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ORIGINAL ARTICLE

Predictive factors for taxane acute pain syndrome determined by ordered logistic regression analysis

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Abstract

This retrospective study was undertaken to identify predictive factors for developing taxane acute pain syndrome (TAPS) and to determine new strategies for improving QoL in patients undergoing chemotherapy. Between November 2010 and May 2018, we enrolled 121 breast cancer patients at our outpatient chemotherapy center who were undergoing chemotherapy with nanoparticle albumin-bound paclitaxel (nab-PTX) every 3 weeks. Variables related to the development of TAPS were extracted from the patients' clinical records and used for regression analysis. The degree of TAPS was classified as grade 0 = not developed; grade 1 = developed but did not require analgesics; grade 2 = developed but alleviated by analgesics such as acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs); or grade 3 = syndrome developed, causing sleep problems or interfering with daily living activities, but not alleviated by analgesics such as acetaminophen or NSAIDs thus requiring opioids. Multivariate ordered logistic regression analysis was performed to identify predictive factors for the development of TAPS. Significant factors identified for the development of TAPS included dose of nab-PTX (odds ratio (OR) = 11.717, 95% confidence interval (CI) = 11.6161–11.8182; $P = 0.0421$) and the administration of dexamethasone for up to 3 days (OR = 0.133, 95% CI = 0.0235–0.7450; $P = 0.0223$). In conclusion, a high dose of nab-PTX and the lack of dexamethasone administration for up to 3 days were identified as significant predictors of the development of TAPS.

Keywords TAPS · Taxanes · Nanoparticle albumin-bound paclitaxel · Dose · Dexamethasone

Introduction

Taxanes such as docetaxel, paclitaxel, and nanoparticle albumin-bound paclitaxel (nab-PTX) are commonly used chemotherapeutic agents in the treatment of a wide variety of malignancies [1–3]. Taxanes are highly active chemotherapeutic agents, especially when used in the treatment of early-stage and metastatic breast cancer. However, it has been well established that this agent can also cause serious adverse events such as taxane acute pain syndrome (TAPS), which is an acute adverse reaction shown to be associated with taxanes [4–8]. TAPS has also been referred to as paclitaxel-associated acute pain syndrome (PAPS) or taxane-induced pain [9, 10]. The presence of both myalgias and arthralgias is typically reported for TAPS at 2–3 days after taxane infusion, with the symptoms then lasting for 5–7 days [9]. Although TAPS is transient and non-life-threatening, symptom onset is painful and can interfere with daily living activities, along with leading to a lower quality of life (QoL). In addition,

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these symptoms can lead to chemotherapy dose reductions, treatment delays, and discontinuation of the administration [11]. At present, however, there have yet to be any effective strategies developed for preventing or treating TAPS. In order to avoid the Cremophor vehicle that is used in the solvent-based paclitaxel, the biologically interactive, solvent-free, 130-nm-sized albumin-bound paclitaxel (nab-PTX) was developed [3]. Due to improvements in the formulation, it is now possible to administer higher doses of nab-PTX. However, side effects such as TAPS as well as those for PTX still occur, which lowers the patient's QoL [11, 12]. Thus, this retrospective study was undertaken to identify predictive factors for the development of TAPS due to nab-PTX in addition to helping develop future strategies that could improve the QoL of patients undergoing chemotherapy.

Patients and methods

Study period and participants

Between November 2010 and May 2018, this study enrolled 128 breast cancer patients who were undergoing nab-PTX chemotherapy every 3 weeks at our outpatient chemotherapy center. The Medical Ethics Review Committee of the Kyoto Prefectural University of Medicine approved this study (approval no. ERB-C-867-1).

Extraction of variables

Variables were extracted by manual abstraction from clinical records and used for the regression analysis of factors related to the nab-PTX-related acute pain syndrome. The evaluated variables included factors that could potentially impact the occurrence of TAPS (age, body mass index (BMI), body surface area (BSA), height, body weight, nab-PTX dose, administration of dexamethasone for up to 3 days, presence of metastasis, combination of anti-cancer drug or bisphosphonate, and history of treatment with taxane). Treating physicians, nurses, and/or pharmacists interviewed patients during their daily routine clinical practice and collected information on the degree of TAPS that was present after undergoing their first cycle of nab-PTX chemotherapy. The degree of TAPS was classified as 0 = not developed; grade 1 = developed but did not require analgesics; grade 2 = developed but alleviated by analgesics such as acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs); or grade 3 = syndrome developed, causing sleep problems or interfering with daily living activities, but not alleviated by analgesics such as acetaminophen or NSAIDs thus requiring opioids.

