Statistical Identification of Predictors for Paclitaxel-induced Peripheral Neuropathy in Patients with Breast or Gynaecological Cancer

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Abstract. *Aim: The aim of this study was to identify predictors for paclitaxel-induced peripheral neuropathy (PIPN). Patients and Methods: We conducted a retrospective analysis of 227 patients who had been treated with paclitaxel at a single institution between January 2008 and July 2011. At the time of chemotherapy completion, the severity of PIPN was graded on a scale of 0-5, in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0. Multivariate-ordered logistic regression analysis was employed to examine the relationship between various predictive factors and the occurrence of PIPN. Results: Diabetes mellitus [odds ratio (OR)=0.070], age (OR=1.991), co-administration of neurotropin (OR=3.654), co-administration of opioids (OR=0.312), co-administration of vitamin B12 (OR=2.554), co-administration of antidepressant (OR=4.754) and co-administration of gabapentinoids (OR=14.620), were significantly associated with reduction of or less serious PIPN. Conclusion: Our study indicates that PIPN may be alleviated by co-administration of opioids.*

Paclitaxel is used in the treatment of breast and gynaecological cancer. Unfortunately, the drug induces disabling and potentially long-lasting sensory neuropathy, which manifests in the form of diverse symptoms, and significantly reduces the patients' quality of life (QOL). In fact, paclitaxel-induced peripheral neuropathy (PIPN) is a major drug-induced adverse reaction that becomes a dose-limiting toxicity (1-6). Additionally, PIPN may represent the initial stage in the development of neuropathic pain (7). Various studies have statistically analyzed the predictive factors for PIPN (5, 6). Nevertheless, effective strategies for managing PIPN among affected patients remain elusive. Thus, in addition to improving the QOL for patients undergoing chemotherapy, there is an unmet need to better-identify patients at risk for PIPN. Accordingly, the aim of this study was to identify predictors for PIPN among patients undergoing paclitaxel-based chemotherapy.

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Key Words: Peripheral neuropathy, paclitaxel, nab-paclitaxel, chemotherapy, opioids.

Patients and Methods

Study term and participants. We performed a retrospective analysis of 227 patients who were treated with paclitaxel, including nanoparticle albumin-bound (nab)-paclitaxel at the University Hospital at Kyoto Prefectural University of Medicine, between January 2008 and July 2011. This study protocol was approved by the Ethical Review Boards of Kyoto Prefectural University of Medicine E-339.

Statistical analysis. Extraction of variables: Predictive variables associated with PIPN included sex, age, comorbidity and concomitant drug use. Concomitant drug use was defined as the administration of another drug for ≥2 weeks at the time of evaluation of the severity of PIPN. Binary scales were used for sex (female=0; male=1) and other variables (no=0; yes=1). Age was graded according to an ordinal scale (<60 years=0; 60-69 years=1; ≥70 years=2). The severity of PIPN (=response *Y*) was assessed at chemotherapy completion, and was graded from 0-5 in accordance with the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v4.0 (CTCAE) (8), terms of neuropathy-sensory. The NCI-CTCAE sensory neuropathy grading was as follows: Grade 0=normal; grade 1=asymptomatic, loss of deep tendon reflexes or paraesthesia; grade 2=moderate symptoms, limiting instrumental activities of daily living (ADL); and grade 3=severe symptoms, limiting self-care ADL; grade 4=life-threatening consequences, urgent intervention indicated; grade 5=death. Patients with a history of peripheral neuropathy (PN) were excluded from analysis. The NCI-CTCAE sensory neuropathy grades in the records were written by the treating physician and/or primary nurse.

Table I. *Clinical characteristics of study patients.*

	N=227
Nab-paclitaxel	9 (4.0)
Demographic	
Mean (SD) age, years	56.3 (10.9)
Age category[a], 0/1/2	128/75/24
Comorbidity	
Diabetes mellitus, N (%)	5 (2.2)
Concomitant medication, N (%)	
Opioids	16 (7.0)
Morphine	3 (1.3)
Oxycodone	8 (3.5)
Fentanyl	5 (2.2)
NSAIDs	55 (24.2)
COX-2	22 (9.7)
Neurotropin	15 (6.6)
Steroids	6 (2.6)
Gabapentinoids	12 (5.3)
Pregabalin	7 (3.1)
Gabapentin	5 (2.2)
Vitamin B12	28 (12.3)
Shakuyaku-kanzo-to	10 (4.4)
Gosha-jinki-gan	26 (11.5)
Antidepressant	7 (3.1)
Benzodiazepine	54 (23.8)
Zoledronic acid	11 (4.8)
Concomitant use of cancer drugs, N (%)	
Capecitabine	12 (5.3)
Carboplatin	84 (37.0)
Nedaplatin	4 (1.8)
Mean no.(range) of chemotherapy cycles	*13.4 (1-114)*
Mean (range)duration of chemotherapy, days	*216 (0-1449)*
Type of cancer, N (%)	
Breast	142 (62.6)
Ovarian	51 (22.5)
Uterine	34 (15.0)
Uterine corpus	19 (8.4)
Uterine cervix	15 (6.6)

