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Predictors of the development of nab-paclitaxel-induced peripheral neuropathy in breast cancer patients: post hoc analysis of a prospective, phase II, self-controlled clinical trial

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Abstract

In a previous study, we showed that cryotherapy and compression therapy have comparable efficacy in preventing nab-paclitaxel-induced peripheral neuropathy. However, even with cryotherapy or compression therapy, there were patients with National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 grade ≥ 2 and/or Patient Neurotoxicity Questionnaire (PNQ) grade ≥ D peripheral neuropathies. Therefore, this post hoc analysis was performed to identify predictors of nab-paclitaxel-induced peripheral neuropathy. The clinical data in this post hoc analysis were the data of 38 breast cancer patients receiving chemotherapy with nanoparticle albumin-bound paclitaxel (nab-PTX) at our outpatient chemotherapy center from August 2017 to March 2019. The number of patients was analyzed assuming that there were data for 76 hands. Variables related to the development of nab-PTX-induced peripheral neuropathy were used for regression analysis. Multivariate-ordered logistic regression analysis was performed to identify predictors for the development of nab-PTX-induced peripheral neuropathy. Significant factors included smoking history [odds ratio (OR) 4.64, 95% confidence interval (CI) 1.60–13.5; $P = 0.0048$] with neuropathy evaluated by CTCAE, body mass index (BMI) (OR 1.13, 95% CI 1.01–1.26; $P = 0.039$) with neuropathy evaluated by PNQ (sensory), and smoking history (OR 3.80, 95% CI 1.40–10.30; $P = 0.0087$) and age (OR 1.06, 95% CI 1.01–1.11; $P = 0.012$) with neuropathy evaluated by PNQ (motor). In conclusion, smoking history, BMI and age were identified as significant predictors of the development of nab-PTX-induced-peripheral neuropathy.

Keywords Nab-paclitaxel · Chemotherapy-induced peripheral neuropathy · Smoking · Breast cancer-affected side · BMI · Advanced age

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Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) can become a major drug-induced adverse reaction that becomes a dose-limiting toxicity of chemotherapy [1–5]. In recent years, the efficacy of cryotherapy using frozen gloves (FGs) and compression therapy using surgical gloves (SGs) to prevent taxane-induced peripheral neuropathy has been reported [6–8]. However, no reports appear to have compared the efficacy of cryotherapy and compression therapy. We therefore planned a prospective, self-controlled trial to compare the efficacy of cryotherapy using FGs and compression therapy using SGs to prevent nanoparticle albumin-bound paclitaxel (nab-PTX) -induced peripheral neuropathy [9]. It was found that cryotherapy and compression therapy showed comparable efficacy in preventing CIPN. However, even with cryotherapy or compression therapy, there were patients with National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 grade ≥ 2 (18.4%) and/or Patient Neurotoxicity Questionnaire (PNQ) grade $\geq$ D peripheral neuropathies [9]. As for taxane-based chemotherapy, previous study reported advanced age, diabetes, alcohol, obesity and menopause are predictors for CIPN [10–12]. Duloxetine, which is currently recommended for the treatment of painful neuropathy in the guidelines [13, 14]. However, Smith et al. state that duloxetine is more effective in CIPN with platinum-based anticancer drugs than with taxanes [15]. Various studies have statistically analyzed the predictive factors for CIPN [10–12]. Nevertheless, effective strategies for managing CIPN among affected patients remain elusive. Thus, in addition to improving the quality of life for patients undergoing chemotherapy, there is an unmet need to better-identify patients at risk for CIPN. Therefore, a sub-analysis to identify predictors of nab-PTX-induced peripheral neuropathy was performed.

Patients and methods

Study design and participants

This is a post hoc analysis of a previously published a prospective, phase II, self-controlled clinical trial conducted between August 2017 and March 2019 (registered with the University Hospital Medical Information Network, date of first registration 24/12/2017: UMIN000030536). (https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000034856) [9]. This trial was approved by the Medical Ethics Review Committee of Kyoto Prefectural University of Medicine, in accordance with the tenets of the Declaration of Helsinki (Approval No. ERB-C-906-1). Written, informed consent was obtained from all patients prior to their enrollment including possibility to use data for post hoc analysis. Exclusion criteria were as follows: peripheral sensory/motor neuropathy (CTCAE grade ≥ 2), underlying diseases that could potentially cause peripheral neuropathy (such as diabetes mellitus or postherpetic neuralgia), allergy to the material of FGs (polyurethane and nylon) or the material of SGs (latex), brain metastases, or any other reasons based on the judgment of the primary physician. Breast cancer patients who received 260 mg/m^2 of nab-PTX as 30-min intravenous infusion every 3 weeks for four cycles were eligible to participate in this trial. Human epidermal growth factor receptor 2 (HER2)-positive patients received trastuzumab after administration of nab-PTX during each cycle. Patients wore an FG on one hand and two SGs of the same size (i.e., one size smaller than the size that best fit their hand) on the other hand during chemotherapy.