Statistical analysis

Variables were examined for multicollinearity (correlation coefficient $|r| \geq 0.7$), as when correlations exist among the variables, this can lead to the use of an inappropriate model. Variables were selected in consideration of correlation strength with the degree of TAPS (response) or clinical use. In the first step, we performed univariate ordered logistic regression analysis between the outcomes and each potential independent variable. Subsequently, we constructed a multivariate ordered logistic regression model using the stepwise selection procedure among the potential candidate variables. *P* levels for the model used a variable entry criterion of 0.25 and a variable retention criterion of 0.15. The bootstrap procedure was performed to validate the optimal model. The degree of TAPS was evaluated by a graded scale, as it was possible that multiple factors could potentially be predictive factors for the development of TAPS, thereby making it necessary to simultaneously evaluate the factors. To overcome this issue, we performed an ordered logistic regression analysis. Threshold measurements were examined using a receiver operating characteristic (ROC) curve [13]. All statistical analyses were performed using JMP® version 13.1.0 (SAS Institute, Cary, NC, USA) with a two-sided significance level of 0.05.

Results

Of the 128 breast cancer patients who underwent chemotherapy with nab-PTX, 7 were excluded from this study due to difficulties in the evaluations (5 had already been prescribed opioids for pain treatment; 1 had a somnolence tendency; 1 patient was male). Table 1 presents the clinical characteristics of the 121 enrolled patients, the potential variables related to the development of TAPS, and the results of univariate analysis. The stepwise selection procedure identified four of the variables (dose of nab-PTX, BMI, age, and administration of dexamethasone for up to 3 days). These variables also remained as variables with high contribution to the model by using a bootstrap procedure. When applied to this model, it appeared that it was possible to judge well "degree of TAPS" using ROC analysis (AUC = 0.8336). These variables were then used for multivariate ordered logistic regression analysis. Significant factors identified for the development of TAPS included dose of nab-PTX (odds ratio (OR) = 11.717, 95% confidence interval (CI) = 11.6161–11.8182; *P* = 0.0421) and administration of dexamethasone for up to 3 days (OR = 0.133, 95% CI = 0.0235–0.7450; *P* = 0.0223). The accuracy of our model was 63/121. The accuracy was determined as the ratio of the patients whose expected value was equal to the observed value (Table 2). The ROC curve analysis of the group likely to develop TAPS (grade 3) revealed that the threshold for the nab-PTX dose was 410.2 mg or above, with a sensitivity of 84.2% and specificity of 43.1% (area under the curve (AUC) =

Table 1 Patient characteristics, extracted variables, and results of univariate analyses ($n = 121$)

