors for TIPN receiving pharmacological treatment along with the prescribing patterns of anti-neuropathic drugs in breast cancer patients treated with taxane-based chemotherapy.

Overall, 21.8% of breast cancer patients who were treated with taxane received anti-neuropathic pain medication for neuropathic symptoms during and after treatment. The incidence observed in this study was lower compared with the overall incidence from previous reports and higher than those with severe PN (ranging from 2 to 33% for paclitaxel and from 3 to 14% for docetaxel) [5]. We can infer that not all patients experiencing PN but patients with severe PN were treated with anti-neuropathic pain medications. The observed higher incidence of PN in the paclitaxel-treated group compared with the docetaxel group (41.2 vs. 16.0%, $p < 0.001$) in this study was in line with the results from previous studies [1, 5, 17, 18].

In accord with the previous reports, significantly earlier treatment of PN was observed in the paclitaxel group compared with the docetaxel group. Shimozuma et al. reported that the severity of CIPN peaked earlier (cycle 3 to 7 months) in patients receiving paclitaxel compared with those receiving docetaxel (cycle 5 to 7 months) [19]. It has been shown that the onset of PN generally depends on the cumulative dose of taxane. The mean cumulative dose of docetaxel was 254.6 ± 145.0 mg/m^2, and the mean cumulative dose of paclitaxel was 527.7 ± 434.3 mg/m^2 at the onset of PN. These observed cumulative doses were a bit lower than those from the previous reports. A neurotoxic threshold was reported around 400 mg/m^2 for docetaxel and 1000 mg/m^2 for paclitaxel [20]. A phase III metastatic breast cancer study [17] documented that the mean cumulative dose to the onset of grade 2 or greater neuropathy was 371 mg/m^2 for docetaxel and 715 mg/m^2 for paclitaxel.

In this study, the likelihood of developing PN increased at age of 40–60 years and further increased at age more than 60 years. A recent E5103 study showed a 12.9% increase in the risk of taxane-induced PN per decade of life [21]. However, other trials failed to show any association between age and neuropathy [18, 22].

This study identified overweight as an independent predictor for PN in breast cancer. Ting Bao et al. showed that being obese was associated with increased risk of PN among non-

Table 4 Status of therapy and reasons for discontinuation at 1 month and 1 year after anti-neuropathic medication start

	At 1 month (%)	At 1 year (%)
Continue the anti-neuropathic medication	202 (60.8)	16 (4.8)
Initial agent only	193 (58.1)	13 (3.9)
Medication change	6 (1.8)	1 (0.3)
Medication addition	3 (0.9)	2 (0.6)
Discontinue the anti-neuropathic medication	130 (39.2)	316 (95.2)
Initial agent only	130 (39.2)	282 (84.9)
Medication change	0 –	24 (7.2)
Medication addition	0 –	10 (3.0)
Reasons for discontinuing therapy		
Lack of efficacy	42 (32.3)	83 (26.3)
Improved symptom	52 (40.0)	158 (50.0)
Adverse effect	4 (3.1)	6 (1.9)
No record	31 (23.8)	47 (14.9)
Follow up loss, transfer, or death	1 (0.8)	22 (7.0)
Status of taxane therapy at the time of discontinuation		
Taxane continue	51 (39.2)	65 (20.6)
Taxane discontinued	79 (60.8)	251 (79.4)

metastatic breast cancer patients who received taxane-based chemotherapy in a cross-sectional analysis [23].

In line with the previous results, the incidence of PN treatment in metastatic breast cancer was 2.1 times higher than in non-metastatic breast cancer. This observation may be related with the fact that metastatic breast cancer patients have a greater chance of being exposed to other neurotoxic agents like cisplatin, which may render patients prone to developing PN [24].

This study showed that PN treatment was more likely to occur in the 3-weekly taxane schedule compared with the weekly regimen. This finding was in accord with previous results from a meta-analysis that showed the incidence of grade 3/4 severe PN was significantly lower in weekly taxane schedules (OR 0.718, CI 0.539–0.956) [25]. However, considering that the proportion (5.5%) of patients who received weekly taxane was not large enough to provide reliable power, we could not cogently conclude that a 3-weekly taxane schedule is more neurotoxic than a weekly schedule.