Evaluation of peripheral neuropathy

Peripheral neuropathy was evaluated by treating pharmacists and/or nurses using NCI-CTCAE version 4.0 at the following times: pretreatment (baseline); just before each treatment cycle; and six weeks after chemotherapy completion (± 2 weeks). Peripheral neuropathy was also evaluated using the Japanese version of the PNQ, a validated patient-reported questionnaire on neuropathy and activities of daily living that correlates with quality of life [16]. The PNQ comprises two items (sensory and motor neuropathy). The subjective responses to each item are graded from A to E by the patient. Each item of the PNQ was defined as A (no neuropathy), B (mild neuropathy), C (moderate neuropathy that does not interfere with activities of daily living (ADL), D (moderate neuropathy that interferes with ADL), or E (severe neuropathy that interferes with ADL). In this trial, PNQ grades were coded as 1–5, with higher scores indicating more severe peripheral neuropathy. In this post hoc analysis, the values of CTCAE (sensory and motor grades) and PNQ (sensory and motor grades) at the final evaluation were used as the objective variables. As for CTCAE, the same result was obtained for sensory and motor grades, so in the present study, the objective variables that were analyzed were CTCAE, PNQ (sensory), and PNQ (motor).

Evaluation of fingertip temperatures

To investigate mechanisms underlying protection against peripheral neuropathy, the temperature at each fingertip was measured by thermography at the first cycle of nab-PTX. Temperatures at each fingertip on both hands were measured

before wearing gloves and 30 min after the end of nab-PTX infusion using a thermographic camera (INFRA-EYE 2000; Fujitsu, Tokyo, Japan).

Explanatory variables

The following patient data were collected and analyzed to identify the predictors for CIPN. Variables evaluated included factors that could potentially impact the development of CIPN: demographic data [age, height, weight, and body mass index (BMI)], Eastern Cooperative Oncology Group performance status, smoking history, presence of comorbidity (diabetes mellitus), the dominant side hand on the breast cancer-affected side, combination therapy with trastuzumab, surgical glove size, average fingertip temperature after administration, and average difference in fingertip temperature before and after administration. The clinical information before the first dose of nab-PTX was used.

Statistical analysis

The analysis was performed assuming that each hand was independent. Since there is a possibility of a correlation between two hands of the same individual, a univariate analysis was performed by adding the patient identification (ID) number to the explanatory variable.

Explanatory variables were examined for multicollinearity (correlation coefficient $|r| \geq 0.7$), since when correlations exist among the variables, this can lead to incorrect results of regression analyses. Explanatory variables were selected based on correlation strength with the level of the CIPN (objective variable) or clinical significance. First, univariate ordered logistic regression analysis between the outcomes and each potential explanatory variable was performed. Subsequently, a multivariate-ordered logistic regression model was constructed using the stepwise backward selection procedure with the potential candidate variables. Ordered logistic regression analysis was performed, because the level of CIPN was evaluated by a graded scale, and multiple factors potentially involved as predictors for the development of CIPN had to be evaluated simultaneously.

For all statistical analyses, values of $P < 0.05$ (2-tailed) were considered significant. All analyses were performed using JMP version 14.3.0. (SAS Institute, Cary, NC, USA).

Results

Between August 2017 and March 2019, a total of 43 patients with breast cancer were enrolled, of whom 38 were evaluated in this trial [9]. Tables 1, 2, and 3 presents the clinical characteristics for a total of 76 hands (38 patients), the potential variables related to the development of CIPN, and

the results of univariate analysis evaluating CTCAE, PNQ (sensory) and PNQ (motor), respectively. Although surgical glove size and average difference in fingertip temperature before and after administration were significant predictors on univariate analysis, they were not used for multivariate analysis due to missing data. Multicollinearity was observed in body weight and BMI. BMI, which was considered the most clinically relevant predictor for CIPN, was used in the analysis. The backward stepwise selection procedure identified two variables (smoking history, the dominant side hand on the breast cancer-affected side) with neuropathy evaluated by CTCAE, two variables (smoking history and BMI) with neuropathy evaluated by PNQ (sensory) and two variables (smoking history and age) with neuropathy evaluated by PNQ (motor).