	Grade 0 ($n = 11$)	Grade 1 ($n = 32$)	Grade 2 ($n = 59$)	Grade 3 ($n = 19$)	*P* value	Odds ratio (95% CI)
Age (years), median (range)	58 (36–71)	51 (27–73)	59 (33–84)	56 (40–74)	0.455	1.011 (0.982–1.040)
Dose (mg) of nab-PTX, mean (range)	362.7 (200–426.9)	360.6 (270–429.7)	382.9 (227–475.2)	379.4 (240–444.3)	0.039*	1.007 (1.001–1.014)
Dose (mg/m^2) of nab-PTX (mg/m^2), mean (range)	240.8 (159.3–269.1)	245.1 (172.7–277.0)	253.2 (178.4–291.7)	256.1 (177.3–330.8)	0.182	1.007 (0.997–1.016)
History of chemotherapy, *n* (%)	5 (4.13)	15 (12.4)	21 (17.36)	9 (7.44)	0.702	0.876 (0.446–1.722)
Pre-treatment history of taxane, *n* (%)	3 (2.48)	5 (4.13)	10 (8.26)	3 (2.48)	0.651	0.818 (0.340–1.961)
Bone meta, *n* (%)	3 (2.48)	3 (2.48)	9 (7.44)	2 (1.65)	0.652	0.798 (0.308–2.072)
Regimen						
nab-PTX, *n* (%)	7 (5.79)	18 (14.88)	38 (31.4)	15 (12.4)	0.180	1.613 (0.802–3.245)
nab-PTX + trastuzumab, *n* (%)	3 (2.48)	11 (9.09)	20 (16.53)	3 (2.48)	0.409	0.737 (0.358–1.518)
nab-PTX + TS-1, *n* (%)	1 (0.83)	3 (2.48)	1 (0.83)	1 (0.83)	0.203	0.373 (0.082–1.699)
Concomitant medication						
Administration of dexamethasone for up to 3 days, *n* (%)	0 (0.0)	5 (4.13)	0 (0.0)	0 (0.0)	0.064	0.206 (0.039–1.097)
Bisphosphonate, *n* (%)	3 (2.48)	1 (0.83)	4 (3.31)	4 (3.31)	0.512	1.456 (0.473–4.480)
Location of the primary tumor						
Right, *n* (%)	8 (6.61)	19 (15.7)	24 (19.83)	7 (5.79)	0.016*	0.429 (0.216–0.852)
Left, *n* (%)	3 (2.48)	12 (9.92)	28 (23.14)	11 (9.09)	0.064	1.907 (0.964–3.772)
Both, *n* (%)	0 (0.00)	1 (0.83)	7 (5.79)	1 (0.83)	0.347	1.855 (0.512–6.722)
Physical/physiological parameters						
Height (cm), mean (range)	157.9 (145.8–171.1)	157.7 (148.4–173)	157.8 (142.5–172.6)	155.1 (145–163)	0.226	0.965 (0.911–1.022)
Body weight (kg), mean (range)	54.3 (39.6–62)	52.5 (41.2–80)	55.8 (38.95–78.1)	55.1 (32–75)	0.250	1.021 (0.985–1.059)
BMI (kg/m^2), mean (range)	21.9 (17.8–29.2)	21.1 (17.2–29.6)	22.4 (15.6–31.7)	22.9 (14.0–29.4)	0.079	1.085 (0.991–1.189)
BSA (m^2), mean (range)	1.50 (1.26–1.64)	1.47 (1.27–1.89)	1.51 (1.25–1.81)	1.49 (1.15–1.75)	0.586	2.057 (0.153–27.564)
Purpose of chemotherapy						
Neoadjuvant chemotherapy, *n* (%)	5 (4.13)	16 (13.22)	22 (18.18)	9 (7.44)	0.616	0.842 (0.430–1.649)
Adjuvant chemotherapy, *n* (%)	2 (1.65)	8 (6.61)	17 (14.05)	6 (4.96)	0.410	1.372 (0.646–2.910)
Recurrence chemotherapy, *n* (%)	4 (3.31)	8 (6.61)	20 (16.53)	4 (3.31)	0.790	0.906 (0.438–1.874)

nab-PTX, nanoparticle albumin-bound paclitaxel; *TS-1*, tegafur/gimeracil/oteracil; *BMI*, body mass index; *BSA*, body surface area; *CI*, confidence interval

*$P < 0.05$

0.64). All patients were treated with 3.3–6.6 mg dexamethasone as a premedication prior to the nab-PTX infusion. While it was necessary to reduce the dose in one patient to 3.3 mg due to diabetes mellitus, all other patients received 6.6 mg of dexamethasone. Five patients received 4–8 mg/day of dexamethasone on days 2 and 3. The most common pain interventions for patients with TAPS were NSAIDs ($n = 98$, 81%), acetaminophen ($n = 15$, 12%), pregabalin ($n = 23$, 19%), Shakuyakukanzoto ($n = 9$, 7%), and tramadol ($n = 10$, 8%) (duplicate data). There were 19 patients classified as grade 3 TAPS. Among these, 1 patient had to discontinue the chemotherapy due to TAPS.