Gabapentin and pregabalin were shown to be widely prescribed as anti-neuropathic drugs in TIPN in this study. Although both agents were shown to have significant anti-hyperalgesic and anti-allodynic effects in experimental paclitaxel-induced neuropathic pain animal models [26], the efficacy of these agents has not yet been demonstrated in clinical trials. Gabapentin is frequently used for treating neuropathic pain in patients with diabetes mellitus. However, in a double-blind, placebo-controlled trial, gabapentin was no better than the placebo in reducing PN scores in 115 patients with chemotherapy-induced PN from a variety of agents [10]. Pregabalin has a similar mechanism of action to gabapentin and is approved for neuropathic pain treatment associated with diabetic peripheral neuropathy. It has also failed to show sufficient effects for chemotherapy-induced PN [27]. Currently, there is no approved effective treatment for chemotherapy-induced PN. Nonetheless, in clinical practice, both gabapentin and pregabalin are considered as helpful in treating PN. Only two patients were prescribed with duloxetine for PN (one for initial treatment, the other one for an alternative treatment). Duloxetine is a serotonin and norepinephrine reuptake inhibitor (SNRI) and has FDA-approved indications for painful diabetic neuropathy. Although, duloxetine at a dose of 60 mg per day was shown to be effective at alleviating chemotherapy-induced pain in a well-designed randomized control trial in 2013 [14], this information was not available at the time most current patients were being treated.

According to the physician's description in the medical record, 32.3% of early discontinuation (≤1 month) cases listed the reason as "lack of efficacy," and no alternative agent was administered in any of these cases, which implies that some physicians do not treat TIPN with more medications because there are limited medications available to appropriately treat this clinical problem along with the concerns regarding the adverse effects and expenses associated with treatments.

In addition, the physician's record showed that 9.9% of patients with TIPN receiving pharmacologic treatment discontinued taxane-based chemotherapy due to TIPN. Also, a previous retrospective study showed that CIPN-associated dose reduction occurred in 17% of the breast cancer sample [28]. Considering the clinical implications of TIPN-associated treatment discontinuation and dose reduction, investigations for effective prevention and treatment strategies for TIPN should be continued.

To the best of our knowledge, this was the first study that described the incidence and pattern of pharmacologic treatment with anti-neuropathic pain medications in breast cancer patients, with both non-metastatic and metastatic cancer, who underwent taxane-based chemotherapy. However, a few limitations should be considered in interpreting the study findings. First, due to the possibility of incomplete records, we could not include patients with neuropathy that were not treated with anti-neuropathic pain medications, and this might have led to an underestimation of the incidence of TIPN in breast cancer patients. Thus, we confined TIPN to TIPN receiving pharmacologic treatment. Second, efficacy assessment of pharmacologic treatment of PN was not performed due to the incomplete available data. A large-scale prospective randomized controlled study is necessary to evaluate the efficacy of these drugs for treatment of taxane-induced neuropathy in breast cancer patients. Third, we could not assess the severity grade of PN due to insufficient data. However, we can infer that the PN defined in this study would be equal to or greater than grade 2 considering that intervention was implemented in this population. Finally, this study was conducted in a single center, and patients might have visited other healthcare facilities to control neuropathy, leading to an underestimation of the incidence.

Conclusions

This retrospective cohort study demonstrates that one-fifth of breast cancer patients who were treated with taxane-based chemotherapy received pharmacologic treatment for PN and the median time to start anti-neuropathic pain medication was 64 days, with a significantly earlier onset time in those taking paclitaxel. Paclitaxel use, older age, overweight, and metastatic cancer increased the risk for PN.

Compliance with ethical standards The institutional review board of the Seoul National University Hospital approved this study (IRB No. H-1508-139-697).

Conflict of interest The authors have no conflict to disclose. For this type of study, formal consent is not required.

All datasets generated and/or analyzed during the current study are under the control of authors and are available from the corresponding author on reasonable request.

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