These variables were then entered into the multivariate-ordered logistic regression analysis. Significant factors identified for the development of CIPN included smoking history [odds ratio (OR) 4.64, 95% confidence interval (CI) 1.60–13.5; $P = 0.0048$] with neuropathy evaluated by CTCAE (Table 4), BMI (OR 1.13, 95% CI 1.01–1.26; $P = 0.039$) with neuropathy evaluated by PNQ (sensory) (Table 5), and smoking history (OR 3.80, 95% CI 1.40–10.30; $P = 0.0087$) and age (OR 1.06, 95% CI 1.01–1.11; $P = 0.012$) with neuropathy evaluated by PNQ (motor) (Table 6). The accuracy of our model was 46/76 (evaluated by CTCAE), 43/76 [evaluated by PNQ (sensory)] and 48/76 [evaluated by PNQ (motor)], respectively. The accuracy was determined as the ratio of the patients whose expected value was equal to the observed value (Tables 4, 5, 6).

Discussion

The multivariate-ordered logistic regression analysis performed in the present study showed that the significant predictors for the development of nab-PTX-induced peripheral neuropathy included smoking history with neuropathy evaluated by CTCAE, BMI with neuropathy evaluated by PNQ (sensory), and smoking history and advanced age with neuropathy evaluated by PNQ (motor). The dominant side hand on the breast cancer-affected side tended to develop CIPN evaluated by CTCAE. Surgical glove size and average difference in fingertip temperature before and after administration were also predictors on univariate analysis.

Several studies have reported that smoking was the predictor for CIPN development [17–20]. The result of the current study is consistent with this previous finding. Thus, clinicians need to know that the incidence and severity of CIPN are higher in patients with a smoking history.

Greenlee et al. in their prospective, observational, cohort study showed that obesity was associated with CIPN in

Table 1 Clinical characteristics, extracted variables, and results of univariate analyses for CTCAE ($n = 76$)

	Grade 0 ($n = 16$)	Grade 1 ($n = 46$)	Grade 2 ($n = 10$)	Grade 3 ($n = 4$)	P value	Odds ratio (95% CI)
Demographic data						
Age (y), median (range)	59 (45–73)	58 (34–76)	61 (40–66)	66 (62–70)	0.29	1.02 (0.98–1.07)
Height (cm), median (range)	157 (154–159)	156 (148–165)	159 (155–162)	157 (151–163)	0.37	1.05 (0.95–1.15)
Weight (kg), median (range)	47.8 (41.7–67.5)	54 (41.7–79.3)	64.6 (47–67)	44.4 (36.8–52)	0.15	1.04 (0.99–1.09)
BMI (kg/m^2), median (range)	19.5 (17.2–27.3)	22.2 (15.7–30.6)	25.5 (17.9–27.7)	17.9 (16.1–19.7)	0.27	1.07 (0.95–1.20)
PS (0/1)	16/0	44/2	10/0	2/2	0.015*	11.17 (1.59–78.20)
Smoking history, n (%)	2 (12.5)	12 (26.1)	4 (40.0)	4 (100.0)	0.004*	4.79 (1.65–13.92)
The dominant side hand on the breast cancer-affected side, n (%)	6 (37.5)	26 (56.5)	8 (80.0)	2 (50.0)	0.085	2.27 (0.89–5.78)
Combination therapy with trastuzumab, n (%)	6 (37.5)	20 (43.5)	4 (40.0)	2 (50.0)	0.62	1.26 (0.51–3.11)
Treatment						
Neo-adjuvant, n (%)	10 (62.5)	30 (65.2)	6 (60.0)	4 (100.0)	0.51	1.38 (0.54–3.54)
Adjuvant, n (%)	8 (50.0)	10 (21.7)	4 (40.0)	0	0.11	0.44 (0.16–1.20)
Palliative, n (%)	0	4 (8.7)	0	0	0.87	1.19 (0.16–8.78)
Surgical glove size, mean ± SD	5.69 ± 0.25	5.85 ± 0.38	6.00 ± 0.33	5.75 ± 0.29	0.017*	5.67 (1.37–23.50)
Average fingertip temperature after administration (°C), median (range)	23.9 (15.3–30.6)	28.5 (12.6–32.6)	29.0 (17–31.1)	28.5 (27.6–29.5)	0.095	1.10 (0.98–1.24)
Average difference in fingertip temperature before and after administration (°C), median (range)	8.1 (1.7–16.3)	3.3 (0.2–18.4)	5.3 (2.1–11.8)	5.1 (4.1–6.0)	0.14	0.91 (0.79–1.03)

CTCAE the National Cancer Institute Common Terminology Criteria for Adverse Events, *CI* confidence interval, *BMI* body mass index, *PS* performance status, *SD* standard deviation

*$P < 0.05$

breast cancer patients who received taxane treatment [21]. In this study, BMI was a predictor for CIPN development. The result of the current study is consistent with this previous finding [21–24]. Clinicians need to pay particular attention to the development of CIPN in obese patients.