[a]Age was categorized as follows: 0, <60 years; 1, 60-69 years; 2, ≥70 years. PN, Peripheral neuropathy; NSAID, non-steroidal anti-inflammatory drug; COX, cyclooxygenase.

Statistical analytical approach. Multivariate-ordered logistic regression analysis was employed to examine the relationship between various predictive factors and the occurrence of PIPN, as PIPN was evaluated by a graded scale and as multiple factors involved in PIPN were to be evaluated simultaneously. All potential predictive variables were screened for multi-collinearity, which was defined as a correlation coefficient of >0.7 between any two predictors. The lack of multi-collinearity ensured the appropriate use of a multivariate regression model. Variables were further screened with the forward selection procedure, after which multivariate logistic regression analysis was performed with the selected variables. All statistical analyses were performed using JMP® Version 9 (SAS Institute, Cary, NC, USA) at the two-sided 0.05 significance level.

Table II. *Distribution of sensory peripheral neuropathy severity using Common Terminology Criteria for Adverse Events (CTCAE) v4.0 and response (Y): categorization of data.*

CTCAE v4.0	Number of patients	Response (*Y*)	Number of patients
0	76	0	76
1	79	1	79
2	66	2	66
3	6		
4	0	3	6
5	0		

Results

Table I presents the clinical characteristics of the patients who were administered paclitaxel (including nab-paclitaxel), as well as the selected predictors related to the risk of PIPN. The chemotherapeutic regimen consisted of a single administration of paclitaxel (paclitaxel; 80-100mg/m^2 six times in an 8-week cycle), or the combination of paclitaxel with capecitabine, carboplatin or nedaplatin.

Table II shows data on the severity of PIPN at the time of chemotherapy completion, rated as grade 0-5 in accordance with the CTCAE. The minimum number of patients necessary to form a category of the response (*Y*) was 4 in logistic regression analysis, and each category of *Y* was divided into 4 (Table II). As documented in Table III, regression analyses revealed that diabetes mellitus [odds ratio (OR)=0.070; confidence interval (CI)=0.006-0.856; p=0.0373], age (OR=1.991; CI=1.364-2.907; p=0.0004), co-administration of neurotropin (OR=3.654; CI=1.100-12.146; p=0.0344), co-administration of opioids (OR=0.312; CI=0.103-0.942; p=0.0388), co-administration of vitamin B12 (OR=2.554; CI=1.054-6.192; p=0.0379), co-administration of antidepressant (OR=4.754; CI=1.050-21.516; p=0.043) and co-administration of gabapentinoids (OR=14.620; CI=3.802-56.212; p<0.0001), were associated with reduction of or less serious PIPN.

Discussion

Our study indicates that PIPN may be alleviated by the co-administration of opioids, and that advanced age is a significant predictor for PIPN. Additionally, patients with diabetes mellitus might be less sensitive to noticing symptoms of PIPN. Finally, the administration of various agents used to relieve the symptoms derived from PIPN itself during chemotherapy, including neurotropin, vitamin B12, antidepressant and gabapentinoids (pregabalin or gabapentin), did not show adequate therapeutic efficacy.

Oxycodone has been reported to be effective in relieving symptoms of PN (9, 10). Arbaiza *et al*. suggested that tramadol

Table III. *Results of logistic regression analysis for variables extracted by forward selection in 227 patients (accuracy ratio[a] 121/227).*

Variable	EV	SE	χ^2 value	*p*-value	OR	95% CI of OR	
						Lower	Upper
Nab-paclitaxel	–0.790	0.710	1.24	0.2657	0.454	0.113	1.824
Diabetes mellitus	–2.653	1.274	4.34	0.0373*	0.070	0.006	0.856
Age category[b]	0.689	0.193	12.72	0.0004*	1.991	1.364	2.907
Neurotropin	1.296	0.613	4.47	0.0344*	3.654	1.100	12.146
Opioids	–1.165	0.564	4.27	0.0388*	0.312	0.103	0.942
Vitamin B12	0.938	0.452	4.31	0.0379*	2.554	1.054	6.192
Gosha-jinki-gan	0.576	0.418	1.89	0.1687	1.779	0.783	4.038
Antidepressants	1.559	0.770	4.10	0.043*	4.754	1.050	21.516
Steroids	1.636	0.843	3.77	0.0521	5.136	0.985	26.782
Gabapentinoids	2.682	0.687	15.24	<0.0001*	14.620	3.802	56.212