Discussion

The multivariate ordered logistic regression analysis performed in this study clarified that the significant predictors for the development of TAPS included the dose of nab-PTX and the administration of dexamethasone for up to 3 days. ROC curve analysis of the potential factors responsible for the development of TAPS determined that the cut-off value for the nab-PTX dose was 410.2 mg or above.

The results of our current study are consistent with the findings of previous studies that reported the development of

Table 2 Ordered logistic regression analysis results for variables extracted by the stepwise selection procedure (accuracy = 63/121)

Variable	*P* value	Odds ratio	95% CI	
			Lower 95%	Upper 95%
Dose (mg) of nab-PTX	0.0421*	11.717**	11.6161	11.8182
BMI	0.829	1.012	0.9069	1.1296
Age	0.1278	1.025	0.9930	1.0573
Administration of dexamethasone for up to 3 days	0.0223*	0.133	0.0235	0.7450

nab-PTX, nanoparticle albumin-bound paclitaxel; *BMI*, body mass index; *CI*, confidence interval

*$P < 0.05$

**Range odds ratio

TAPS was dose-dependent [10, 14]. In our current study, we determined that the nab-PTX dose cut-off value for the occurrence of TAPS was 410.2 mg or above. Thus, clinicians need to be alerted that TAPS is likely to occur in patients receiving high doses of nab-PTX, especially in patients who are receiving more than 410.2 mg of nab-PTX. Our current study also showed that BSA was not a significant factor. Although the administered dose in many of the nab-PTX cases was 260 mg/m^2, the dose was reduced or modified during the first chemotherapy cycle in some cases. Thus, this is perhaps one reason why the BSA was not found to be a predictor of TAPS.

Our present study also suggested that TAPS can be prevented by the administration of dexamethasone for up to 3 days. Thus, clinicians might need to consider using an initial prophylaxis of dexamethasone during the first 3 days. Furthermore, a previous study has additionally reported on the usefulness of corticosteroids for reducing TAPS [15]. Corticosteroids have also been used as analgesic adjuvants against cancer pain [16, 17], as it has been suspected that the occurrence of joint pain and myalgia significantly decreased due to the enhanced action. Since the 2016 MASCC and ESMO guidelines have reported that there is a low emetic risk for nab-PTX [18], in many cases, dexamethasone was only administered on day 1. However, clinicians need to administer dexamethasone for more than 3 days in patients on high doses of nab-PTX, especially for those receiving 410 mg or more.

Although various analgesics were used in this study, in some of the patients, these drugs were found to be ineffective. Moreover, there have been an increasing number of medications that have become available to oncology teams for the prevention of TAPS. Even so, there has yet to be any strong evidence of benefit from these interventions [19–21]. These previous reports are consistent with our current findings. However, risk factors for paclitaxel-induced peripheral neuropathy (PIPN), such as gene polymorphisms, have already been reported [22, 23]. Since TAPS shares some of the clinical characteristics with PIPN (in conjunction with the fact that TAPS can be associated with subsequent PIPN) [6, 11], it is possible that there could also be a genetic predisposition to the susceptibility of TAPS. A further study will need to be undertaken in order to verify this potential interrelationship between TAPS and gene polymorphism.

There were several limitations for our current study. First, the retrospective nature of our investigation may have decreased the reliability of the data collected. Second, as this study was performed at a single institute, it only examined a relatively small number of patients. Therefore, a larger multicenter study will need to be performed in order to confirm our current results.

In conclusion, high doses of nab-PTX combined with the lack of any administration of dexamethasone for up to 3 days were identified as significant predictors of the development of TAPS. However, these preliminary findings will need to be confirmed in further studies. Nevertheless, the identification of potential predictors of TAPS may assist in developing strategies that can be used to improve the QoL of patients undergoing chemotherapy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The Medical Ethics Review Committee of Kyoto Prefectural University of Medicine approved this study. All procedures were performed in accordance with the ethical standards of the Kyoto Prefectural University of Medicine Institutional Medical Ethics Review Committee and the 1964 Helsinki Declaration and its later amendments. No prospective studies with human participants or animals were performed by any of the authors for this article.

Informed consent Due to the retrospective nature of this work, informed consent was waived for the individual participants included in the study in accordance with the standards of the Kyoto Prefectural University of Medicine Institutional Medical Ethics Review Committee.

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