Furthermore, the present study also found that advanced age is a predictor for CIPN [19, 25]. This result is consistent with previous studies. Therefore, clinicians also should be aware that the risk of CIPN increases with age.

In addition, the current study, dominant side hand on the breast cancer-affected side tended to develop CIPN evaluated by CTCAE, though it was not significant. This result was also consistent with findings in routine clinical practice.

Therefore, clinicians should be aware that, in breast cancer patients, the risk of developing CIPN is higher in patients whose dominant side is the breast cancer-affected side. It was suggested that excessive use of the breast cancer-affected side hand (dominant hand) in daily life may be a predictor for the development of CIPN. Further verification of this is needed.

Surgical glove size (small) and average difference (large) in fingertip temperature before and after administration were also predictors on univariate analysis. In other words, it was suggested that CIPN could be prevented if the glove pressure is strong, or the cooling temperature is low. This is consistent with the results of previous studies [6–8].

Table 2 Clinical characteristics, extracted variables, and results of univariate analyses for PNQ (sensory) ($n=76$)

	A ($n=17$)	B ($n=39$)	C, D or E ($n=20$)	P value	Odds ratio (95%CI)
Demographic data					
Age (y), median (range)	55 (34–73)	60 (34–76)	63.5 (40–70)	0.084	1.04 (0.99–1.08)
Height (cm), median (range)	157.3 (151–165)	155.9 (148–165)	162 (151.1–165)	0.041*	1.12 (1.01–1.22)
Weight (kg), median (range)	50 (41.7–67.5)	50 (41.7–67)	62.5 (36.8–79.3)	0.0038*	1.07 (1.02–1.13)
BMI (kg/m^2), median (range)	19.8 (17.2–27.3)	20.1 (15.7–30.6)	23.6 (16.1–29.1)	0.047*	1.12 (1.01–1.26)
PS (0/1)	16/1	38/1	18/2	0.45	2.09 (0.31–14.26)
Smoking history, n (%)	5 (29.4)	8 (20.5)	9 (45.0)	0.22	1.82 (0.70–4.71)
The dominant side hand on the breast cancer-affected side, n (%)	7 (41.2)	21 (53.8)	14 (70)	0.077	2.22 (0.92–5.39)
Combination therapy with trastuzumab, n (%)	7 (41.2)	16 (41.0)	9 (45)	0.62	1.26 (0.51–3.11)
Treatment					
Neo-adjuvant, n (%)	11 (64.7)	23 (59.0)	16 (80.0)	0.30	1.62 (0.65–4.01)
Adjuvant, n (%)	6 (35.3)	13 (33.3)	3 (15.0)	0.11	0.44 (0.16–1.20)
Palliative, n (%)	1 (5.9)	2 (5.1)	1 (5.0)	0.87	1.19 (0.16–8.78)
Surgical glove size, mean±SD	5.71±0.31	5.82±0.39	5.95±0.28	0.025*	4.77 (1.22–18.70)
Average fingertip temperature after administration (°C), median (range)	21.0 (15.3–26.9)	29.0 (12.6–32.6)	31.1 (13.3–31.1)	0.082	1.12 (0.99–1.24)
Average difference in fingertip temperature before and after administration (°C), median (range)	11.5 (3.3–16.3)	3.5 (0.9–18.4)	4.1 (0.2–11.8)	0.018*	0.84 (0.73–0.97)

PNQ the Patient Neurotoxicity Questionnaire, *CI* confidence interval, *BMI* body mass index, *PS* performance status, *SD* standard deviation

*$P < 0.05$

There were several limitations to the current study. First, both hands of the same patient were considered to be independent. Second, the methods of evaluating CIPN is subjective which may underestimate the real number of patients with CIPN. Third, since this study was conducted at a single institute, it only analyzed a relatively small number of patients. Therefore, a prospective, multicenter study will be needed to confirm these results.

In conclusion, smoking history, BMI, and advanced age were identified as significant predictors of the development of CIPN in cancer patients treated with nab-PTX. CIPN may develop more easily in dominant hand on the breast cancer-affected side. However, these preliminary findings will need to be confirmed in a larger randomized-controlled trial. Nevertheless, these findings may assist in developing chemotherapeutic strategies, including of taxane chemotherapy, with better safety and efficacy, and to improve the quality of life of patients.