*$p<0.05$. EV, Estimated value; SE, standard error; CI, confidence interval; OR, odds ratio; Nab-paclitaxel, nanoparticle albumin-bound –paclitaxel. [a]Accuracy ratio is the ratio of patients whose expected value is equal to the observed value. [b]Age was coded into three categories as follows: <60 years, 60-69 years, and ≥70 years.

is a therapeutic option for the control of neuropathic pain and improving QOL in patients with cancer. In fact, the analgesic effect of tramadol is independent of changes in anxiety, depression and nervous system function (11). A previous study also clarified the efficacy and safety of tramadol in the management of pain due to diabetic neuropathy (12). Recently, tramadol became available for use in Japan. Since tramadol is located on the second step of the World Health Organization analgesic ladder, it is not designated as a narcotic, making it easy to use in Japan. Our study also indicates that PIPN may be alleviated by the co-administration of opioids. In the future, we hope to perform a prospective study to examine the efficacy of opioids, such as tramadol, in PIPN management.

Akerley *et al*. proposed that elderly patients have a higher risk of manifesting taxane-induced PN (13). In another study, age emerged as the most relevant risk factor for bortezomib-induced PN, accounting for a 6% risk increase of PN per year of age (14). Molloy *et al*. also noted that older age and cumulative dose were possible contributing factors of thalidomide-induced neuropathy (15). Our results support these findings and indicate that advanced age is a significant predictor of PIPN risk. On the other hand, Argyriou *et al*. indicated that elderly cancer patients did not have a greater risk of chemotherapy-induced PN (CIPN) (1). This latter study also revealed that advanced age was not associated with the severity of CIPN. Thus, the impact of age requires further characterization.

Badros *et al*. reported that the administration of thalidomide predicted bortezomib-induced PN among patients with diabetes mellitus (16). Our study indicated that patients with diabetes mellitus might be less sensitive to noticing PIPN symptoms. Further investigation is necessary.

In the current study, analgesic adjuvants such as neurotropin, vitamin B12, antidepressants and gabapentinoids used to relieve the symptoms of PN during chemotherapy did not show adequate therapeutic efficacy. This finding supports earlier observations that no effective analgesic adjuvants are currently available for PIPN (1-6).

Recently, the usefulness of gabapentinoids in the management of CIPN was studied (17). In our study, due to the low number of patients (n=12), the efficacy of gabapentinoids for PIPN was not clarified. Moreover, the efficacy of pregabalin in diabetic neuropathy and post herpetic neuropathy was already reported (18-20). Since pregabalin has only become available for use in Japan as of June 2010, we have little experience with its use. Further research will be needed to elucidate the efficacy of pregabalin for managing CIPN.

In this study, there was no difference in PIPN risk in response to treatment with nab-paclitaxel (21) and traditional paclitaxel. However, since nab-paclitaxel only became available in Japan as of September 2010, so a few patients (n=9) in our study were treated with nab-paclitaxel. Further examination of this issue is needed.

Some studies have also investigated the relationship between genetic factors and taxane-induced PN. For instance, in their pilot study, Sissung *et al*. suggested that PIPN might be linked to inherited variants of ATP binding cassette gene-B1 (*ABCB*) through a mechanism that is unrelated to altered plasma pharmacokinetics (22). While risk factors for PIPN, such as gene polymorphisms, have already been reported, the interrelationship of PIPN and gene polymorphism will need to be verified at a later date.

In conclusion, our preliminary study indicates that PIPN may be alleviated by co-administration of opioids. Additionally, advanced age is a significant predictor for PIPN and patients with diabetes mellitus might be less sensitive to noticing PIPN symptoms. Lastly, analgesic

adjuvants (neurotropin, vitamin B12, antidepressants and gabapentinoids) used to relieve the symptoms derived from PIPN itself during chemotherapy did not show adequate therapeutic efficacy. Although our preliminary study is limited in terms of the retrospective nature of the investigation and the relatively small number of patients analysed, the statistical identification of predictors for PIPN should contribute to establishing evidence-based medicine for the prevention and treatment of PIPN and the improvement of QOL for patients undergoing paclitaxel-based chemotherapy. Further research focusing on the potential PIPN prophylactic or treatment effects of agents such as opioids and gabapentinoids is warranted.

Conflicts of Interest

None declared.

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