Table 3 Clinical characteristics, extracted variables, and results of univariate analyses for PNQ (motor) ($n=76$)

	A ($n=41$)	B ($n=26$)	C, D or E ($n=9$)	*P* value	Odds ratio (95%CI)
Demographic data					
Age (y), median (range)	58 (34–69)	61(40–76)	65 (61–70)	0.013*	1.06 (1.01–1.11)
Height (cm), median (range)	157.3 (148–165)	156.8 (148–165)	158.3 (151.1–162.5)	0.96	1.00 (0.91–1.10)
Weight (kg), median (range)	54 (41.7–67.5)	50.5 (41.7–79.3)	64.6 (36.8–67)	0.48	1.02 (0.97–1.06)
BMI (kg/m^2), median (range)	20.1 (15.7–30.6)	21.4 (17.2–29.1)	24.8 (16.1–27.2)	0.62	1.03 (0.92–1.15)
PS (0/1)	39/2	26/0	7/2	0.24	3.10 (0.47–20.47)
Smoking history, *n* (%)	7 (17.1)	10 (38.5)	5 (55.6)	0.0093*	3.65 (1.38–9.69)
The dominant-side hand on the breast cancer-affected side, *n* (%)	21 (51.2)	17 (65.4)	4 (44.4)	0.65	1.22 (0.51–2.96)
Combination therapy with trastuzumab, *n* (%)	17 (41.5)	11 (42.3)	4 (44.4)	0.86	1.08 (0.45–2.61)
Treatment					
Neo-adjuvant, *n* (%)	28 (68.3)	14 (53.8)	8 (88.9)	0.98	1.01 (0.41–2.54)
Adjuvant, *n* (%)	10 (24.4)	11 (42.3)	1 (11.1)	0.63	1.27 (0.49–3.30)
Palliative, *n* (%)	3 (7.3)	1 (3.8)	0	0.38	0.35 (0.034–3.61)
Surgical glove size, mean ± SD	5.82 ± 0.40	5.81 ± 0.29	5.94 ± 0.30	0.47	1.63 (0.43–6.17)
Average fingertip temperature after administration (°C), median (range)	26.1 (12.6–32.6)	29.1 (17.0–31.5)	29.5 (13.3–29.5)	1.00	1.00 (0.89–1.12)
Average difference in fingertip temperature before and after administration (°C), median (range)	5.2 (0.2–18.4)	4.7 (1.5–13.5)	5.8 (0.6–9.3)	0.55	0.96 (0.83–1.10)

PNQ the Patient Neurotoxicity Questionnaire, *CI* confidence interval, *BMI* body mass index, *PS* performance status, *SD* standard deviation

*$P<0.05$

Table 4 Results of multivariate-ordered logistic regression analysis for CTCAE ($n=76$, accuracy46/76)

Variable	*P* value	Odds ratio	95% CI	
			Lower 95%	Upper 95%
Smoking history	0.0048*	4.64	1.60	13.5
The dominant side hand on the breast cancer-affected side	0.081	2.29	0.90	5.79

CI confidence interval

*$P<0.05$

Table 5 Results of multivariate-ordered logistic regression analysis for PNQ (sensory) ($n = 76$, accuracy 43/76)

Variable	P value	Odds ratio	95%CI	
			Lower 95%	Upper 95%
Smoking history	0.16	1.99	0.76	5.23
BMI	0.039*	1.13	1.01	1.26

CI confidence interval, *BMI* body mass index

*$P < 0.05$

Table 6 Results of multivariate-ordered logistic regression analysis for PNQ (motor) ($n = 76$, accuracy 48/76)

Variable	P value	Odds ratio	95%CI	
			Lower 95%	Upper 95%
Smoking history	0.0087*	3.80	1.40	10.30
Age	0.012*	1.06	1.01	1.11

CI confidence interval, *SBP* systolic blood pressure, *RAS* renin-angiotensin system

*$P < 0.05$

Declarations

Conflict of interest Isao Yokota has received a speaker's fee from Chugai Pharmaceutical Co., Ltd. Norito Katoh has been a speaker and investigator for Taiho Pharmaceutical Co., Ltd. Tetsuya Taguchi received a speaker's fee and research funds from Taiho Pharmaceutical and Chugai Pharmaceutical Co., Ltd. All other authors declare that they have no conflicts of interest concerning this work.

Consent for publication Written, consent for publication was obtained from all patients prior to their enrollment.

Ethical approval This trial was approved by the Medical Ethics Review Committee of Kyoto Prefectural University of Medicine, in accordance with the tenets of the Declaration of Helsinki (approval no. ERB-C-906-1).

Informed consent Written, informed consent was obtained from all patients prior to their enrollment.

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